Age and gender relationships with systemic corticosteroid induced morbidity in asthma: A cross-sectional population-based study of computerised medical records

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Abstract

Background: Treatment of severe asthma may include high dose systemic-corticosteroid therapy which is associated with substantial additional morbidity. We examine the relationships between age, gender, comorbidity, and patterns of healthcare cost across groups differentiated by corticosteroid exposure.

Methods: Patients with severe asthma (n=808) were matched by age and gender with patients with mild/moderate asthma (n=3,975) and a non-asthma control cohort (n=2,412) from the Optimum Patient Care Research Database (OPCRD). Regression analysis was used to investigate the odds of a number of corticosteroid-induced comorbidities as it varied by cohort, age-group and gender. Prescribed drugs and publicly funded healthcare activity were monetised and annual costs per patient estimated.

Findings: Patients aged 60 years or less with high oral corticosteroid (OCS) exposure had greater odds of osteopenia, osteoporosis, glaucoma, dyspeptic disorders, chronic kidney disease, cardiovascular disease, cataracts, hypertension and obesity ($p < 0{\cdot}01$) relative both to those with mild/moderate asthma and low OCS exposure and to non-asthmatics. This difference in odds was much less evident in older patients. There was also evidence of gender-related differences for the odds of most comorbidities related to high dose OCS. This differential pattern of comorbidity prevalence was reflected in mean healthcare costs per patient per year.

Interpretation: These data demonstrate important differential prevalence of corticosteroid-induced morbidity by age and gender which is paralleled by differences in healthcare costs. This is important

for cost-effectiveness analysis of corticosteroid-sparing therapies as these therapies may exhibit different incremental cost-effectiveness ratios for specific subgroups, notably younger patients.

Introduction

Asthma is a condition affecting approximately 334 million people worldwide (1). It gives rise to a significant disease burden in terms both of morbidity and financial costs (2-4) to which severe asthma is known to contribute disproportionately (5). Oral corticosteroids (OCS) used in the treatment of asthma and other inflammatory conditions have been implicated in a range of morbidities and adverse events (6-8). Utilisation of these is known to increase with asthma severity, indeed severe refractory asthma is defined on the basis of the need for high dose corticosteroid exposure (9). As understanding of the relationship between corticosteroid exposure and comorbidity has increased, so too have efforts to incorporate the financial and morbidity effects of induced morbidity into assessments of overall economic burden (10-18). This is particularly relevant as novel biologic therapies that are corticosteroid-sparing become available.

The roles of age and gender are important in the natural history of many diseases. Patient cohorts with severe refractory asthma consistently have mean age over 50 years and a preponderance of females (19-21). Moreover, older patients with moderate asthma are also more likely to experience treatment failure with standard inhaled therapy relative to younger patients (22). While there is evidence for age-related differences in comorbidity between those with and without asthma (23) there is a paucity of data examining patterns of corticosteroid-induced morbidity and associated financial costs in patients with severe asthma differentiated by age and gender.

Establishing if distinct patterns of disease burden exist across groups differentiated by age and gender associated with corticosteroid exposure is important for clinicians planning care pathways and in assessing the cost-effectiveness of corticosteroid-sparing therapies. Indeed NICE guidelines for methods of technology appraisal recommend defining 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' (24).

In this paper we examine the relationships between age and gender and the prevalence of a range of comorbidities across cohorts of patients differentiated by their corticosteroid exposure. We extend this analysis to include aspects of the financial as well as morbidity burden associated with corticosteroid exposure and discuss possible policy implications.

Methods

Cohort Definition

The demographic details of the matched patient cohorts have been published before (12). In brief, patients with severe asthma (SA) (n = 808) requiring regular OCS (defined as Global Initiative for Asthma (GINA) step 5 treatment (16, 25) and ≥4 prescriptions for OCS in each of two consecutive study years) were matched by age, gender and year of birth (due to differing data extraction dates – data were extracted between 2008 and 2013) with patients with a diagnosis of mild/moderate asthma (asthma diagnosis, GINA step 2/3 (25); n = 3975) and a non-asthmatic control group, which all 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 (11). Subjects were required to be over 12 years of age 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 one year.

Patients were included in the non-asthmatic control group if they had a rhinitis diagnosis with no asthma diagnosis/asthma drug prescription and no exposure to OCS as evidenced by the patterns of

service use and prescribed medicines in 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 supplement for list of conditions). Thus the mild/moderate asthma group had inhaled corticosteroid (ICS) exposure and some OCS exposure. Comparing the severe and moderate/mild asthma groups permitted study of the effects of OCS exposure controlling for any effects of asthma that were not specific to OCS use. The data included details of all publicly funded healthcare consultations, including primary and secondary care as well as details of prescribed therapies/drugs. Additional details of cohort definition have been well documented in previous research using this data (12).

Morbidity Status

The data from the OPCRD contains information on patients' healthcare activity, documented through Read codes (26), which are the clinical classification system currently used in primary care in the UK. A list of morbidities was identified in previous research using this data as having a greater prevalence in the high OCS exposure relative to the low and no OCS exposure groups and as being associated, in the literature, with OCS exposure (12). The NHS Read code browser was used to identify Version 2 Read codes relating to these morbidities and these were subsequently used to identify morbidity status of individuals within the sample.

Costing

OPCRD contained information on patients' healthcare activity through Read codes and also patients' prescriptions, documented using British National Formulary (BNF) codes (27) and product descriptions. This information was used to assign unit costs for healthcare activities, e.g. a general practice visit or outpatient visit, using the Personal Social Services Research Unit unit cost data 2013 (28). BNF codes and product descriptions were used to assign drug costs using the Northern Ireland Prescription Cost Analysis 2013 (29). Costs were aggregated for the individual to calculate the annual costs per person. Upon investigation of outliers, one individual from the non-asthma cohort was removed from the economic analysis because they had no information on prescription quantities (see supplement). Full details of this costing procedure have been published previously (18).

Statistical Analysis

Cross-tabulations were used to explore relationships between corticosteroid exposure, morbidity, age and gender. Graphs were used to display the prevalence of various morbidities by corticosteroid-exposed group differentiated by age-group and gender along with 95% confidence intervals (CI) for each. Conditional logistic regression analysis was used to explore the effects of corticosteroid exposure on comorbidity in groups partitioned by age-group and gender whilst taking account of the matching and adjusting for region. Odds ratios (with 95% CI's) were calculated between severe asthma and mild/moderate patients and separately between severe asthma and non-asthma patients in samples partitioned first by age and then by gender.

Where the analysis above concerns differences in morbidity between OCS exposure groups within each age-group and within each gender, conditional logistic regressions were also fitted on the pooled sample to examine differences across age-groups and across gender. Age-group effects, that is differences in the odds of a comorbidity between OCS exposure groups across age-groups, and corresponding gender effects are presented below. Further age-group by gender interactions were included to test for age-group effects within each gender or gender effects within each age-group. Where the number of individuals was too small within an age-group to allow comparative analysis, younger age-groups were combined (table 1 and supplement table 3).

Graphs for mean annual healthcare costs (total, clinical activity only, medication only based on two year costs divided by two) per person (with 95% CI's) partitioned by exposure group and within group by age and gender were used to demonstrate differences in costs related to cohort, age and gender. Age analysis was based on an approximate quartile split of the sample: less than 46 years, 46-60 years,

61-70 years or older than 70 years (supplement: table 2). Analyses were performed using Stata release 14 (StataCorp, College Station, TX).

Role of funding source

The study dataset was supported by the Respiratory Effectiveness Group through their academic partnership with Optimum Patient Care. Ciaran O'Neill was funded under a HRB Research Leader Award (RL/13/16).

Results

Demographic details of the patient cohorts can be found in previous publications using this data (12, 18) or also in summary in table 1 in the supplement. In short, the group without OCS exposure (non-asthma), with low exposure (mild/moderate asthma) and high OCS exposure (severe asthma) had 61% (1481/2412), 63% (2515/3975) and 63% (507/808) females and a mean age of 58 years (95% CI: 25-91), 58 years (CI: 26-90) and 59 years (CI: 26-91) respectively. Figure one shows the prevalence of the various comorbidities partitioned by age-group. Figure two provides a breakdown of the prevalence of these comorbidities by gender. These highlight varying patterns of morbidity prevalence between corticosteroid exposure groups across age-groups and genders.

[Figure 1]

[Figure 2]

When partitioning the cohorts by gender, males with high OCS exposure relative to those with low exposure (mild/moderate asthma) (table 1) had greater odds of chronic kidney disease (CKD), osteoporosis, osteopenia, hypertension, psychiatric conditions, cataracts, dyspeptic disorders and hypercholesterolemia ($p < 0{\cdot}01$). Females with high OCS exposure relative to those with low exposure (supplement: table 3) had greater odds of osteoporosis, osteopenia, fractures, sleep disorders, psychiatric conditions, cardiovascular disease, non-insulin dependent diabetes mellitus (NIDDM), obesity (body mass index (BMI) > 30kg/m^2) and dyspeptic disorders ($p < 0{\cdot}01$). Gender differences between those with high OCS exposure and no OCS exposure can be found in table 3 in the supplement but in summary males, in addition to those conditions mentioned above, had greater odds of obesity ($p < 0{\cdot}01$), and females of cataracts, hypertension and CKD ($p < 0{\cdot}01$). There were not enough cases of osteopenia in males without OCS exposure to determine the odds for this group compared to males with high OCS exposure.

When partitioning the sample by age, for some comorbidities e.g. osteoporosis, in the youngest age-group (≤45 years) there were not enough cases of comorbidity with which to conduct the analysis and in those cases the younger age-groups were combined. Across these 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 ($p < 0{\cdot}01$) and NIDDM and psychiatric disorders ($p < 0{\cdot}05$) for the high OCS exposure relative to the low OCS exposure group (table 1). Those aged 61-70 had greater odds of CKD, dyspeptic disorders and osteoporosis ($p < 0{\cdot}01$); osteopenia and psychiatric conditions were significant at $p < 0{\cdot}05$. Those aged over 70 with high OCS exposure relative to low exposure had greater odds of osteoporosis, osteopenia and dyspeptic disorders ($p < 0{\cdot}01$); cataracts and fractures were significant at $p < 0{\cdot}05$.

Age-related differences between those with high OCS exposure and no OCS exposure can be found in table 3 in the supplement. In summary the younger age-groups (≤45 years and 46-60 years), in addition to those described above, showed greater odds of hypercholesterolemia ($p < 0{\cdot}01$) and sleep disorders ($p < 0{\cdot}05$) while psychiatric conditions became slightly less significant ($p < 0{\cdot}05$). Those aged 61-70 had additional odds of cataracts, hypertension and psychiatric conditions ($p < 0{\cdot}01$), and hypercholesterolemia ($p < 0{\cdot}05$), while those aged over 70 had greater odds of obesity and cataracts ($p < 0{\cdot}01$).

Table 1: Odd's ratios (95% confidence interval) for the risk of comorbidities of each age group and gender in the severe asthma (high OCS exposure) cohort relative to the mild/moderate asthma (low OCS exposure) cohort.

Severe asthma (high OCS exposure) cohort relative to the mild/moderate asthma (low OCS exposure) cohort							
	Sex		Age Group				Total
	Male	Female	<46	46-60	61-70	>70	
NIDDM	1·1 (0·7-1·7)	1·7*** (1·3-2·4)	4·7** (1·5-15·1)	3·0*** (1·9-4·9)	1·2 (0·7-2)	0·8 (0·5-1·3)	1·5*** (1·1-1·9)
Obesity	1·2 (0·9-1·6)	1·4*** (1·2-1·8)	2·0*** (1·4-2·8)	1·6*** (1·2-2·1)	1 (0·7-1·4)	1 (0·7-1·4)	1·4*** (1·2-1·6)
Osteoporosis†	42·1*** (14·3-123·9)	3·6*** (2·7-4·9)	13·9*** (7·4-26·1)		6·9*** (4-11·9)	2·8*** (1·9-4·3)	5·2*** (4-6·9)
Osteopenia†	22·5***θ (8·5-59·1)	3·9*** (2·7-5·7)	11·8*** (6·7-20·5)		2·2** (1·1-4·2)	3·6*** (1·8-7)	5·3*** (3·8-7·4)
Hypertension	1·7*** (1·3-2·3)	1·2 (0·9-1·5)	2·4*** (1·3-4·4)	1·7*** (1·2-2·3)	1·3 (0·9-1·8)	1 (0·7-1·3)	1·4*** (1·1-1·6)
Chronic Kidney Disease†	2·5*** (1·6-3·7)	1·5** (1·1-2·1)	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	3·4*** (2·6-4·6)	4·4*** (3·5-5·7)	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	1·5*** (1·1-2)	1·4*** (1·2-1·7)	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	0·9 (0·4-2·3)	2·2*** (1·4-3·5)	2·6* (0·9-7·4)	2·6*** (1·3-5)	1·4 (0·5-3·8)	1 (0·4-2·7)	1·7*** (1·2-2·6)
Hypercholesterolemia	1·8*** (1·3-2·6)	0·9 (0·6-1·1)	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)
Cataract†	2·8*** (1·7-4·4)	1·5* (1-2·2)	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†	1·1 (0·7-1·6)	1·7*** (1·1-2·4)	2·9*** (1·5-5·5)		1·2 (0·7-2·2)	1·1 (0·8-1·7)	1·4** (1-1·8)
Fractures	0·6 (0·3-1·5)	2·1*** (1·3-3·1)	0·4 (0·1-1·9)	1·6 (0·8-3·4)	2·1* (0·9-4·7)	2** (1·1-3·5)	1·5** (1·1-2·2)
Glaucoma†	1·3 (0·7 - 2·4)	1·1 (0·6-1·8)	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<0·1, ** P<0·05, *** P<0·01

†Age groups '<46 y' and '46-60 y' were combined

θ Region not controlled for in this regression due to a lack of convergence

Differences in odds ratios across gender were found for osteopenia, osteoporosis and hypercholesterolemia for those with high OCS exposure relative to low exposure ($p < 0{\cdot}01$). Thus for these conditions there is a different pattern of corticosteroid-induced morbidity between males and females, specifically that males are at greater risk (supplement: table 4). There are differences in odds across gender for NIDDM, osteoporosis and fractures (supplement: table 4) for those with high OCS exposure relative to no OCS exposure ($p < 0{\cdot}01$).

Across age-groups, differences in odds ratios were found for NIDDM, osteoporosis, osteopenia, CKD and dyspeptic disorders ($p < 0{\cdot}01$) between those with high OCS exposure and those with low exposure (supplement: table 4). In essence where differences in odds ratios are evident across age-groups it can be explained by significant differences in odd's ratios being observed among younger age-groups but not among older age-groups. For those with high OCS exposure relative to no exposure, age-related differences were noted for all of the same conditions as well as obesity and sleep disorders (supplement: table 4).

The investigation of combined age-group and gender interaction effects revealed no significant difference for any comorbidities (supplement: table 4), though there were not enough cases of

osteopenia or osteoporosis in males with low or no OCS exposure with which to test these two comorbidities. This indicates that there does not seem to be a difference in the age-group effects between genders or in the gender effects between age-groups. Therefore the differences in odds between OCS exposure groups can be described sufficiently using gender and age-group effects separately without needing to consider combined age-gender effects.

[Figure 3]

Figure 3 compares the unadjusted mean annual clinical, medication and total healthcare costs per person (with 95% CI's) by group and sub-group related to age-group and gender. The pattern 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 gender. While a difference in costs is evident across age-groups, costs appear to converge among older age-groups.

Discussion

This study provides compelling evidence that corticosteroid exposure is associated with a range of comorbid conditions in severe asthma and extends previous work (12, 17) by demonstrating differences in risk profiles between groups differentiated by age and gender. Younger subjects had a broader range of comorbid difference; those with high OCS exposure had greater odds of a number of recognised corticosteroid-induced morbidities (osteopenia, osteoporosis, glaucoma, dyspeptic disorders, CKD, cardiovascular disease, cataracts, hypertension and obesity; $p < 0{\cdot}01$) compared to those with low corticosteroid exposure. Older subjects had a narrower range of comorbid difference; those aged over 70 years with high corticosteroid exposure only had greater odds of osteoporosis, osteopenia, dyspeptic disorders ($p < 0{\cdot}01$) compared to age-matched asthmatic subjects with less corticosteroids exposure.

The pattern of difference in disease prevalence – 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 declare themselves later in life. While this explanation seems likely to be due to the effects of earlier corticosteroid exposure, further research is required to ensure it is not earlier identification of conditions within asthmatic subjects with high exposure due to resultant medical care or a direct causal comorbid condition effect of having severe asthma, although the clear convergence at older ages argues against the likelihood of a detection bias.

In addition, differences with respect to gender suggest that earlier identification of comorbid conditions in severe asthmatic subjects is unlikely as it is unclear why the service would manage women differently from men. Our data demonstrates that many corticosteroid-induced morbidities have differential gender prevalence. Women with high OCS exposure relative to those with low exposure have greater odds of nine comorbidities (osteoporosis, osteopenia, sleep disorders, cardiovascular disease, NIDDM, psychiatric conditions, fractures, dyspeptic disorders and obesity; $p < 0{\cdot}01$) while men only have greater odds of eight comorbidities (CKD, osteoporosis, osteopenia, hypertension, psychiatric conditions, cataracts, dyspeptic disorders and hypercholesterolemia; $p < 0{\cdot}01$). This again is an important observation in severe asthma as a majority of females are consistently seen in severe asthma cohorts (11, 19, 21, 30).

Interestingly though we can only confirm a statistically significant difference between gender-specific odds for osteopenia, osteoporosis and hypertension, whereby males with high OCS exposure are at a higher risk relative to females with high OCS exposure as well as males and females with low OCS exposure. This provides reassurance as to the results provided here because these conditions are also associated with the onset of menopause. So if there was a corticosteroid-inducing effect we would expect to see a stronger signal in males in our sample than in females; in essence females may be likely to develop these conditions regardless of corticosteroid exposure.

These findings have potentially significant implications for the management of patients with severe asthma and in particular with regard to the use of expensive corticosteroid-sparing therapies among

such patients. NICE guidelines encourage the consideration of plausible biological and social mechanisms when investigating the cost-effectiveness of new therapies (24). The data presented in this paper suggest that differences in the risk of corticosteroid-induced morbidity are evident with respect to age and gender. Differences in the incremental cost-effectiveness ratio (ICER) of corticosteroid-sparing therapies are likely to mirror the differences in odds demonstrated here. Thus, while systemic corticosteroids may provide an effective way to treat severe asthma in older patients who have a lower risk of suffering many of the adverse effects, for younger patients their use is accompanied with an elevated risk of induced comorbidity that will impact the economic burden of the disease and cost-effectiveness of corticosteroid-sparing therapies. The difference in ICERs may be such that younger persons are afforded access to corticosteroid-sparing therapies while those who are older are not. While this remains to be demonstrated definitively it does raise possible issues of ageism. Given the distribution of healthcare expenditures across age groups, that any savings related to the rational use of corticosteroid-sparing therapies would likely be disproportionately spent on services used by older persons should perhaps allay concerns in this regard.

While prevalence of certain comorbidities is higher amongst the severe asthma cohort, the mechanism or cause of the effect is unclear. However, a number of studies have suggested potential mechanisms between corticosteroids, asthma and comorbidity (6, 14) and the morbidities we have shown have been consistently related to corticosteroid exposure. Factors such as family history of diabetes, hypertension, higher mean dose of prednisolone, high BMI and cumulative dose increased the likelihood of corticosteroid-induced diabetes (31). It was also found that obese patients with early onset asthma relative to obese patients with late-onset asthma had much greater risk of corticosteroid exposure and reported more problems with airway obstruction and bronchial hyperresponsiveness (32).

A limitation with this study is that it is cross-sectional in design and it is not possible to examine the impact of corticosteroid exposure over time on individual's morbidity and healthcare cost profile. It is difficult to determine whether the older patients are fundamentally different from the younger patients with severe asthma within and across cohorts. However Dalal *et al* (2016) have noted significant dose-response relationship between systemic corticosteroid exposure and the accumulation of many systemic corticosteroid-related complications (17). In this paper, 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 corticosteroid-related comorbidities with implications for the economic burden of OCS.

A further 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, though attempts to estimate this have been made elsewhere (15, 16, 18). It is complicated in this patient group because severe refractory asthma is largely defined on the basis of treatment requirements and specifically corticosteroids (33). However, we believe this is not relevant as the focus of this paper was not necessarily to disentangle this effect and rather to investigate the age and gender relationships within groups differentiated by corticosteroid exposure on morbidity and financial burdens.

In summary, we have shown differential odds ratios for multiple corticosteroid-induced morbidities and healthcare costs by age and gender in well-matched subjects with different systemic corticosteroid exposure. This data is important for cost-effectiveness analysis of novel corticosteroid-sparing therapies as considering age and gender effects may make these therapies more cost-effective at a certain threshold, for certain subgroups of the population. Clinicians may also need to consider the consequences of placing younger patients with severe asthma on OCS.

Ethics approval and consent to participate: OPCRD has been reviewed and ethically approved by the NHS Health Research Authority to hold and process anonymised data as part of our service delivery

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

Consent for publication: Not applicable

Availability of data and materials: Please contact author for data requests.

Declaration of Interest: No conflicting interests

Authors Contributions: LB, LH, CON, CP and JS designed the research. DP provided the data along with data support. LB, LH, CON, CP and JS formatted and analysed the data. All authors provided comment for the manuscript.

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