

Age and Sex Associations with Systemic Corticosteroid-Induced Morbidity in Asthma



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What is already known about this topic? It has been shown previously that those with high exposure to oral corticosteroids are more likely to experience adverse events or greater comorbidity.

What does this article add to our knowledge? This burden does not appear to be shared equally by men and women. Furthermore, it seems that younger patients, relative to older patients, suffer the most as a result of corticosteroid-induced morbidity.

How does this study impact current management guidelines? The results allow clinicians to better understand the risks of placing patients with severe asthma on systemic corticosteroids and are also important in economic evaluations.

BACKGROUND: Treatment of severe asthma may include high-dose systemic corticosteroid therapy, which is associated with substantial comorbidity. There is evidence to suggest that this burden is not evenly distributed across age, sex, and corticosteroid exposure levels.

OBJECTIVE: To examine the associations between age, sex, comorbidity, and patterns of health care cost across groups differentiated by corticosteroid exposure.

METHODS: Patients with severe asthma ($n = 808$) were matched by age and sex with patients with mild/moderate asthma ($n = 3975$) and nonasthma control subjects ($n = 2412$) from the Optimum Patient Care Research

Database. Regression analysis was used to investigate the odds of a number of corticosteroid-induced comorbidities as it varied by cohort, age group, and sex. Prescribed drugs and publicly funded health care activity were monetized and annual costs per patient estimated.

RESULTS: Patients aged 60 years or younger with high oral corticosteroid (OCS) exposure had greater odds of osteopenia, osteoporosis, glaucoma, dyspeptic disorders, chronic kidney disease, cardiovascular disease, cataracts, hypertension, and obesity ($P < .01$) relative to those with mild/moderate asthma (low OCS exposure) as well as to those with no asthma. This difference in odds was much less evident in older patients.

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Abbreviations used

CKD- Chronic kidney disease
NIDDM- Non-insulin-dependent diabetes mellitus
OCS- Oral corticosteroids
OPCRD- Optimum Patient Care Research Database

Sex-related differences for the odds of most comorbidities related to high-dose OCS were also observed. This differential pattern of comorbidity prevalence was reflected in mean health care costs per patient per year.

CONCLUSIONS: Results demonstrate important differential prevalence of corticosteroid-induced morbidity by age and sex, which is paralleled by differences in health care costs. This is important for clinicians in better understanding the risks of placing different age groups or sexes on systemic corticosteroids. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2014-23)

Key words: Asthma; Corticosteroid; Comorbidity; Economic; Age; Sex

INTRODUCTION

Asthma is a condition affecting approximately 334 million people worldwide.¹ It gives rise to a significant disease burden in terms of both comorbidity and financial costs²⁻⁴ to which severe asthma is known to contribute disproportionately.⁵ Oral corticosteroids (OCSs) used in the treatment of asthma and other inflammatory conditions have been implicated in a range of comorbidities and adverse events.⁶⁻¹⁰ Use of OCSs is known to increase with asthma severity; indeed severe refractory asthma is defined on the basis of the need for high-dose corticosteroid exposure.¹¹ As our understanding of the association between corticosteroid exposure and comorbidity has increased, so too have efforts to incorporate these costs into assessments of economic burden.¹²⁻²⁰ This is particularly relevant because the cost-effectiveness of novel corticosteroid-sparing biologic therapies may hinge on the incorporation of the potential savings related to induced morbidity that they produce.

The roles of age and sex are important in the natural history of many diseases. Heterogeneity in comorbidity related to age, sex, and corticosteroid exposure may provide insights into the accumulation of corticosteroid-induced morbidity and when savings from the use of corticosteroid-sparing therapies might exist. Patient cohorts with severe refractory asthma consistently have a mean age of more than 50 years and have a preponderance of females.²¹⁻²³ Moreover, older patients with moderate asthma are also more likely to experience treatment failure with standard inhaled therapy relative to younger patients.²⁴ Although there is evidence for age-related differences in comorbidity between those with and without asthma,²⁵ there is a paucity of data examining patterns of corticosteroid-induced morbidity and the associated financial costs in patients with severe asthma differentiated by age and sex.

Establishing whether distinct patterns of disease burden exist across groups differentiated by age and sex associated with corticosteroid exposure is important for clinicians planning care pathways and in assessing the cost-effectiveness of corticosteroid-sparing therapies. Indeed, UK's National Institute for Health and

Care Excellence guidelines for the methods of technology appraisal recommend defining specific patient subgroups “on the basis of an expectation of differential clinical or cost-effectiveness because of known, biologically plausible mechanisms, social characteristics or other clearly justified factors.”²⁶

In this study, we examine the associations between age and sex and the prevalence of a range of comorbidities across groups of patients with asthma differentiated by their corticosteroid exposure. We extend this analysis to include aspects of the financial burden, as well as the comorbidity burden associated with corticosteroid exposure, and discuss possible policy implications.

METHODS

Literature review

In MEDLINE, Embase, Scopus, and ScienceDirect databases we searched the titles, abstracts, and keywords of all English journal articles from the year 2000 to the present (September 2017) using “asthma” and a combination of “age,” “gender” or “sex,” and “corticosteroid” or “steroid,” and “comorbidity” or “adverse.” The title of each publication was assessed for relevance, abstracts were subsequently sought and read, and the most relevant articles were read in full.

Cohort definition

The demographic details of the matched patient cohorts have been published previously.¹⁴ In brief, patients with severe asthma (n = 808) requiring OCSs regularly (defined as Global Initiative for Asthma step 5 treatment^{18,27} and ≥4 prescriptions for OCSs in each of 2 consecutive study years) were matched by age, sex, and year of birth (because of differing data extraction dates—data were extracted between 2008 and 2013) with patients having a diagnosis of mild/moderate asthma (asthma diagnosis, Global Initiative for Asthma step 2/3²⁷; n = 3975) and with a nonasthma control group, all of which had a diagnosis of rhinitis (n = 2412). Data were obtained from the Optimum Patient Care Research Database (OPCRD), a large, nationally representative, primary care practice database.¹³ Subjects were required to be older than 12 years and to have at least 2 years of continuous medical records, so that 24 months of continuous primary care data were available for analysis to mitigate any aberrations that may occur with any 1 year.

Patients were included in the nonasthma control group if they had a rhinitis diagnosis with no asthma diagnosis/asthma drug prescription and no exposure to OCSs as evidenced by the patterns of service use and prescribed medicines in the OPCRd. To avoid any risk of non-asthma-related exposure to corticosteroids, subjects with conditions for which systemic corticosteroids may be prescribed were removed from the data (see this article's [Online Repository](http://www.jaci-inpractice.org) at www.jaci-inpractice.org for a list of conditions). Thus, the mild/moderate asthma group may have had inhaled corticosteroid exposure and some degree of OCS exposure. Comparing the severe and moderate/mild asthma groups permitted estimation of the effects of OCS exposure while controlling for any effects of asthma that were not specific to OCS use. The data included details of all publicly funded health care consultations, including primary and secondary care, as well as details of prescribed therapies/drugs.

Morbidity status

The data from the OPCRd contain information on patients' health care activity, documented through “Read codes,”²⁸ which make up the clinical classification system currently used in primary care in the United Kingdom. Read codes are used to report details on

TABLE 1. Odds ratios (95% CIs) for the risk of comorbidities across sex in the severe asthma (high OCS exposure) cohort relative to the mild/moderate asthma (low OCS exposure) cohort

Comorbidity	Sex		Total
	Male	Female	
NIDDM	1.1 (0.7-1.7)	1.7* (1.3-2.4)	1.5* (1.1-1.9)
Obesity	1.2 (0.9-1.6)	1.4* (1.2-1.8)	1.4* (1.2-1.6)
Osteoporosis	42.1* (14.3-123.9)	3.6* (2.7-4.9)	5.2* (4.0-6.9)
Osteopenia	22.5* [†] (8.5-59.1)	3.9* (2.7-5.7)	5.3* (3.8-7.4)
Hypertension	1.7* (1.3-2.3)	1.2 (0.9-1.5)	1.4* (1.1-1.6)
CKD	2.5* (1.6-3.7)	1.5 [‡] (1.1-2.1)	1.8* (1.4-2.3)
Dyspeptic disorders	3.4* (2.6-4.6)	4.4* (3.5-5.7)	4.0* (3.3-4.8)
Psychiatric disorders	1.5* (1.1-2.0)	1.4* (1.2-1.7)	1.4* (1.2-1.7)
Sleep disorders	0.9 (0.4-2.3)	2.2* (1.4-3.5)	1.7* (1.2-2.6)
Hypercholesterolemia	1.8* (1.3-2.6)	0.9 (0.6-1.1)	1.2 (0.9-1.4)
Cataracts	2.8* (1.7-4.4)	1.5 (1.0-2.2)	1.9* (1.4-2.6)
Cardiovascular disease	1.1 (0.7-1.6)	1.7* (1.1-2.4)	1.4 [‡] (1.0-1.8)
Fractures	0.6 (0.3-1.5)	2.1* (1.3-3.1)	1.5 [‡] (1.1-2.2)
Glaucoma	1.3 (0.7-2.4)	1.1 (0.6-1.8)	1.1 (0.8-1.7)

* $P < .01$.[†]Region was not controlled for in this regression; because the likelihood function in this instance was flat, it was not possible to produce model estimates.[‡] $P < .05$.

interactions with patients including procedures undertaken, disease classifications, symptom documentation, and other actions taken by clinicians, such as referrals made; codes are arranged in a hierarchical fashion; for example, all codes beginning with “N” denote “musculoskeletal and connective tissue diseases”; the Read code N330.00 denotes, more specifically, “osteoporosis.”

A range of comorbidities were identified in previous research using the OPCR data as having a greater prevalence in the high OCS exposure group relative to the low and no OCS exposure groups and as being associated, in the literature, with OCS exposure.¹⁴ The National Health Service Read code browser was used to identify version 2 Read codes relating to these comorbidities and these were subsequently used to identify comorbidity status of individuals within the sample. Although the use of Read codes may have resulted in broad categories for some comorbidities, this approach has been used to identify comorbidities in previous work^{14,20} and the authors believe they provide a reasonable basis on which to identify corticosteroid-induced morbidity across groups.

Costing

The OPCR contained information on patients' health care activity through Read codes and also patients' prescriptions, documented using British National Formulary codes²⁹ and product descriptions. This information was used to assign unit costs for health care activities, for example, a general practice visit or outpatient visit, using the Personal Social Services Research Unit cost data 2013.³⁰ British National Formulary codes and product descriptions were used to assign drug costs using the Northern Ireland Prescription Cost Analysis 2013.³¹ Costs were aggregated for the individual to calculate the annual costs per person and converted to 2013 US dollars applying purchasing power parity.³² Upon investigation of outliers, 1 individual from the nonasthma cohort was removed from the economic analysis because there was no information on prescription quantities (see Figure E1 in this article's

Online Repository at www.jaci-inpractice.org). Full details of this costing procedure have been published previously.²⁰

Statistical analysis

Cross-tabulations were used to explore associations between corticosteroid exposure, comorbidity, age, and sex. Conditional logistic regression analysis was used to explore the effects of corticosteroid exposure on comorbidity in groups partitioned by age group and sex while taking account of the matching and adjusting for region. Odds ratios (with 95% CIs) were calculated for each group compared with the reference group (severe asthma) in samples partitioned first by age and then by sex.

When the aforementioned analysis concerned differences in comorbidity between OCS exposure groups within each age group and within each sex, conditional logistic regressions were also fitted on the pooled sample to examine differences across age groups and across sex. Furthermore, age group and sex interactions were included to test for age group effects within each sex or sex effects within each age group. When the number of individuals was too small within an age group to allow comparative analysis, younger age groups were combined.

Graphs for mean annual health care costs (total, clinical activity only, medication only based on 2-year costs divided by 2) per person (with 95% CIs) stratified by exposure group and within group by age and sex were used to demonstrate differences in costs related to cohort, age, and sex. Age analysis was based on an approximate quartile split of the sample: 45 years or younger, 46 to 60 years, 61 to 70 years, or older than 70 years (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Statistical significance was achieved for P values less than α (0.05). Analyses were performed using Stata release 14 (StataCorp, College Station, Texas).

The OPCR has been reviewed and ethically approved by the National Health Service Health Research Authority to hold and process anonymized data as part of our service delivery (Research

TABLE II. Odds ratios (95% CIs) for the risk of comorbidities for each age group in the severe asthma (high OCS exposure) cohort relative to the mild/moderate asthma (low OCS exposure) cohort

Comorbidity	Age group				Total
	≤45 y	46-60 y	61-70 y	>70 y	
NIDDM	4.7* (1.5-15.1)	3.0† (1.9-4.9)	1.2 (0.7-2.0)	0.8 (0.5-1.3)	1.5† (1.1-1.9)
Obesity	2.0† (1.4-2.8)	1.6† (1.2-2.1)	1.0 (0.7-1.4)	1.0 (0.7-1.4)	1.4† (1.2-1.6)
Osteoporosis‡	13.9† (7.4-26.1)		6.9† (4.0-11.9)	2.8† (1.9-4.3)	5.2† (4.0-6.9)
Osteopenia‡	11.8† (6.7-20.5)		2.2* (1.1-4.2)	3.6† (1.8-7.0)	5.3† (3.8-7.4)
Hypertension	2.4† (1.3-4.4)	1.7† (1.2-2.3)	1.3 (0.9-1.8)	1.0 (0.7-1.3)	1.4† (1.1-1.6)
CKD‡	5.0† (2.9-8.4)		2.2† (1.4-3.6)	1 (0.7-1.4)	1.8† (1.4-2.3)
Dyspeptic disorders	5.4† (3.7-7.8)	5.3† (3.8-7.4)	3.7† (2.5-5.5)	2.1† (1.4-3.1)	4† (3.3-4.8)
Psychiatric disorders	1.6* (1.1-2.2)	1.5† (1.2-2.1)	1.5* (1.1-2.1)	1.1 (0.8-1.6)	1.4† (1.2-1.7)
Sleep disorders	2.6 (0.9-7.4)	2.6† (1.3-5.0)	1.4 (0.5-3.8)	1.0 (0.4-2.7)	1.7† (1.2-2.6)
Hypercholesterolemia	1.6 (0.6-4.1)	1.2 (0.8-1.8)	1.3 (0.9-1.9)	1 (0.7-1.4)	1.2 (0.9-1.4)
Cataracts‡	5.5† (2.4-12.3)		1.4 (0.7-2.6)	1.7* (1.1-2.5)	1.9† (1.4-2.6)
Cardiovascular disease‡	2.9† (1.5-5.5)		1.2 (0.7-2.2)	1.1 (0.8-1.7)	1.4* (1.0-1.8)
Fractures	0.4 (0.1-1.9)	1.6 (0.8-3.4)	2.1 (0.9-4.7)	2.0* (1.1-3.5)	1.5* (1.1-2.2)
Glaucoma‡	3.6† (1.6-7.8)		1.1 (0.5-2.4)	0.6 (0.3-1.2)	1.1 (0.8-1.7)

* $P < .05$.

† $P < .01$.

‡Age groups ≤45 y and 46-60 y were combined.

Ethics Committee reference 15/EM/0150). The OPCRd is governed by the Anonymised Data Ethics Protocols and Transparency Committee and application to use the data in this article was reviewed and approved by the committee. No consent was required.

RESULTS

Demographic details of the patients are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. The group without OCS exposure (nonasthma), the group with low exposure (mild/moderate asthma), and the group with high OCS exposure (severe asthma) had 61% (1481 of 2412), 63% (2515 of 3975), and 63% (507 of 808) females and a mean age of 58 years (95% CI, 25-91), 58 years (95% CI, 26-90), and 59 years (95% CI, 26-91), respectively. Figure 1 shows the prevalence of the various comorbidities stratified by age group, and Figure 2 shows a breakdown of the prevalence of these comorbidities by sex. These 2 figures highlight the varying patterns of prevalence of comorbidity between corticosteroid exposure groups across age groups and sex.

When stratifying the cohorts by sex, males with high OCS exposure (severe asthma) relative to those with low OCS exposure (mild/moderate asthma) (Table I) had greater odds of chronic kidney disease (CKD), osteoporosis, osteopenia, hypertension, psychiatric conditions, cataracts, dyspeptic disorders, and hypercholesterolemia ($P < .01$). Females with high OCS exposure relative to those with low OCS exposure (Table I) had greater odds of osteoporosis, osteopenia, fractures, sleep disorders, psychiatric conditions, cardiovascular disease, non-insulin-dependent diabetes mellitus (NIDDM), obesity (body mass index >30 kg/m²), and dyspeptic disorders ($P < .01$).

Sex differences between those with high OCS exposure and those with no OCS exposure are given in Table E3 in this article's Online Repository at www.jaci-inpractice.org. In brief, males, in addition to those conditions mentioned earlier, had greater odds of obesity ($P < .01$) and females had greater odds of

cataracts, hypertension, and CKD ($P < .01$). There were not enough cases of osteopenia in males without OCS exposure to determine the odds for this group compared with males with high OCS exposure.

Across the younger age groups (≤45 years and 46-60 years) there was a difference noted in the odds of osteopenia, osteoporosis, glaucoma, dyspeptic disorders, CKD, cardiovascular disease, cataracts, hypertension, obesity ($P < .01$), NIDDM, and psychiatric disorders ($P < .05$) for the high OCS exposure group relative to the low OCS exposure group (Table II). Those aged 61 to 70 years had significantly greater odds of CKD, dyspeptic disorders, and osteoporosis ($P < .01$); osteopenia and psychiatric conditions were significant at $P < .05$. Those older than 70 years with high OCS exposure relative to low OCS exposure had greater odds of osteoporosis, osteopenia, and dyspeptic disorders ($P < .01$); cataracts and fractures were significant at $P < .05$.

Age-related differences between those with high OCS exposure and those with no OCS exposure are given in Table E3 in this article's Online Repository at www.jaci-inpractice.org. The younger age groups (≤45 years and 46-60 years), in addition to the conditions described earlier, showed greater odds of hypercholesterolemia ($P < .01$) and sleep disorders ($P < .05$), whereas psychiatric conditions became slightly less significant ($P < .05$). Those aged 61 to 70 years had odds of cataracts, hypertension, and psychiatric conditions ($P < .01$) as well as hypercholesterolemia ($P < .05$), whereas those older than 70 years had greater odds of obesity and cataracts ($P < .01$) in addition to those found between the high and low OCS exposure groups.

Differences in odds ratios across sex were found for osteopenia, osteoporosis, and hypercholesterolemia for those with high OCS exposure relative to those with low OCS exposure ($P < .01$). Thus, for these conditions there is a different pattern of corticosteroid-induced morbidity between males and females, specifically that males are at greater risk (Table III). There are differences in odds across sex for NIDDM, osteoporosis, and

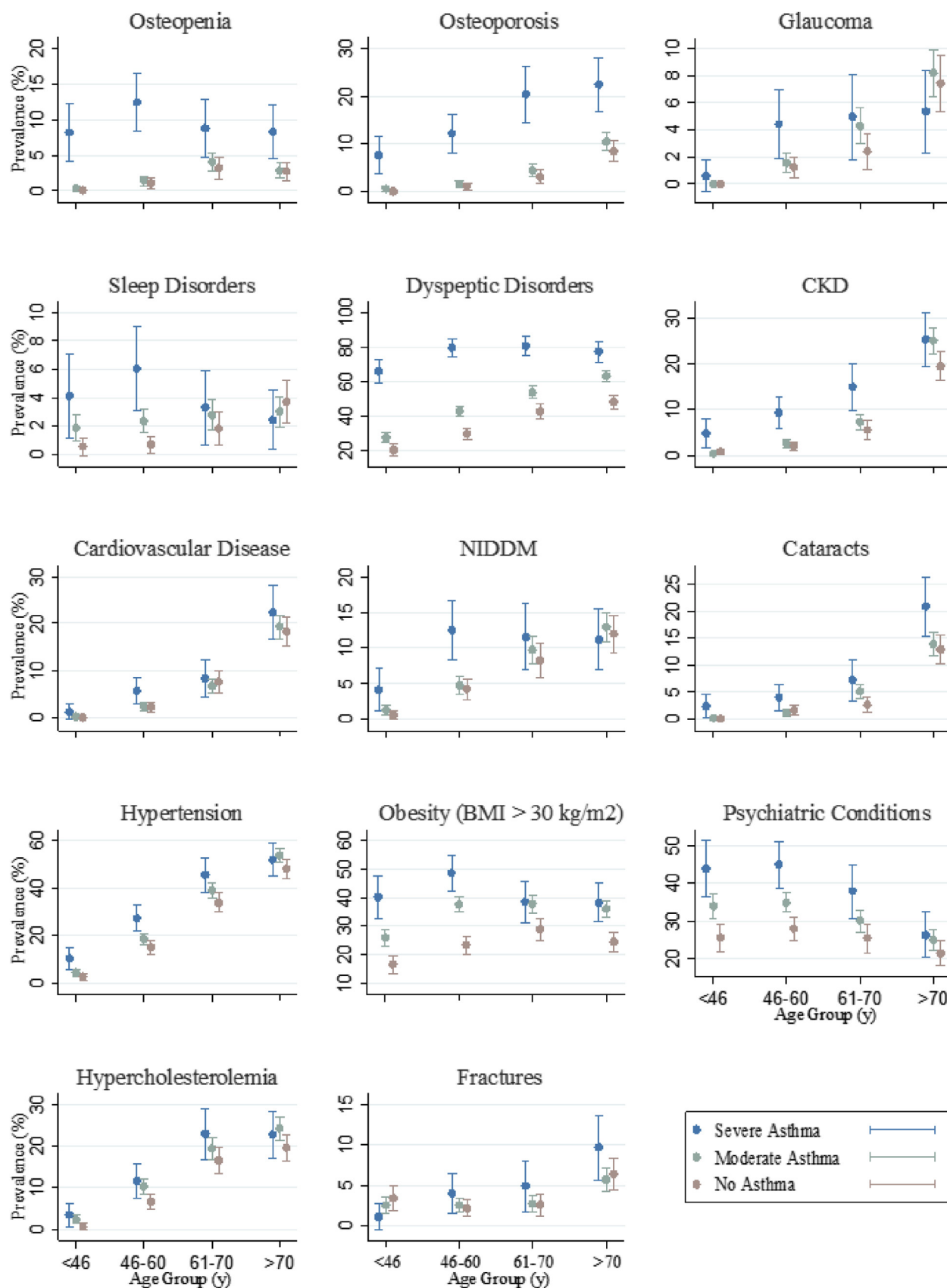


FIGURE 1. Sample prevalence with 95% CIs of corticosteroid-related comorbidities across cohorts partitioned by age group. Note that the y-axis varies according to comorbidity.

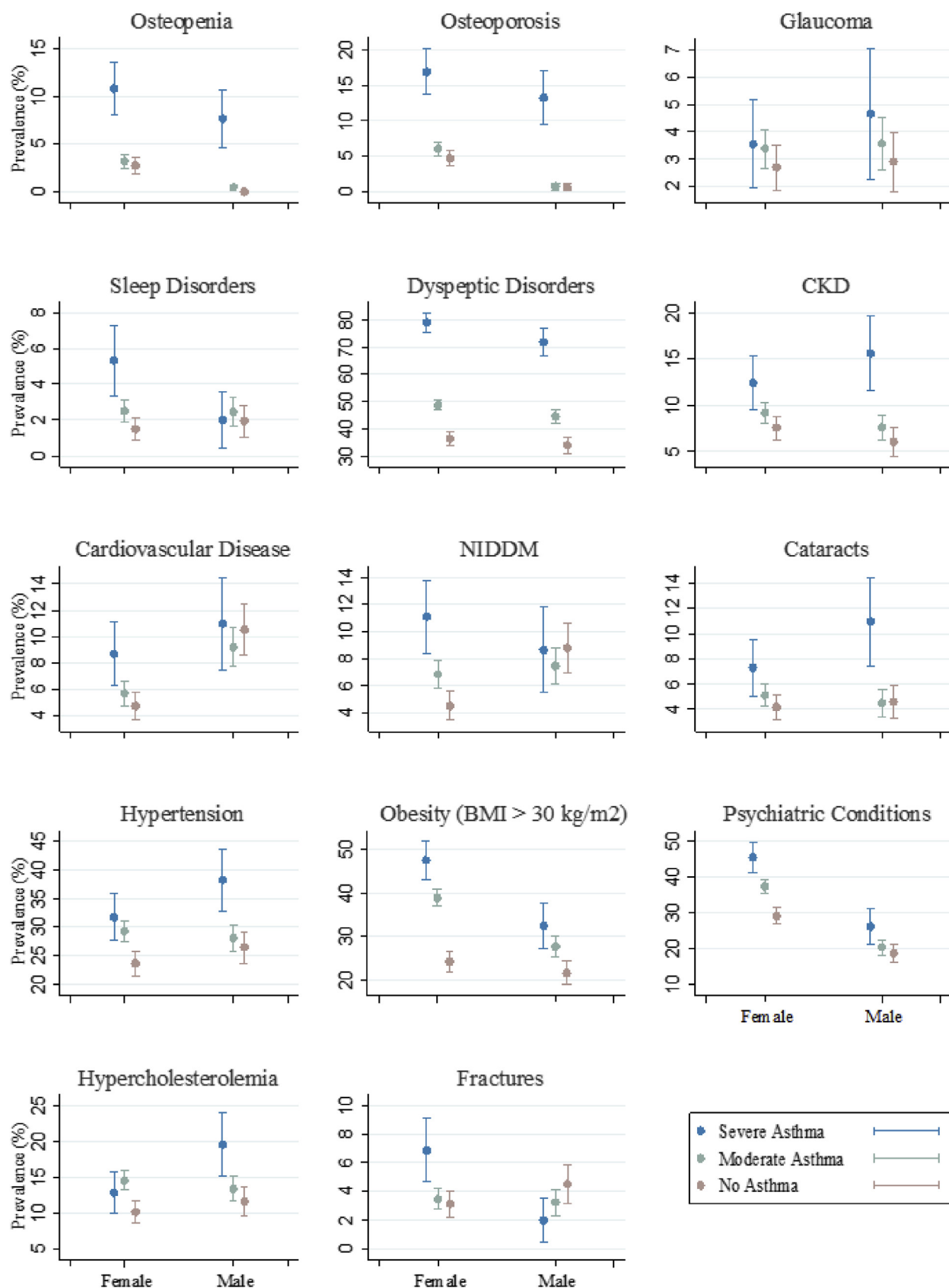


FIGURE 2. Sample prevalence with 95% CIs of corticosteroid-related comorbidities across cohorts partitioned by sex. Note that the y-axis varies according to comorbidity. *BMI*, body mass index.

TABLE III. Tests for the differences in odds ratios by age group and sex and by age group and sex interaction

Outcome	Number of age groups	Severe asthma vs mild/moderate asthma			Severe asthma vs nonasthma		
		<i>P</i> to compare age groups	<i>P</i> to compare sex	<i>P</i> to test age group × sex interaction	<i>P</i> to compare age groups	<i>P</i> to compare sex	<i>P</i> to test age group × sex interaction
NIDDM	4	.001	.25	.69	.002	.004	.062
Obesity	4	.02	.36	.41	<.001	.02	.13
Osteoporosis	3	<.001	<.001	—*	<.001	<.001	—*
Osteopenia	3	<.001	.002	—*	<.001	—*	—*
Hypertension	4	.01	.06	.26	.01	.67	.38
CKD	3	<.001	.14	.47	<.001	.04	.53
Dyspeptic disorders	4	.001	.2	.7	.007	.18	.07
Psychiatric conditions	4	.57	.87	.14	.12	.15	.37
Sleep disorder	4	.17	.04	.67	.009	.1	.91
Hypercholesterolemia	3/4†	.89	.003	.71	.14	.21	.71
Fractures	4	.61	.04	.99	.34	.003	.64
Cataracts	3	.04	.09	.78	.15	.46	.88
Cardiac disease	3	.03	.09	.4	.04	.03	.19
Glaucoma	3	.003	.24	.13	.003	.44	.05

Because of the multiple tests of significance, the 1% significance level ($P < .01$) was used. Significant results are boldfaced.

*“*P* to compare age groups” provides evidence of a difference in the effects of high corticosteroid dose (for asthma) between the 4 age groups: ≤ 45 , 46–60, 61–70, and > 70 y (or if 3 age groups, with the youngest 2 combined).

†“*P* to compare sex” provides evidence of a difference in the effects of high corticosteroid dose (for asthma) between men and women.

‡“*P* to test Age group × Sex interaction” provides evidence of different age effects in each sex (or vice versa).

*Very few men in both control groups had osteopenia or osteoporosis and so statistical comparison was not reliable.

†Three age groups were used for severe asthma vs nonasthma (rhinitis) because of lack of observations, but 4 age groups were used for severe asthma vs mild/moderate asthma.

fractures (Table III) for those with high OCS exposure relative to those with no OCS exposure ($P < .01$).

Across age groups, differences in odds ratios were found for NIDDM, osteoporosis, osteopenia, CKD, and dyspeptic disorders ($P < .01$) between those with high OCS exposure and those with low OCS exposure (Table III). In essence, when differences in odds ratios are evident across age groups it can be explained by significant differences in odds ratios being observed among younger age groups but not among older age groups. For those with high OCS exposure relative to those with no OCS exposure, age-related differences were noted for all the same conditions as well as obesity and sleep disorders (Table III).

The investigation of combined age group and sex interaction effects revealed no significant difference for any comorbidities (Table III), though there were not enough cases of osteopenia or osteoporosis in males, with low or no OCS exposure, with which to test these 2 comorbidities. This indicates that there does not seem to be a difference in the age group effects between sexes or in sex effects between age groups. Therefore, the difference in odds between OCS exposure groups can be described sufficiently using sex and age group effects separately without needing to consider combined age-sex effects.

Figure 3 compares the unadjusted mean annual clinical, medication, and total health care costs per person (with 95% CIs) by group and subgroup related to age group and sex. The patterns in costs reflect those seen in the prevalence of many comorbidities. Those with high OCS exposure have much greater mean annual costs per person across sexes. Although a difference in costs is evident across age groups, costs appear to converge among older age groups.

DISCUSSION

It is well recognized that corticosteroid exposure is associated with a range of comorbid conditions in severe asthma and this

study extends previous work^{14,19} by demonstrating differences in risk profiles between groups differentiated by age and sex. Younger subjects with severe asthma and high OCS exposure had greater odds of a number of recognized corticosteroid-induced morbidities (osteopenia, osteoporosis, glaucoma, dyspeptic disorders, CKD, cardiovascular disease, cataracts, hypertension, and obesity) compared with those with moderate asthma and low OCS exposure. Older subjects with severe asthma and high OCS exposure had a narrower comorbidity differential, with those older than 70 years having greater odds of only osteoporosis, osteopenia, and dyspeptic disorders ($P < .01$), compared with age-matched subjects with mild/moderate asthma and low OCS exposure.

The pattern of difference in the prevalence of many comorbidities—wider at younger ages and converging at older ages—could be interpreted as corticosteroid exposure “bringing forward” the expression of conditions that in subjects with lower or no corticosteroid exposure tend to present later in life. Thus, a “plateau effect” is seen for age-convergent conditions, which are known to increase with age; for example, it would appear that only a subgroup of patients with systemic corticosteroid exposure will develop diabetes, and earlier exposure “brings forward” this condition in predisposed individuals. Although this explanation seems plausible, further research is required to ensure it is not earlier identification of conditions in subjects with asthma with high systemic corticosteroid exposure or a direct causal comorbid condition effect of having severe asthma. The clear convergence at older ages argues against the likelihood of a detection bias as one would expect early identification to remain relatively constant across age groups.

Our data also demonstrate that many corticosteroid-induced comorbidities have differential sex prevalence. Women with high OCS exposure relative to those with low OCS exposure have greater odds of 9 comorbidities ($P < .01$): osteoporosis,

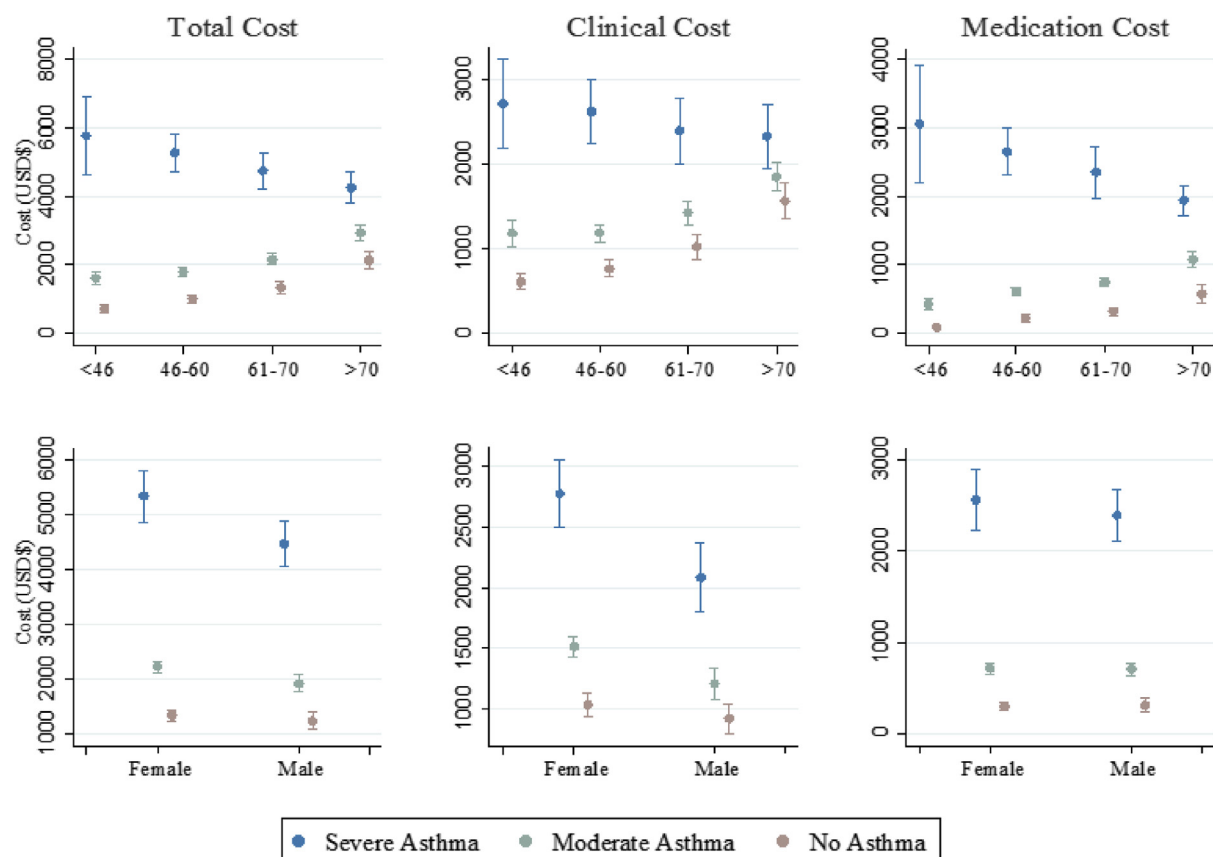


FIGURE 3. Mean annual total, clinical, and medication costs per person across cohorts partitioned by age group and sex separately with 95% CIs. Note that the y-axis varies according to cost group.

osteopenia, sleep disorders, cardiovascular disease, NIDDM, psychiatric conditions, fractures, dyspeptic disorders, and obesity (Table I). However, men have greater odds of 8 comorbidities ($P < .01$): CKD, osteoporosis, osteopenia, hypertension, psychiatric conditions, cataracts, dyspeptic disorders, and hypercholesterolemia (Table I). The sex difference is an important observation in severe asthma because the prevalence of severe asthma is higher among women.^{10,13,21,23,33} There is evidence in some circumstances of women being managed differently than men; for example, DEXA scans are recommended for postmenopausal women in the United Kingdom,³⁴ which may result in some underdiagnosis of osteoporosis or osteopenia in men who are not exposed to corticosteroids. However, we believe that the effects of corticosteroid exposure have been robustly demonstrated in women, which supports a similar pattern in men.

These findings have implications for the management of patients with severe asthma and, in particular, with regard to the use of more expensive corticosteroid-sparing therapies. The National Institute for Health and Care Excellence guidelines encourage the consideration of plausible biological and social mechanisms when evaluating new therapies.²⁶ Our data suggest that differences in the risk of corticosteroid-induced morbidity are evident across ages and between sexes and should help inform discussions with patients about the potential benefits from corticosteroid-sparing treatments. For example, a patient

older than 60 years, with little or no corticosteroid-induced morbidity, is likely to continue to do well with systemic corticosteroids to treat their asthma. In addition, we do not know whether corticosteroid-induced morbidity when established can be “reversed” when an effective corticosteroid-sparing treatment is introduced, which may suggest that these therapies should be introduced much earlier in younger patients, because they have greater odds of developing corticosteroid-induced morbidity after progressing to maintenance corticosteroids. Along with the elevated risk of corticosteroid-induced morbidity in younger patients, there is a parallel impact on the economic burden of the disease and cost-effectiveness of corticosteroid-sparing therapies. Corticosteroid-sparing therapies might therefore be more favorable for reimbursement at different ages because of the elevated risk from corticosteroid exposure for younger patients. Any extra cost for their provision at younger age groups might be justified in terms of reduced downstream comorbidities.

A limitation of this study is that it is cross-sectional in design and it was not possible to examine the impact of corticosteroid exposure over time on an individual’s comorbidity and health care costs. However, the morbidities we explored have been consistently identified in patients with severe asthma with increased systemic corticosteroid exposure.^{6,16} Similarly, it is difficult to determine whether the older patients are systematically different from the younger patients with severe asthma

within and across exposure status. However, Dalal et al¹⁹ have noted a significant dose-response association between systemic corticosteroid exposure and the accumulation of many systemic corticosteroid-related complications. In our study, matching of cohorts *a priori*, the consistency in the pattern of results with differences in prevalence and cost declining as groups differentiated by corticosteroid exposure age suggest a greater risk of the earlier onset of many comorbidities associated with corticosteroid exposure.

Another limitation of the study is that it is difficult to disentangle the cost associated with severe asthma from the cost associated with corticosteroid-induced comorbidity, although attempts to estimate this have been made elsewhere.^{17,18,20} The complication arises because severe refractory asthma is largely defined on the basis of treatment, specifically, corticosteroids.³⁵ However, the focus of this study was not necessarily to disentangle this effect but rather to investigate the age and sex associations within groups differentiated by corticosteroid exposure on comorbidity and economic burden.

Last, the use of retrospective administrative data also has limitations. Although the quality of administrative prescribing data in the United Kingdom improved after policy changes in 2004, many patients with asthma were in receipt of corticosteroids before this date, which complicates the identification of incident cases. Similarly, retrospective extraction of data on the basis of prespecified criteria did not allow us to identify when asthma status may have changed over the 2 years, with respect to patients with mild/moderate asthma especially. The absence of certain characteristics such as ethnicity or socioeconomic status restricts the potential for increased explanatory power; for example, Zeiger et al¹⁰ note that being nonwhite was associated with a significant likelihood of chronic OCS use in adults with persistent asthma in the United States. However, the authors believe that the criteria chosen for each year of observation provide reassurance as the consistency of the patients' asthma severity, and although additional data on patient characteristics would have been preferable, the authors feel that the objectives of this article have been sufficiently addressed with the data available.

CONCLUSIONS

This study has shown differential likelihood for multiple corticosteroid-induced comorbidities and health care costs by age and sex in well-matched subjects with different systemic corticosteroid exposure. Clinicians may need to consider the consequences of placing younger patients with severe asthma on OCSs. These results are also important for cost-effectiveness analysis of novel corticosteroid-sparing therapies that have larger implications for reimbursement decisions and health system sustainability. Considering age and sex effects may make these therapies more cost-effective for certain subgroups of the population.

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METHODS

Exclusion conditions for corticosteroid exposure

Patients were excluded if they had been diagnosed with any of the following diseases for which corticosteroids are used for treatment:

- Crohn disease;
- ulcerative colitis;
- autoimmune hepatitis;
- rheumatoid arthritis;
- polymyalgia rheumatica;
- chronic obstructive pulmonary disease;
- bronchiectasis;
- cystic fibrosis;
- interstitial pulmonary fibrosis; and
- tuberculosis.

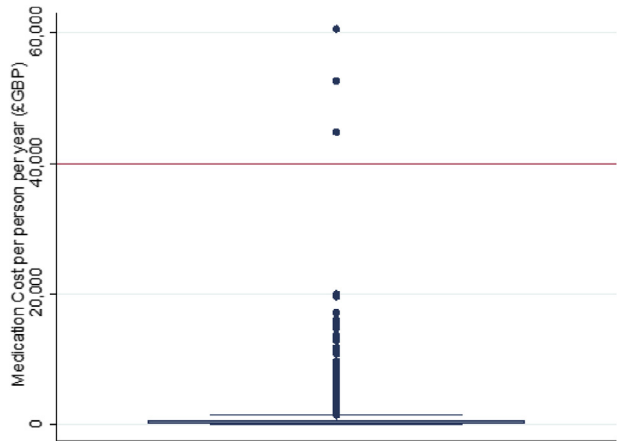


FIGURE E1. Boxplot of medication costs per patient per year to show outliers that merited further investigation. Red line denotes twice the value of the next highest medication cost (€40,000).

Outlier investigation

After the costing, it was noted that 3 patients exhibited cost data of more than twice that of the next largest medication cost (Figure E1). These 3 individuals were investigated further: 1 individual was removed because there were no prescription quantity data, and as such it may not have been reliable; 1 individual had a prescription deleted because the quantity was so large that it was deemed an input error; and 1 individual was kept because there was no obvious reason for exclusion and therefore costs could be plausible.

TABLE E1. Number of patients per cohort split by age group

Age group	Nonasthma	Moderate asthma	Severe asthma	Total
<46 y	171	855	552	1578
46-60 y	249	1245	739	2233
61-70 y	182	910	500	1592
>70 y	206	965	621	1792
Total	808	3975	2412	7195

TABLE E2. Baseline demographic characteristics and corticosteroid exposure across cohorts

Characteristic	All (N = 7195)	Nonasthma (no OCS exposure) (n = 2412)	Mild/moderate asthma (low OCS exposure) (n = 3975)	Severe asthma (high OCS exposure) (n = 808)
Sex: female, n (%)	4503 (63)	1481 (61)	2515 (63)	507 (63)
Age (y), mean $\pm$ SD	58 $\pm$ 17	58 $\pm$ 17	58 $\pm$ 16	59 $\pm$ 17
Geographical region, n (%)				
London	597 (8)	198 (8)	344 (9)	55 (7)
South of England	903 (13)	333 (14)	477 (12)	93 (12)
East of England	1064 (15)	333 (14)	616 (16)	115 (14)
Midlands	2146 (30)	685 (28)	1213 (31)	248 (31)
North of England	1648 (23)	581 (24)	874 (22)	193 (24)
Scotland/Northern Ireland/Wales/unknown	837 (12)	282 (12)	451 (11)	104 (13)
Inhaled corticosteroid dose in beclometasone dipropionate μ g equivalence, mean $\pm$ SD	—	—	499 $\pm$ 323 (n = 3898)	1411 $\pm$ 846 (n = 738)
OCS prescriptions per year, mean $\pm$ SD	—	—	1.2 $\pm$ 1.8 (n = 995)	11 $\pm$ 9 (n = 808)
Number of corticosteroid-related comorbidities, n (%)				
NIDDM	512 (7)	149 (6)	281 (7)	82 (10)
Obesity (body mass index >30 kg/m ²)	2285 (32)	561 (23)	1385 (35)	339 (42)
Osteopenia	204 (3)	41 (2)	85 (2)	78 (10)
Osteoporosis	362 (5)	74 (3)	162 (4)	126 (16)
Fractures	263 (4)	88 (4)	134 (3)	41 (5)
Dyspeptic disorders	3342 (46)	851 (35)	1874 (47)	617 (76)
Cataracts	370 (5)	105 (4)	195 (5)	70 (9)
Cardiovascular disease	522 (7)	168 (7)	277 (7)	77 (10)
Hypertension	2017 (28)	596 (25)	1145 (29)	276 (34)
Psychiatric conditions	2155 (30)	607 (25)	1238 (31)	310 (38)
Hypercholesterolemia	943 (13)	258 (10)	561 (14)	124 (15)
Sleep disorder	172 (2)	40 (2)	99 (3)	33 (4)
CKD	619 (9)	167 (7)	342 (9)	110 (14)
Glaucoma	236 (3)	67 (3)	137 (3)	32 (4)

TABLE E3. Odds ratios (95% CIs) for the risk of comorbidities of each age group and sex in the severe asthma (high OCS exposure) cohort relative to the nonasthma (no OCS exposure) cohort

Comorbidity	Sex		Age group				Total
	Male	Female	<46 y	46-60 y	61-70 y	>70 y	
NIDDM	1.0 (0.6-1.6)	2.8* (1.8-4.1)	4.4† (1.1-18)	4.0* (2.2-7.2)	1.7 (0.8-3.2)	0.9 (0.6-1.6)	1.8* (1.3-2.4)
Obesity	1.8* (1.3-2.4)	2.8* (2.2-3.5)	3.7* (2.4-5.6)	3.3* (2.4-4.6)	1.4‡ (1.0-2.1)	1.8* (1.3-2.6)	2.4* (2.0-2.9)
Osteoporosis§	49.2* (11.2-217.2)	4.7* (3.2-6.8)	28.7* (10.2-80.6)		8.7* (4.1-18.1)	3.4* (2.1-5.5)	6.5* (4.6-9.2)
Osteopenia§	¶	4.5* (2.8-7.3)	50.4* (12.1-211.2)		2.7† (1.2-6.3)	3.2* (1.5-6.6)	6.7* (4.3-10.4)
Hypertension	1.9* (1.4-2.6)	1.7* (1.3-2.2)	4.1* (1.9-8.9)	2.4* (1.6-3.4)	1.7* (1.2-2.5)	1.2 (0.9-1.7)	1.8* (1.4-2.1)
CKD§	3.9* (2.4-6.4)	1.9* (1.3-2.7)	7.7* (3.6-16.8)		3.2* (1.7-5.9)	1.4‡ (1.0-2.1)	2.4* (1.8-3.2)
Dyspeptic disorders	5.5* (4.0-7.6)	7.8* (5.9-10.3)	9.4* (5.8-15.2)	9.8* (6.5-14.7)	6.2* (3.9-9.8)	3.7* (2.5-5.5)	6.7* (5.5-8.3)
Psychiatric disorders	1.6* (1.2-2.2)	2.0* (1.6-2.6)	2.6* (1.8-3.9)	2.1* (1.6-2.9)	1.8* (1.2-2.5)	1.3 (0.9-2.0)	1.9* (1.6-2.3)
Sleep disorders	1.2 (0.4-3.4)	3.5* (1.6-6.7)	12.9† (1.6-102.8)	8.1* (2.1-30.3)	2.3 (0.7-7.5)	0.6 (0.2-1.8)	2.5* (1.5-4.1)
Hypercholesterolemia§	2.1* (1.4-3.1)	1.4‡ (1.0-1.9)	2.5* (1.5-4.2)		1.7† (1.1-2.8)	1.2 (0.8-1.8)	1.6* (1.3-2.1)
Cataracts§	2.9* (1.7-4.9)	2.3* (1.4-3.8)	4.2* (1.8-9.8)		4.6* (1.6-13.4)	2* (1.3-3.1)	2.4* (1.7-3.4)
Cardiovascular disease§	1.1 (0.7-1.7)	2.3* (1.5-3.5)	5.8* (2.3-14.6)		1.2 (0.6-2.5)	1.3 (0.9-2.0)	1.6* (1.1-2.2)
Fractures	0.4‡ (0.2-1.1)	2.5* (1.6-4.0)	0.4 (0.1-1.9)	2.0 (0.8-4.7)	1.3 (0.5-3.9)	1.8† (1.0-3.3)	1.6† (1.0-2.3)
Glaucoma§	1.5 (0.7-3.0)	1.4 (0.7-2.6)	23.5* (2.1-257.6)		2.8 (0.8-9.7)	0.7 (0.4-1.5)	1.4 (0.9-2.3)

*P < .01.

†P < .05.

‡P < .1.

§Age groups <45 y and 46-60 y were combined.

||Region was not controlled for in this regression; because the likelihood function in this instance was flat, it was not possible to produce model estimates.

¶Too few cases of comorbidity for analysis.