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To cite this article: Khalid Al Efraij, Kate M. Johnson, Darrin Wiebe, Mohsen Sadatsafavi & J. Mark FitzGerald (2018): A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma, Journal of Asthma, DOI: [10.1080/02770903.2018.1539100](https://doi.org/10.1080/02770903.2018.1539100)

To link to this article: <https://doi.org/10.1080/02770903.2018.1539100>

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 Published online: 04 Dec 2018.

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A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma

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ABSTRACT

Background: Oral corticosteroids (OCSs) are often used to achieve asthma control. OCS-related comorbidities increase the burden of disease for patients and healthcare providers. Most studies characterizing OCS use and risk of adverse events (AEs) are in non-asthma patients. We sought to systematically review the literature on the burden of OCS use among adults with asthma. **Methods:** We systematically reviewed the literature including MEDLINE (1946–May 2017), EMBASE (1974–May 2017), and the Cochrane Library (2005–May 2017) to identify studies that considered AEs due to OCS treatment of adults with asthma, their burden on healthcare utilization, and costs. **Results:** We retrieved 9,589 citations; and 15 studies were included. AEs were significantly higher among OCS-users compared with non-OCS users with pooled adjusted odds ratio (OR) 1.68 (95% CI 1.15–2.46) for diabetes mellitus and 1.34 (95% CI 1.23–1.46) for hypertension. Among high dose OCS-users (>10 mg) compared with non-OCS users, the pooled adjusted ORs for development of any complication was 3.35 (95% CI 2.94–3.82), and bone and muscle complications 2.30 (95% CI 2.18–2.42). The risk of any complication increased with higher doses of OCS, with pooled adjusted OR from 2 studies of 2.26 (95% CI 1.37–3.72), 2.94 (95% CI 2.62–3.29) and 3.35 (95% CI 2.94–3.82) for low dose (<6 mg), medium dose (5–12 mg) and high dose (>10 mg) respectively compared with no OCS use. **Conclusions:** The use of OCS in the management of asthma is associated with a higher risk of complications. This risk is higher as the OCS dose increases.

ARTICLE HISTORY

Received 20 June 2018
Revised 16 October 2018
Accepted 18 October 2018

KEYWORDS

Asthma; oral corticosteroids; adverse events; morbidity; burden; economy

Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is associated with a significant burden on patients and society, affecting 1–18% of the population in different countries. Characterized by chronic symptoms and intermittent flare-ups, asthma as an entity can be life threatening in the context of acute exacerbations, this risk being predicted partially by disease control [1]. Approximately, 5–10% of patients with asthma remain uncontrolled despite use of high doses of inhaled corticosteroids and other controller medications [2]. Oral corticosteroids (OCSs) are used as both acute (management of exacerbations) and chronic (maintenance add-on) therapy, due to their potent anti-inflammatory and immunosuppressive effects [1,3]. In the context of acute asthma exacerbations, there is an extensive body of evidence showing the benefits of

such an intervention but of note there is an emerging body of evidence that at least in adults, quadrupling the dose of ICS can be used to prevent an asthma exacerbation and therefore avoid some of the systemic side effects of a course of OCS [4]. With regard to chronic OCS use for more severe asthma, there is a much less impressive body of evidence supporting efficacy but also a lack of data on the impact on patients specifically with asthma. Studies of different chronic diseases show that long-term exposure to OCSs is associated with a wide range of increased risk of adverse events (AEs) including osteoporosis, hypertension, diabetes, and metabolic syndrome, dyslipidemia, obesity, cataracts, glaucoma, gastrointestinal bleeds/ulcers, tuberculosis, depression, and infections [5–7]. A systematic review of such studies (across different diseases) showed that they increase the risk of gastrointestinal bleeding or perforation by over 40% (OR 1.43, 95% CI 1.22 to 1.66) [8]. In addition another systematic review showed that corticosteroids

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use in rheumatoid arthritis is associated with increased risk of all-cause cardiovascular events (RR, 1.47; 95% CI 1.34–1.60; $p < 0.001$) [9]. OCS-related comorbidities increase the burden of disease for patients and the healthcare system and their use is associated with lower patient quality of life and increased healthcare resource utilization and costs for both patients and the healthcare system [6,10–13].

Most of the studies characterizing OCS use and the risk of AEs relate to conditions other than asthma [5]. Differences in the dosage and duration of use, and possible interaction with the disease mechanisms, may confound the pattern of OCS-induced AEs across diseases. To inform our understanding of the relationship between OCS use in asthma and the risk of AEs, we sought to identify, summarize and quantify existing evidence around the burden of OCS in asthma, including (1) the pooled risk estimate of OCS AEs among users compared with non-OCS users and the dose–response relationship, and (2) the healthcare utilization burden (i.e. ER visits, hospitalizations), and (3) healthcare costs of OCS-related complications in asthma. These findings are particularly important given the emergence of new biologics which have been associated with an ability to reduce the dose of OCS and decrease the number of exacerbations requiring OCS, especially in severe eosinophilic asthma [14,15]. In documenting the benefits of these newer interventions, it is important to also ensure clinicians (and patients) are familiar with the significant risks associated with OCS. The knowledge translation required for this to be successful is challenging in that many patients do not accurately recall taking a course of OCS and from a provider's perspective these medications maybe prescribed in multiple different settings ranging from a regular primary care physician, to a clinician seen in an urgent care or Emergency Department setting. As a prerequisite for this to be successful, it is important that we accurately characterize the risks associated with OCS, especially in the context of asthma. To the best of our knowledge, this is the first systematic review of this topic with particular focus on patients with asthma as opposed to other chronic diseases.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this report [16].

Objectives

The primary outcome of this review is to estimate the risk of different complications related to the use of

OCS in the treatment of asthma acutely or as an add-on to the chronic maintenance therapy. Secondary outcome includes stratification of the risk according to the administered dose of OCS and dose–response effect as well as estimation of the risk for healthcare utilization and costs related to OCS-related complications.

Search strategy and selection criteria

We searched databases including MEDLINE (1946–May 2017), EMBASE (1974–May 2017) and Cochrane Library (2005–May 2017). We simultaneously searched asthma, the commonly used corticosteroids (i.e. prednisone, prednisolone, methylprednisolone, betamethasone and dexamethasone), and adverse events common to corticosteroids (such as myocardial infarction, hypertension, diabetes, adrenal insufficiency, osteoporosis, wound healing, and cataract). Then, we looked for intersection when corticosteroids and their adverse effects were combined. We also included healthcare utilization terms including hospitalization, emergency and healthcare cost and economics (Supplementary material, Figure S1). The reference lists from eligible articles were also searched. The identified articles underwent title and abstract screening followed by full-text screening to determine eligibility. Studies of outcomes of patients with asthma treated with OCS were compared with non-oral corticosteroid-dependent asthma patients with regard to occurrence of AE, their related healthcare utilization and cost. We included studies that measured the occurrence of AEs among groups of patients administered OCS and a comparison group with no OCS therapy. We assessed the impact of OCS dose wherever possible. We also extracted data on the age, gender, healthcare utilization and costs in the OCS and control groups. We excluded studies that only assessed inhaled corticosteroids or corticosteroids administered parenterally, were conducted in a population with pediatric patients or COPD patients, or assessed risk factors instead of final outcomes. We excluded studies that were not published in the English language. Commentaries, letters, descriptive narratives and unpublished conference abstracts were also excluded. Cross sectional and longitudinal (case-control or cohort) studies were eligible for inclusion. Ethics approval was not required for this meta-analysis.

Data extraction strategy

Two independent reviewers (KA, DW) extracted data using a standardized extraction form. This form included study design, duration, country of study,

source of funding, frequency of reported AEs, and healthcare utilizations parameters and cost values. The outcomes were separately collected for each of the three objectives; (1) the pooled risk estimate of OCS AEs among users compared with non-OCS users and the dose–response relationship, and (2) the healthcare utilization burden (i.e. ER visits, hospitalizations), and (3) healthcare costs of OCS-related complications in asthma. Differences were resolved by discussion between the reviewers. There was no need to contact the authors for clarification of any of the eligible articles.

We extracted data on the number of AEs in the OCS and control groups (as well as follow-up time) in order to calculate an unadjusted OR. We extracted adjusted odds ratios (ORs), incidence rate ratios (IRRs), hazard ratios (HRs) and their confidence intervals for studies that used regression modeling to assess the independent impact of OCS on AEs.

Assessment of methodological quality

Study quality was assessed using two standardized tools: the Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies with a maximum score of 9, and the cross-sectional quality assessment developed by Prins et al. with a maximum score of 15 [17,18]. We included all relevant studies regardless of their quality.

Statistical analysis

We used the extracted data to generate pooled unadjusted or adjusted ORs and standard errors for the association between OCS and AEs. Due to the rare occurrence of AEs, ORs, IRRs, and HRs were considered to be equivalent and pooled together in the meta-analysis. ORs for unadjusted analyses were based on contingency tables, and ORs for the adjusted analyses were based on regression models (typically from case-control or cross-sectional studies) in which the effect of OCS on the odds of the adverse event occurring was assessed independently of the covariates in the model. We stratified the associations by OCS dose when reported. We pooled the individual study estimates using the inverse variance method implemented with the ‘meta’ package in R Statistical Software [2] (version 3.3.3) [19,20]. Fixed-effects models were used when only two studies were being pooled or if the null hypothesis that all studies evaluated the same effect was not rejected using Cochran’s Q statistic [21]. Random effects models

were used in all other cases. We did not consider study design when pooling studies that reported similar outcomes and used the same metric (unadjusted or adjusted OR) due to the low number of studies for each outcome. We quantified heterogeneity between studies using the I^2 statistic [22]. We did not pool cost data, as it is heavily affected by contextual variables such as healthcare behavior and health system performance.

Results

In total 9589 citations were identified through database searching, and 15 studies were included in the final set of eligible articles after removing duplicates, article not addressing the search questions, reviews, editorials, pediatric population, or animal studies. (PRISMA flowchart, Figure 1). Of the 15 studies, 11 (73.3%) had a cohort design [10,12,13,23–29], 2 (13.3%) were cross-sectional studies [30,31], and 2 (13.3%) were case-control studies [32,33]. Nine studies were performed in the USA, five in the UK, and one in South Africa. Summary characteristics of the studies and the number of patients are shown in Table 1 and in the supplementary material, Table S1. We included older studies as the complications of oral steroids in asthma patients have been poorly documented and the literature is limited.

Adverse events of OCS among asthma patients using OCS compared with non-OCS control subjects

Combining unadjusted odds ratio (OR) of AEs among OCS-users compared with non-OCS users from studies, there was an increased risk of peptic ulcer 2.86 (95% CI 1.39–5.90), hypertension 1.28 (95% CI 1.20–1.36) and diabetes mellitus 1.30 (95% CI 1.02–1.64) as well as cataracts 1.49 (95% CI 1.29–1.72), infections 1.68 (95% CI 1.51–1.87), and fractures 1.46 (95% CI 1.25–1.70) while the risk of osteoporosis and glaucoma was not significantly different. The risk of other pooled complications is provided in Figure 2.

Adjusted or of adverse events among all OCS-users compared with non-OCS users

The pooled adjusted OR from two studies, that used regression modeling, for the risk of developing hypertension was 1.34 (95% CI 1.23–1.46), diabetes mellitus 1.68 (95% CI 1.15–2.46), obesity 1.32 (95% CI

Table 1. Characteristics of included studies.

Author, year, reference	Study type	Country	Study period	Mean ^s /Median ^d age of Subject [Control]	Subjects number (Females)/ Included subjects	Control number (Females)/ Included subjects	Adjusted/Unadjusted	Study Quality [*]
Barry, 2017 [26]	Cohort	UK	2-year follow-up	59 ± 17 ^s [58 ± 16]	808 (507) Regular OCS and ≥ 4 OCS pre- scription/ year	3975 (2515) Mild/moderate asthma	Unadjusted	7
Broder, 2017 [27]	Cohort	USA	1-year follow-up	56.8 ^s [54.6]	517 (NA) OCS ≥ 30 days or ≥ 6 bursts	2838 (NA) OCS ≤ 30 days or ≤ 1 burst	Adjusted to usage of OCS	4
Cowie, 1987 [21]	Cohort	South Africa	Follow-up: 48.6 +/- 27.6 for cases 30.7 +/- 24.1 for control	37.3 ± 9.4 ^d [36.3 ± 9.5]	52 (0) Maintenance OCS	151 (0) No maintenance OCS	Unadjusted	5
Dalal, 2016 [10]	Cohort	USA	2003–2014	62.4 ± 15.2 ^d [62.6 ± 15.1]	12679 (7471) ≥ 6 months of continuous OCS	12679 (7465) Never exposed to OCS	Adjusted to baseline characteristics gender, age, region, total health-care costs, and whether the patient had ≥ 1 emergency room or inpatient visit at baseline) and time-dependent variables (quarter, Charlson Comorbidity Index, and cost of concomitant medications), and the occurrence of the SCS-related condition of interest at baseline and for the year of index date.	7
Daugherty, 2017 [22]	Cohort	UK	2004–2012	54.8 ± 17.6 ^s [51.5 ± 18.7]	35424 (22861) Cumulative OCS exposure	24994 (14476) No OCS exposure	Adjusted age, gender and other variable depending on category of complication	6
Lefebvre, 2017 [11]	Cohort	USA	1997–2013	57.6 ± 16.3 ^s [27.4 ± 17.7]	3628 (2478) ≥ 6 months of continuous OCS	27987 (16183) Never exposed to OCS	Adjusted to baseline characteristics gender, age, region, total health-care costs, and whether the patient had ≥ 1 emergency room or inpatient visit at baseline) and time-dependent variables (quarter, Charlson Comorbidity Index, and cost of concomitant medications), and the occurrence of the SCS-related condition of interest at baseline and for the year of index date.	5
Lefebvre, 2015 [7]	Cohort	USA	1997–2013	57.6 ± 16.3 ^s	3628 (2478)	NA	Adjusted to baseline characteristics gender, age, region, total health-care costs, and whether the	6

Lieberman, 1972 [30]	Case-control	USA	3 months follow-up	44.8 (15–77) [§] [45.6 (16–76)]	50 (36) Continuous OCS 3011 ± 593 ^a (2453) OCS ≥ 30 days	50 (37) No OCS NA	Unadjusted	6	patient had ≥ 1 emergency room or inpatient visit at baseline) and time-dependent variables (quarter, Charlson Comorbidity Index, and cost of concomitant medications), and the occurrence of the SCS-related condition of interest at baseline and for the year of index date.
Luskin, 2016 [28]	Cross-sectional	USA	2008–2009	56.0 ± 12.1 [§] [45.8 ± 12.2]	Continuous OCS 3011 ± 593 ^a (2453) OCS ≥ 30 days	NA	Adjusted for age group in years, sex, region, Charlson Comorbidity Index score, and chronic obstructive pulmonary disease status.	11	
Spoendlin, 2015 [31]	Case-control	UK	1995–2013	NA	748 ± 472 ^b (NA) Tendon rupture with OCS/ICS exposure 72063 (47497) On OCS	2572 ± 1537 ^b (NA) No tendon rupture with OCS/ICS exposure 72063 (47295) No OCS	Unadjusted	8	
Sullivan, 2017 [23]	Cohort	USA	2000–2014	38.0 [§] [38.1]	72063 (47497) On OCS	72063 (47295) No OCS	Adjusted for age, sex, geographic region, years since the index date, insurance type, use of immunosuppressive medication (yes/no; not OCS), and general comorbidity burden	8	
Sweeney, 2016 [29]	Cross-sectional	UK	2 years for UPCR 1 year for BTS registry	59.0 ± 17 /58.0 ± 16 [§] [50.5 ± 13.7 /48.4 ± 15.5]	808 ± 442 ^c (507 ± 269 ^c) Regular OCS and ≥ 4 OCS pre-scripted/ year 3604 (2453) ≥ 30 days of OCS use/year 3790 (2573) Regular OCS 17671 (11309) Regular OCS	3975 ± 328 ^c (2515 ± 233 ^c) Mild/Moderate asthma 3604 (2453) No OCS	Adjusted for hospital, age and gender	9	
Zazzali, 2015 [24]	Cohort	USA	2008–2009	54.4 ± 12.7 [§] [54.4 ± 12.7]	3604 (2453) ≥ 30 days of OCS use/year 3790 (2573) Regular OCS 17671 (11309) Regular OCS	3604 (2453) No OCS	Unadjusted	8	
Zeiger, 2017 [32]	Cohort	USA	2009–2010	48.3 ± 11.3 [45.8 ± 12.8]	3790 (2573) Regular OCS 17671 (11309) Regular OCS	5756 (3319) No OCS 490295 (NA) No OCS	Unadjusted	5	
Zhang, 2009 [25]	Cohort	UK	1987–2007	56.8 ^d [42.7]	17671 (11309) Regular OCS	490295 (NA) No OCS	Unadjusted	6	

^aHigh OCS use with and without possible side effects, respectively.

^bAchilles tendon rupture and biceps tendon rupture groups respectively.

^cFrom the Optimum Patient Care Research Database (UPCRD) and British Thoracic Society (BTS) Difficult Asthma Registry respectively.

^dMedian age was used in the study.

^eNewcastle-Ottawa Quality Assessment Scale for case-control and cohort studies with a maximum score of 9 and the cross-sectional quality assessment developed by Prins et al. with a maximum score of 15.

[§]Mean age was used in the study.

1.21–1.44), and cataract 1.41 (95% CI 1.20–1.67). The risk was not significantly different for developing lipid disorders 1.32 (95% CI 0.94–1.86), osteoporosis 2.14 (95% CI 0.83–5.57), and glaucoma 1.05 (95% CI 0.86–1.29). More details are provided in [Figure 3](#).

The pooled adjusted OR from 2 studies that reported the relevant adverse events among high-dose OCS-users (>10 mg) compared with non-OCS users were as follows: for the development of any complications 3.35 (95% CI 2.94–3.82), infections 2.68 (95% CI 2.46–2.91), gastrointestinal complications 2.06 (95% CI 1.96–2.17), psychiatric complications 1.66 (95% CI 1.55–1.78), cardiovascular complications 1.82 (95% CI 1.67–1.98), metabolic complications 1.41 (95% CI 1.32–1.50), bone and muscle complications 2.30 (95% CI 2.18–2.42), and ocular complications 1.40 (95% CI 1.31–1.49). This is also provided in [Figure 4](#). More details about the definition of system-related complications are provided in the [supplementary material \(Table S2\)](#).

Dose-response relationship between OCS use and complications

The risk of any complication increased the higher the dose of OCS, with pooled adjusted OR from two studies of 2.26 (95% CI 1.37–3.72), 2.94 (95% CI 2.62–3.29), and 3.35 (95% CI 2.94–3.82) for low dose (< 6 mg), medium dose (5–12 mg) and high dose (>10 mg), respectively, (compared with no OCS use). The additive OR for the risk of any complications was 0.68 (95% CI 0.16–1.20, $p=0.01$) higher for medium-dose OCS, and 1.09 (95% CI 0.57–1.62, $p<0.01$) higher for high-dose OCS compared to low-dose OCS. The two included studies reported different overlapping dose ranges of OCS, which were combined, as the first used 6 and 12 mg cut offs and the second used 5 and 10 mg. For most of the organ system complications, there was a minimal difference in the risk of complications between the intermediate- and high-dose groups, e.g. for the cardiovascular complications 1.85 (95% CI 1.73–1.99) and 1.82 (95% CI 1.67–1.98) for medium dose (5–12 mg) and high dose (>10 mg), respectively. There was no significant difference in the odds of cardiovascular complications between medium-and high-dose OCS ($p=0.70$). More details are given in the [supplementary material \(Table S3\)](#).

OCS use and healthcare utilization and cost data

This is presented in the [supplementary material](#) including [Tables S4–S5](#) and [Figure S6](#).

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis, among asthma patients, reporting the AEs of OCS, its effect on healthcare utilization, and costs. With the availability of newer anti IL-5 targeted therapies and their documented effect on reducing OCS needs in severe asthma [14,15], there has been renewed interest in studying the potential AEs of OCS compared to non-OCS-dependent asthma patients.

This study showed an increased risk for a host of adverse events with OCS use, and demonstrated a significant dose-response relationship between the cumulative effect of increasing doses of OCS and the risk of developing OCS-related complications. The risk of developing any complication was 126%, 194%, and 235% higher compared to non-OCS control subjects for low, medium, and high doses of OCS, respectively. We were unable to demonstrate a dose-response relationship with studying individual AEs, as this was not an outcome for most of the included studies except for the study by Daugherty et al. which reported hazard ratios. Among individual adverse effects, osteoporosis was the highest with an OR of 1.73 (95% CI 1.56–1.93). However, among system organ AEs, infections were the highest among patients using high-dose OCS 2.68 (95% CI 2.46–2.91).

OCS use in the management of asthma is associated with significant AEs, increased healthcare utilization and associated costs. Management strategies that are focused on optimizing asthma control and thus preventing exacerbations and minimizing the use of OCS are fundamental to asthma management. These strategies include adherence to asthma therapies, proper inhaler technique, allergen avoidance and management of comorbidities. All patients should also receive a structured education program. If all of these issues have been addressed and the patient remains uncontrolled or in the context of this review, on OCS, then using tiotropium or biologic agents, including omalizumab, mepolizumab, reslizumab, benralizumab and dupilumab, which have shown efficacy in decreasing asthma exacerbations and a significant OCS sparing effect, is a reasonable next step [14,15,34–41]. Studies primarily assessing the oral corticosteroids sparing effect of omalizumab and reslizumab compared to placebo for are lacking. In the Steroid Reduction with Mepolizumab Study (SIRIUS) trial, patients who received mepolizumab had significantly greater reductions in the maintenance oral glucocorticoid dose (50%) than those receiving placebo. The overall odds ratio for a reduction in the oral

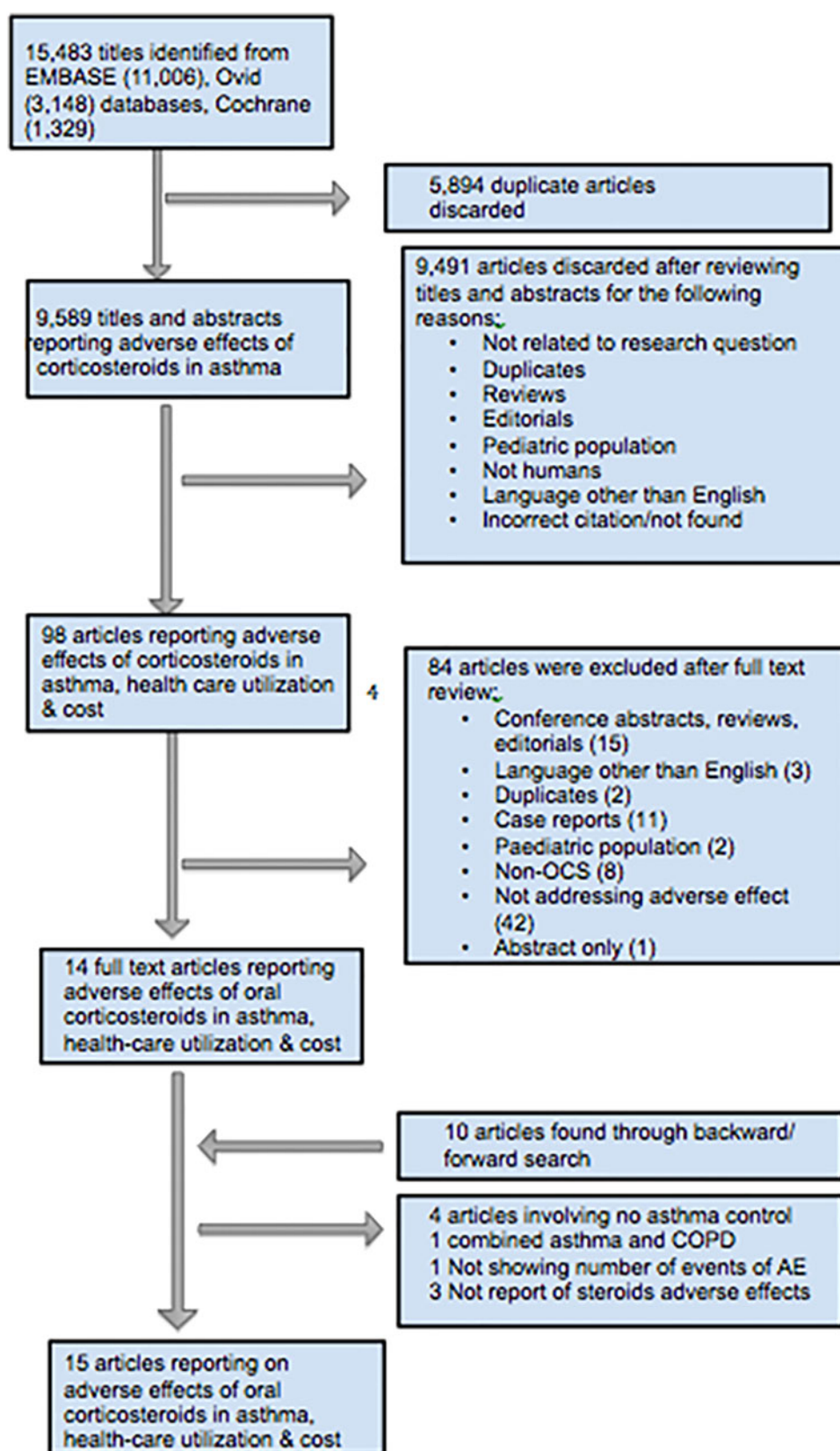
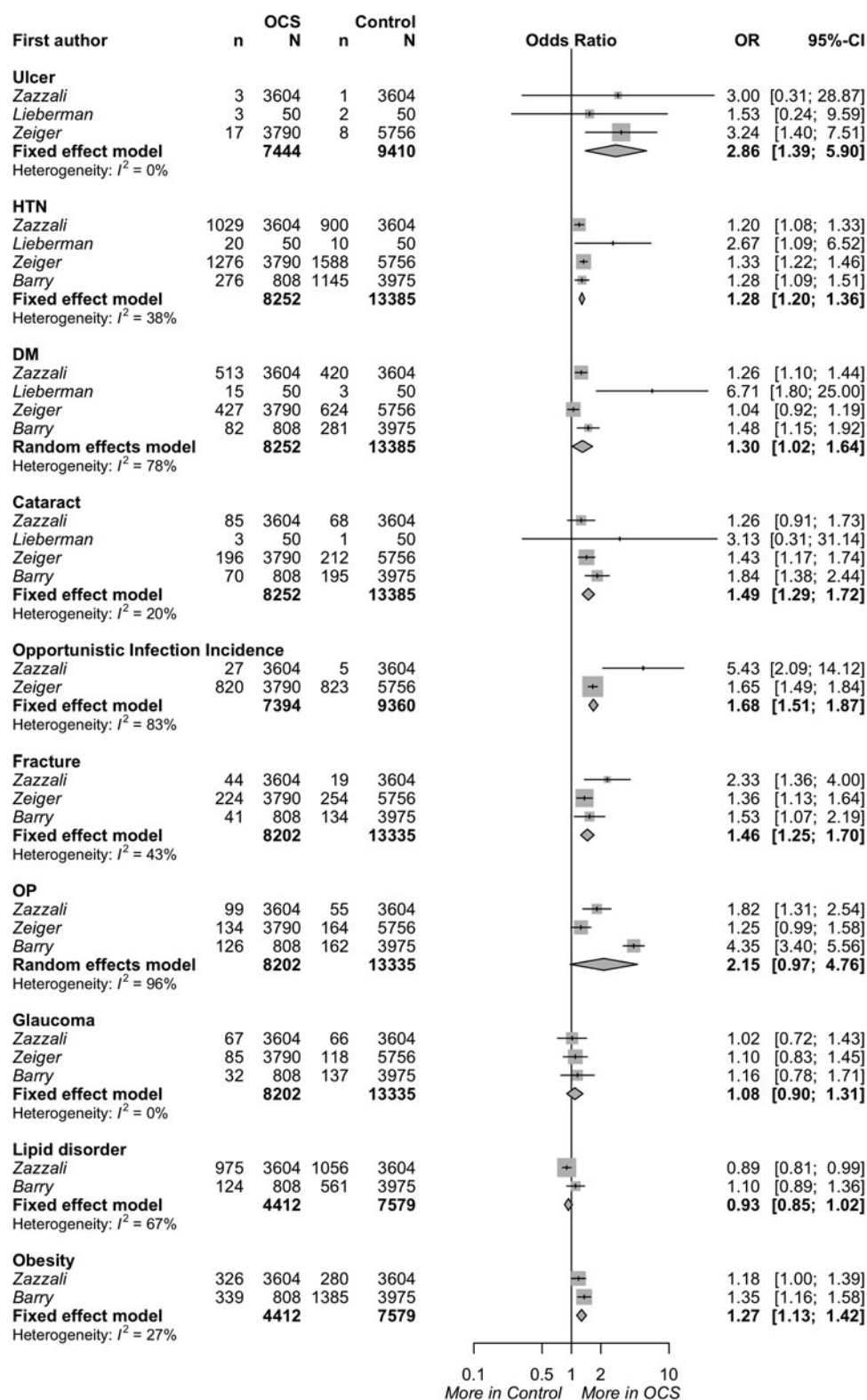


Figure 1. PRISMA flowchart of literature search for studies of OCS AEs in asthma, healthcare utilization and cost.

glucocorticoid dose in the mepolizumab group was 2.39 (95% CI 1.25–4.56; $p=0.008$) [15]. In the ZONDA trial, benralizumab significantly reduced the

OCS dose (75%) in patients who relied on OCS therapy to control their asthma. The odds of a reduction in the oral glucocorticoid dose were 4.09 times (95%

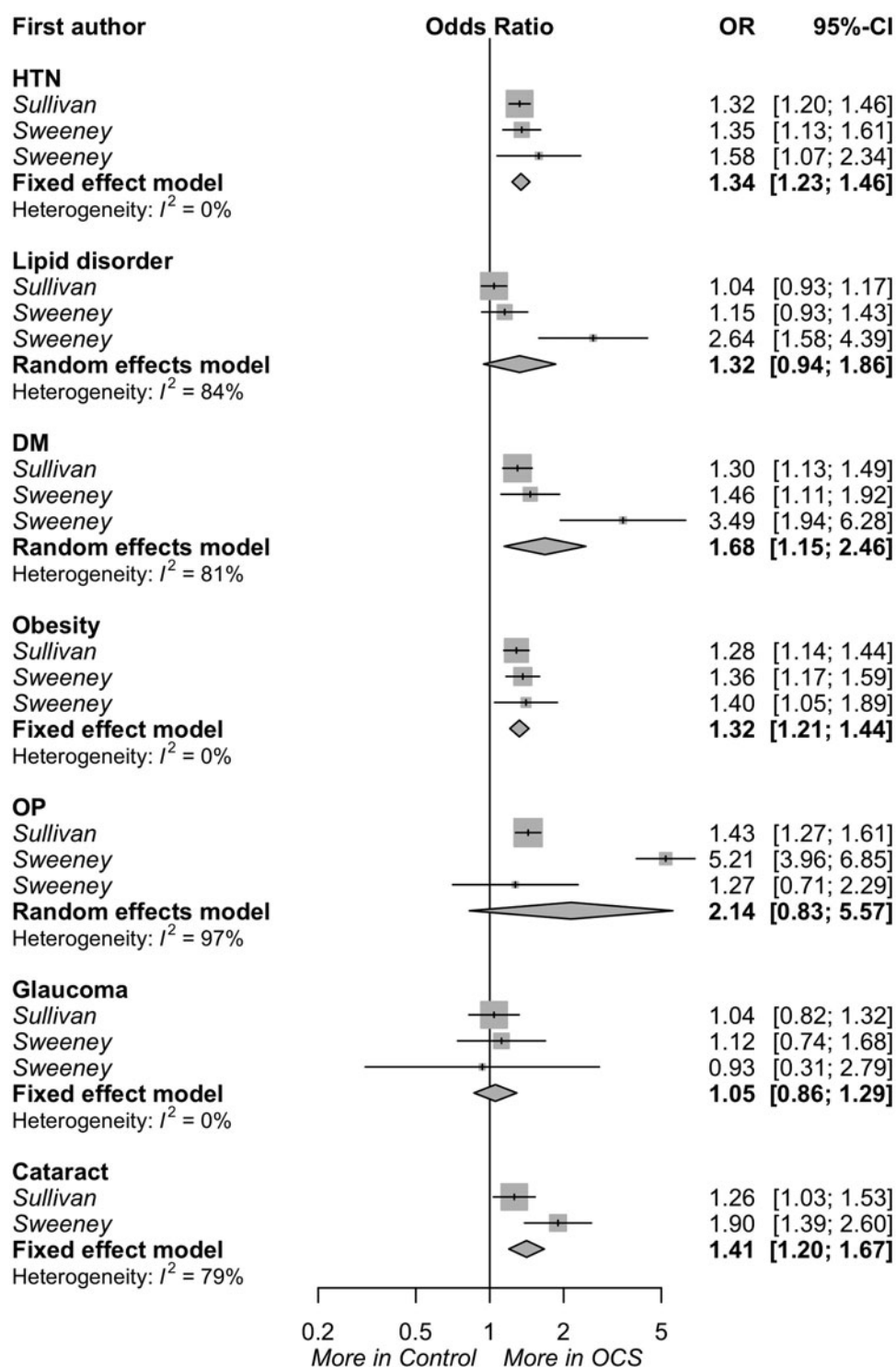


DM: diabetes mellitus, HTN: hypertension, OP: osteoporosis, Peptic (Peptic ulcer)

Figure 2. Unadjusted OR of AE among OCS using asthmatics compared with non-OCS users.

CI 2.22–7.57; $p < 0.001$) and 4.12 times (95% CI 2.22–7.63; $p < 0.001$) that of placebo with benralizumab administered every 4 and 8 weeks, respectively

[14]. In the LIBERTY ASTHMA VENTURE trial, dupilumab was associated with a greater reduction in the dose of oral glucocorticoid than placebo

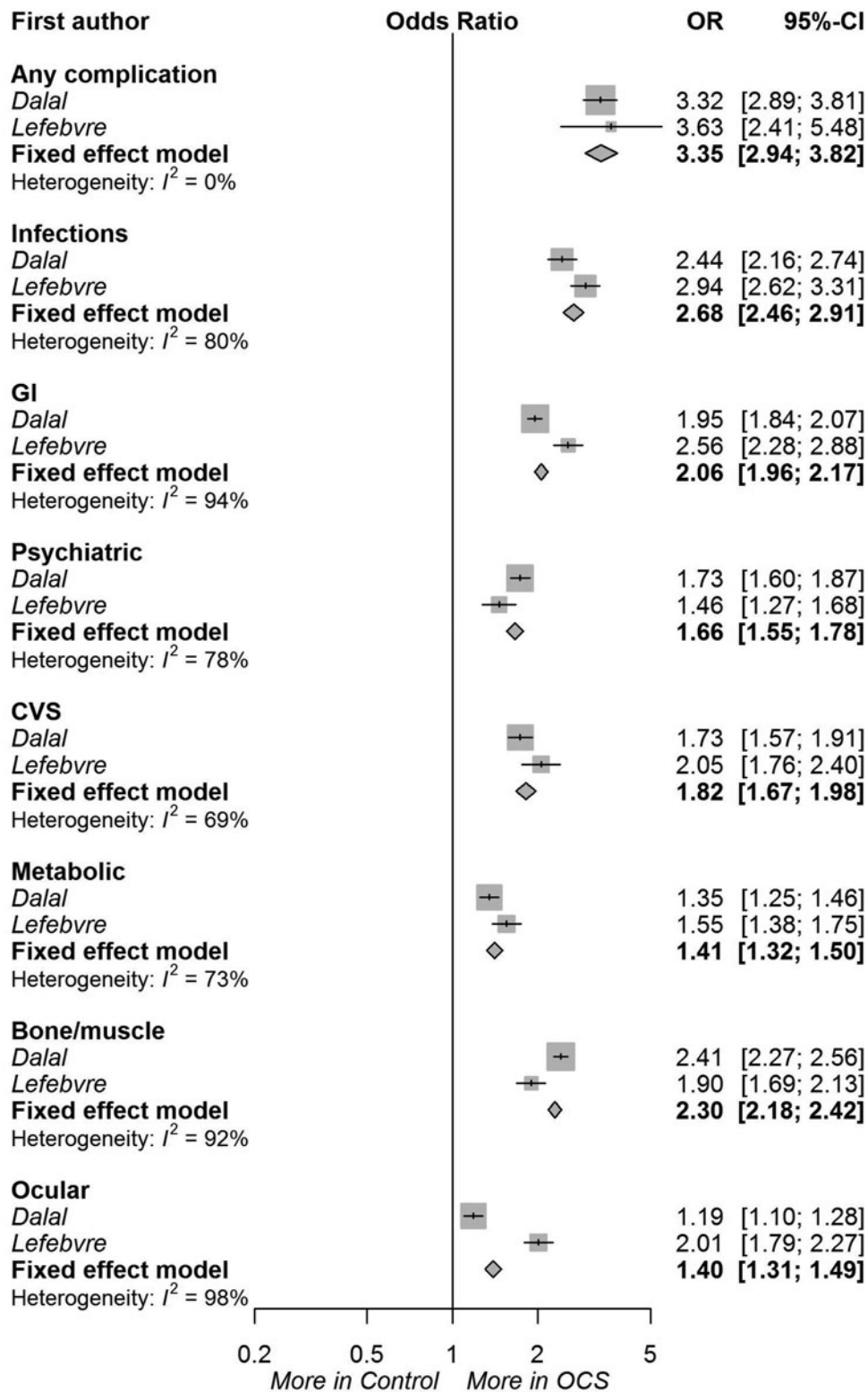


DM: diabetes mellitus, HTN: hypertension, OP: osteoporosis

Figure 3. Adjusted OR of AE among asthmatics who were OCS-users compared with non-OCS users.

$-70.1 \pm 4.9\%$ compared with $-41.9 \pm 4.6\%$ ($P < 0.001$) [38]. While the different biologics were shown to be effective in treatment of severe corticosteroids-dependent asthma, head-to-head comparison trials between different biologics are lacking and could be the focus of new research [42].

Given the substantial additional costs associated with OCS – these costs should also be factored in when considering the cost effectiveness of the new biologics in severe uncontrolled asthma. Of note in both studies although an overall significant reduction in OCS was achieved, subjects



GI: gastrointestinal, CVS: cardiovascular system

Figure 4. Adjusted OR of AE among asthmatics who are high-dose OCS-users (>10 mg) compared with non-OCS users.

were at the same time less likely to exacerbate and require a short course of OCS during the study.

Our study has limitations. Given the heterogeneity of the included studies in reporting AEs and other reported outcomes of interest, we were unable to pool

the data for more than two to four studies for each variable. There was also a high degree of heterogeneity between the included studies for most of the outcomes [22]. Also the included studies used administrative claims data which might be subject to coding errors and reliance on ICD-9-CM codes to identify SCS-related complications that might not have reflected confirmed clinical diagnoses.

Conclusions

The use of OCS in the management of asthma is associated with increased risk of a variety of AEs, health-care utilization and cost. The risk is higher as OCS dose is increased. Optimizing asthma management including appropriate therapy with biologics to reduce OCS exposure is important in reducing the associated significant side effects that we have shown in this review. Our study also highlights the importance of better study designs in describing the AEs associated with OCS to allow for systematic reviews to be more robust and complete.

Conflict of interest

K.A Fellowship in Severe Asthma was funded in part by AstraZeneca and was also supported in part by an unrestricted educational grant from TEVA. K.M.J and D.W have nothing to disclose. M.S has received funding paid directly to UBC outside the submitted work as well as honorarium from AstraZeneca for acting as a member of advisory board. J.M.F received grants from AstraZeneca paid directly to UBC and also reports personal fees for lecturing and consulting.

Author contributions

J. M. F. is the guarantor of the manuscript. J. M. F. is responsible for the concept of the study. K.A and D.W. extracted data from included studies. K.M.J. performed all statistical analyses. K.A. wrote the first draft of the manuscript. All authors critically commented on the manuscript and approved the final version.

Funding

This study was funded by an unrestricted research grant from AstraZeneca Canada, which was provided directly to the University of British Columbia. The sponsor did not have any role in the conduct and reporting of this study.

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Supplementary material:

Table S1: Extracted data from the included studies

[illegible]

		Outpatient visits	< 5mg 5-10 mg >10mg	1.26 (95% CI 1.19-1.34) 1.33 (95% CI 1.28-1.38) 1.53 (95% CI 1.48-1.59)
		ER visits	< 5mg 5-10 mg >10mg	1.57 (95% CI 1.39-1.78) 1.78 (95% CI 1.65-1.92) 2.17 (95% CI 2.00-2.35)
		Other visits	< 5mg 5-10 mg >10mg	1.36 (95% CI 1.19-1.56) 1.56 (95% CI 1.40-1.73) 1.71 (95% CI 1.54-1.89)
		Pharmacy claims	< 5mg 5-10 mg >10mg	1.57 (95% CI 1.50-1.65) 1.77 (95% CI 1.72-1.82) 1.93 (95% CI 1.88-1.98)
Daugerty, 2017	Adjusted HR	Ulcer	> 0	1.13 (95% CI 1.00-1.28)
		Stroke	> 0	1.11 (95% CI 0.97-1.27)
		Myocardial infarction	< 2.5 > 2.5	1.25 (95% CI 1.09-1.43) 2.15 (95% CI 1.67-2.77)
		Diabetes mellitus	< 2.5 > 2.5	1.20 (95% CI 1.11-1.30) 1.70 (95% CI 1.44-2.01)
		Osteoporosis	< 2.5 2.5-5.0 > 5.0	1.64 (95% CI 1.51-1.78) 6.79 (95% CI 5.98-7.73) 12.61 (95% CI 10.45-15.21)
		Cataract	< 2.5 2.5-7.5 > 7.5	1.07 (95% CI 1.00-1.15) 1.76 (95% CI 1.52-2.04) 3.38 (95% CI 2.41-4.73)
Lefebvre, 2017	Adjusted OR	Any complications	< 6 6-12 >12	2.03 (95% CI 1.00-4.14) 2.85 (95% CI 1.85-4.38) 3.64 (95% CI 2.43-5.46)
		Infections	< 6 6-12 >12	1.56 (95% CI 1.34-1.81) 2.53 (95% CI 2.27-2.82) 2.94 (95% CI 2.61-3.33)
		GI	< 6 6-12 >12	1.50 (95% CI 1.28-1.76) 2.31 (95% CI 2.08-2.56) 2.55 (95% CI 2.28-2.84)
		Psychiatric	< 6 6-12 >12	1.40 (95% CI 1.16-1.70) 1.62 (95% CI 1.42-1.84) 1.46 (95% CI 1.28-1.66)
		CVS	< 6 6-12 >12	1.14 (95% CI 0.87-1.48) 2.23 (95% CI 1.93-2.59) 2.06 (95% CI 1.76-2.41)
		Metabolic	< 6 6-12 >12	1.17 (95% CI 0.98-1.40) 1.56 (95% CI 1.38-1.76) 1.55 (95% CI 1.37-1.75)
		Bone and muscle	< 6 6-12 >12	1.09 (95% CI 0.94-1.26) 1.72 (95% CI 1.55-1.92) 1.89 (95% CI 1.68-2.12)
		Ocular	< 6 6-12 >12	1.33 (95% CI 1.14-1.54) 1.63 (95% CI 1.43-1.87) 2.02 (95% CI 1.78-2.29)
		Hematologic and oncologic complications	< 6 6-12 >12	1.58 (95% CI 1.24-2.01) 1.96 (95% CI 1.59-2.41) 1.69 (95% CI 1.35-2.12)
	Adjusted IRR	Inpatient visits	< 6 6-12 >12	1.57 (95% CI 1.41-1.73) 1.92 (95% CI 1.75-2.11) 2.45 (95% CI 2.22-2.70)
		Outpatient visits	< 6 6-12 >12	1.05 (95% CI 0.91-1.21) 1.00 (95% CI 0.88-1.14) 1.15 (95% CI 1.01-1.31)
		ER visits	< 6 6-12 >12	0.97 (95% CI 0.84-1.12) 1.25 (95% CI 1.07-1.47) 1.72 (95% CI 1.39-2.13)
		Other visits	< 6 6-12 >12	1.24 (95% CI 1.05-1.47) 1.31 (95% CI 1.12-1.53) 1.44 (95% CI 1.22-1.71)
		Pharmacy claims	< 6 6-12 >12	1.79 (95% CI 1.68-1.91) 1.77 (95% CI 1.72-1.82) 2.22 (95% CI 2.11-2.35)
Lefebvre, 2015	Adjusted OR	Infections	6-12 >12	1.72 (95% CI 1.37-2.16) 1.91 (95% CI 1.51-2.43)
		GI	6-12	1.63 (95% CI 1.34-1.99)

		Metabolic syndrome Diabetes mellitus Obesity Fracture Osteoporosis Avascular necrosis Glaucoma Cataract		0.84 (95% CI 0.54-1.31) 1.30 (95% CI 1.13-1.50) 1.28 (95% CI 1.13-1.45) 1.21 (95% CI 1.04-1.40) 1.44 (95% CI 1.28-1.63) 1.46 (95% CI 0.57-3.74) 1.04 (95% CI 0.82-1.32) 1.26 (95% CI 1.04-1.52)
Sweeney, 2016	Adjusted OR	Dyspepsia Psychiatric Sleep disorder Chronic kidney disease Hypertension Lipid disorder Cardiovascular Diabetes mellitus Obesity Fractures Osteoporosis Osteopenia Glaucoma Cataracts		3.99 (95% CI 3.37-4.72) & 1.94 (95% CI 1.44-2.61) 1.43 (95% CI 1.22-1.69) & 2.39 (95% CI 1.64-3.49) 1.70 (95% CI 1.13-2.53) & 3.07 (95% CI 1.64-5.77) 1.80 (95% CI 1.39-2.32) 1.35 (95% CI 1.12-1.61) & 1.59 (95% CI 1.07-2.36) 1.15 (95% CI 0.92-1.44) & 2.64 (95% CI 1.60-4.37) 1.36 (95% CI 1.02-1.81) & 0.74 (95% CI 0.41-1.33) 1.46 (95% CI 1.11-1.91) & 3.5 (95% CI 1.94-6.24) 1.36 (95% CI 1.16-1.59) & 1.41 (95% CI 1.06-1.88) 1.54 (95% CI 1.06-2.22) 5.23 (95% CI 3.97-6.89) & 1.27 (95% CI 0.71-2.28) 5.26 (95% CI 3.75-7.37) & 1.23 (95% CI 0.79-1.92) 1.12 (95% CI 0.75-1.68) & 0.93 (95% CI 0.31-2.74) 1.89 (95% CI 1.39-2.56)
Zazzali, 2015		Any complications Infections Pneumonia Ulcer Hypertension Lipid disorder Diabetes mellitus Obesity Glaucoma Cataract Fractures Osteoporosis Bone related complications		1.16 (95% CI 1.06-1.27) 5.43 (95% CI 2.09-14.12) 3.73 (95% CI 2.96-4.69) 3.00 (95% CI 0.31-28.87) 1.20 (95% CI 1.08-1.33) 0.89 (95% CI 0.81-0.99) 1.26 (95% CI 1.10-1.44) 1.18 (95% CI 1.00-1.40) 1.12 (95% CI 0.72-1.43) 1.26 (95% CI 0.91-1.73) 2.33 (95% CI 1.36-4.00) 1.82 (95% CI 1.31-2.54) 1.91 (95% CI 1.43-2.55)
Zeiger	Unadjusted OR	Infections Ulcer Anxiety	<2.5 2.5-5.0 5.0-7.5 >7.5 <2.5 2.5-5.0 5.0-7.5 >7.5 <2.5 2.5-5.0 5.0-7.5	1.58 (95% CI 1.41-1.77) 1.92 (95% CI 1.55-2.37) 1.67 (95% CI 1.12-2.51) 2.51 (95% CI 1.69-3.73) 2.64 (95% CI 1.06-6.56) 7.03 (95% CI 2.29-21.57) 5.02 (95% CI 0.62-40.44) 2.76 (95% CI 0.16-48.10) 1.44 (95% CI 1.25-1.65) 2.07 (95% CI 1.63-2.64) 1.56 (95% CI 0.97-2.52)

		Depression	>7.5 <2.5 2.5-5.0 5.0-7.5	1.46 (95% CI 0.86-2.49) 1.38 (95% CI 1.21-1.58) 1.19 (95% CI 0.91-1.56) 1.14 (95% CI 0.69-1.89)
		Hypertension	>7.5 <2.5 2.5-5.0 5.0-7.5	1.30 (95% CI 0.77-2.18) 1.26 (95% CI 1.15-1.39) 1.58 (95% CI 1.31-1.91) 1.44 (95% CI 1.02-2.04)
		Hypercortisolism	>7.5 <2.5 2.5-5.0 5.0-7.5	2.02 (95% CI 1.40-2.90) 5.11 (95% CI 1.36-19.29) 18.76 (95% CI 4.47-78.74) 54.79 (95% CI 12.15-247.11)
		Diabetes mellitus	>7.5 <2.5 2.5-5.0 5.0-7.5	48.34 (95% CI 9.66-242.00) 1.02 (95% CI 0.89-1.18) 1.10 (95% CI 0.83-1.46) 1.03 (95% CI 0.61-1.74)
		Fractures	>7.5 <2.5 2.5-5.0 5.0-7.5	1.33 (95% CI 0.79-2.24) 1.26 (95% CI 1.03-1.54) 1.67 (95% CI 1.17-2.39) 1.44 (95% CI 0.73-2.87)
		Osteoporosis	>7.5 <2.5 2.5-5.0 5.0-7.5	2.58 (95% CI 1.43-4.65) 1.11 (95% CI 0.86-1.44) 1.66 (95% CI 1.07-2.58) 1.74 (95% CI 0.80-3.78)
		Glaucoma	>7.5 <2.5 2.5-5.0 5.0-7.5	2.39 (95% CI 1.15-4.98) 1.02 (95% CI 0.75-1.39) 1.23 (95% CI 0.69-2.21) 1.37 (95% CI 0.50-3.75)
		Cataract	>7.5 <2.5 2.5-5.0 5.0-7.5 >7.5	2.04 (95% CI 0.82-5.09) 1.38 (95% CI 1.12-1.71) 1.11 (95% CI 0.70-1.75) 1.74 (95% CI 0.88-3.47) 3.67 (95% CI 2.01-6.40)
Zhang, 2009	Relative Risk	Myocardial infarction MI hospitalization		1.50 (95% CI 1.20-1.70) 1.80 (95% CI 1.30-2.60)

Table S2: Definition of system related complications:

Gastrointestinal	• Nausea/vomiting • Gastrointestinal bleeds/ulcers • Dyspepsia
Infections	• Fungal infections • Pneumonia • Sepsis • Tuberculosis • Urinary tract infection • Varicella infection • Bursitis
Bone- and muscle-related	• Fractures • Avascular necrosis • Osteoporosis • Muscle weakness

	• Back pain
Cardiovascular	• Atrial fibrillation/flutter • Hypertension • Myocardial infarction
Metabolic	• Hyperglycemia • Dyslipidemia • Obesity • Diabetes mellitus • Metabolic syndrome
Ocular	• Cataracts • Glaucoma
Psychiatric	• Bipolar disorder • Depression • Sleep disturbances • Steroid psychosis

Table S3: Dose-response relationship of complications among different OCS dose ranges compared with non OCS users.

Adverse effect	OR	95% CI
Any complication		
• Low dose	2.26	(1.37-3.72)
• Medium dose	2.94	(2.62-3.29)
• High dose	3.35	(2.94-3.82)
Cardiovascular		
• Low dose	1.17	(0.96-1.43)
• Medium dose	1.85	(1.73-1.99)
• High dose	1.82	(1.67-1.98)
Gastrointestinal		
• Low dose	1.36	(1.21-1.52)

• Medium dose	2.09	(1.99-2.20)
• High dose	2.06	(1.96-2.17)
Infections		
• Low dose	1.60	(1.40-1.82)
• Medium dose	2.30	(2.18-2.43)
• High dose	2.68	(2.46-2.91)
Psychiatric		
• Low dose	1.03	(0.90-1.17)
• Medium dose	1.37	(1.30-1.44)
• High dose	1.41	(1.32-1.50)
Bone/muscle		
• Low dose	1.20	(1.09-1.33)
• Medium dose	2.11	(2.00-2.12)
• High dose	2.30	(2.18-2.42)
Ocular		
• Low dose	1.08	(0.98-1.18)
• Medium dose	1.21	(1.13-1.29)
• High dose	1.40	(1.31-1.49)

Table S4: Dose-response relationship of OCS use and healthcare utilization because of OCS related complications

Healthcare utilization	IRR	95% CI
Inpatient visits		
• Low dose	1.71	(1.59-1.83)
• Medium dose	2.27	(2.16-2.39)
• High dose	3.09	(2.94-3.25)
Emergency room visits		
• Low dose	1.28	(1.17-1.40)

• Medium dose	1.66	(1.55-1.78)
• High dose	2.10	(1.95-2.26)
Outpatient visits		
• Low dose	1.22	(1.16-1.29)
• Medium dose	1.31	(1.26-1.36)
• High dose	1.50	(1.45-1.56)
Other visits		
• Low dose	1.32	(1.18-1.47)
• Medium dose	1.48	(1.36-1.61)
• High dose	1.64	(1.51-1.79)
Pharmacy claims		
• Low dose	1.63	(1.58-1.69)
• Medium dose	1.79	(1.76-1.83)
• High dose	1.96	(1.93-2.00)

Table S5: Summary of collected cost data (a) studies reporting different cost data:

Study	Cost Category	Cost
Barry, 2017 (26)	Mean annual cost	
	Total cost	4269-7434 US\$ *
	Clinical activity	1494-4590 US\$ *
	Prescription	2775-2844 US\$ *
Broder, 2017 (27)	Mean total annual healthcare cost	40933 US\$
	Adjusted mean total annual healthcare cost excess	17122 +/- 2395 US\$
Luskin, 2016 (28)	Unadjusted mean annual healthcare cost in patients with complications	26355 US\$ (95% CI 25264-27447)
	Adjusted mean cost in patients with complications	
	Annual total healthcare cost	25168 US\$ (95% CI 24223-26133)
	Annual asthma related healthcare cost	4213 US\$ (95% CI 3990-4435)

*Adjusted to 2014 US\$

(b) Comparison of studies reporting similar cost data:

Cost category	OCS dose	Dalal, 2016 (10) Mean difference in US\$ compared with non-OCS	Lefebvre, 2017 (11) Mean difference in US\$ compared with non-OCS	Lefebvre, 2015 (7) Mean difference in US\$ compared with low dose OCS
Pharmacy and medical costs	Low	667 (95% CI 257-937)	678 (95% CI 414-922)	
	Medium	1160 (95% CI 1038-1427)	1181 (95% CI 928-1397)	478 (95% CI 256-733)
	High	<u>2291 (95% CI 2044-2532)</u>	<u>2140 (95% CI 1766-2391)</u>	<u>1370 (95% CI 1018-1720)</u>
Pharmacy Cost	Low	342 (95% CI 302-397)	141 (95% CI 47-212)	
	Medium	422 (95% CI 393-460)	356 (95% CI 253-429)	110 (95% CI 36-198)
	High	<u>416 (95% CI 382-447)</u>	<u>643 (95% CI 511-740)</u>	<u>307 (95% CI 208-417)</u>
All medical cost	Low	390 (95% CI -33-629)	521 (95% CI 291-755)	
	Medium	760 (95% CI 629-1013)	817 (95% CI 613-1009)	369 (95% CI 168-600)
	High	<u>1872 (95% CI 1633-2096)</u>	<u>1497 (95% CI 1189-1719)</u>	<u>1061 (95% CI 731-1402)</u>
Inpatient visit	Low	233 (95% CI -143-467)	195 (95% CI 82-351)	
	Medium	467 (95% CI 331-683)	427 (95% CI 340-548)	239 (95% CI 102-391)
	High	<u>1433 (95% CI 1212-1635)</u>	<u>837 (95% CI 675-972)</u>	<u>620 (95% CI 403-848)</u>
Outpatient visit	Low	82 (95% CI 12-142)	-24 (95% CI -110-96)	
	Medium	182 (95% CI 150-230)	91 (95% CI -17-197)	136 (95% CI 45-215)
	High	<u>282 (95% CI 244-325)</u>	<u>368 (95% CI 195-486)</u>	<u>398 (95% CI 250-514)</u>
ER visit	Low	24 (95% CI 11-45)	1 (95% CI -1-3)	
	Medium	30 (95% CI 24-44)	2 (95% CI 0-4)	2 (95% CI 0-3)
	High	<u>76 (95% CI 49-72)</u>	<u>4 (95% CI 2-7)</u>	<u>4 (95% CI 2-6)</u>
Other visit costs	Low	55 (95% CI 6-93)	249 (95% CI 114-376)	
	Medium	75 (95% CI 52-103)	253 (95% CI 137-363)	35 (95% CI -88-173)
	High	<u>95 (95% CI 78-122)</u>	<u>319 (95% CI 192-450)</u>	<u>116 (95% CI -30-291)</u>
Annual increased cost of	Low	2670	2440	
Complications	Medium	4639	4516	1914
	High	<u>9162</u>	<u>8684</u>	<u>5479</u>
Total cost of acute	Low		984	
complications	Medium		1880	842
	High		<u>4168</u>	<u>2953</u>
Total cost of chronic	Low		2424	
complications	Medium		4028	1767
	High		6816	4492

Low dose: <5 mg in Dalal's study and < 6 mg in Lefebvre's studies

Medium dose: 5-10 mg in Dalal's study and 6-12 mg in Lefebvre's studies

High dose: >10 mg in Dalal's study and >12 mg in Lefebvre's studies

Figure S1: Search Strategy:

-
- 1 exp Asthma/
 - 2 asthma*.mp.
 - 3 1 or 2
 - 4 exp Prednisone/
 - 5 prednisone.mp.
 - 6 exp Prednisolone/
 - 7 prednisolone.mp.
 - 8 exp Dexamethasone/
 - 9 dexamethasone.mp.
 - 10 exp Betamethasone/
 - 11 betamethasone.mp.
 - 12 exp Glucocorticoids/
 - 13 systemic corticosteroid*.mp.
 - 14 or/4-13
 - 15 "Drug-Related Side Effects and Adverse Reactions"/
 - 16 adverse.mp.
 - 17 (ae or si or to or co).fs.
 - 18 (safe or safety).ti,ab.
 - 19 side effect\$.ti,ab.
 - 20 ((adverse or undesirable or harm\$ or serious or toxic) adj3 (effect\$ or reaction\$ or event\$ or outcome\$)).ti,ab.

21 (toxicity or complication\$ or noxious or tolerability).ti,ab.

22 exp Hypertension/

23 Hypertension.mp.

24 exp Myocardial Infarction/

25 myocardial infarction.mp.

26 exp Osteoporosis/

27 osteoporosis.mp.

28 exp Cataract/

29 cataract*.mp.

30 exp Diabetes Mellitus/

31 diabetes.mp.

32 exp Adrenal Insufficiency/

33 adrenal insufficiency.mp.

34 exp Wound Healing/

35 wound healing.mp.

36 or/15-35

37 exp Hospitalization/

38 hospitalization*.mp.

39 economic*.mp.

40 ec.fs.

41 exp "Costs and Cost Analysis"/

42 cost*.mp.

43 exp Health Care Costs/

44 (health adj10 cost*).mp.

45 exp Emergency Service, Hospital/

46 (emergency adj5 visit*).mp.

47 or/37-46

48 exp Cost-Benefit Analysis/

49 cost effectiveness.mp.

50 48 or 49

51 3 and 14 and 36

52 3 and 14 and 47

53 3 and 14 and 50

54 (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab. (1365546)

55 RETRACTED ARTICLE/

56 exp cohort analysis/

57 exp longitudinal study/

58 exp prospective study/

59 exp follow up/

60 cohort\$.tw.

61 exp case control study/

62 (case\$ and control\$).tw.

63 exp case study/

64 (case\$ and series).tw.

65 case report/

66 (case\$ adj2 report\$).tw.

67 (case\$ adj2 stud\$).tw.

68 or/54-67

69 51 and 68

70 52 and 68

71 53 and 68

Figure S2: The risk of development of any complications among different dose ranges of OCS compared with non-OCS users.

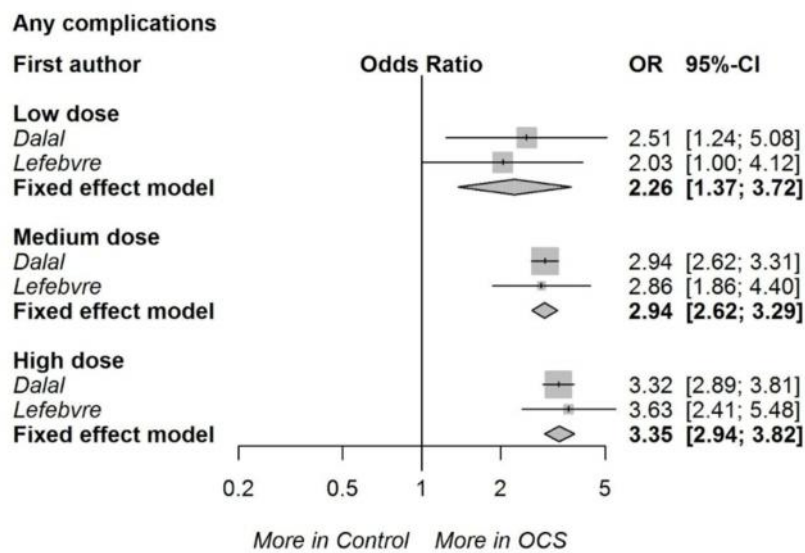


Figure S3: The risk of development of cardiovascular complications among different dose ranges of OCS compared with non-OCS users

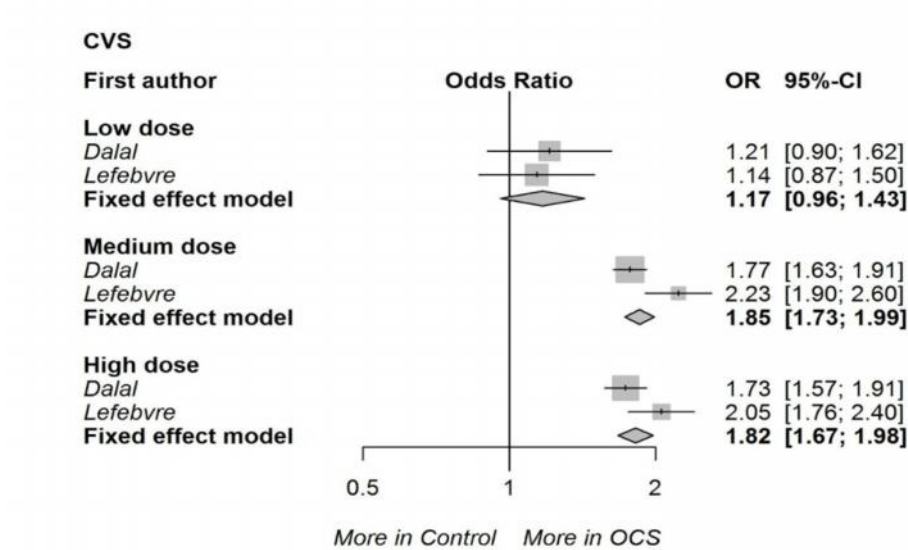


Figure S4: The risk of development of gastrointestinal complications among different dose ranges of OCS compared with non-OCS users.

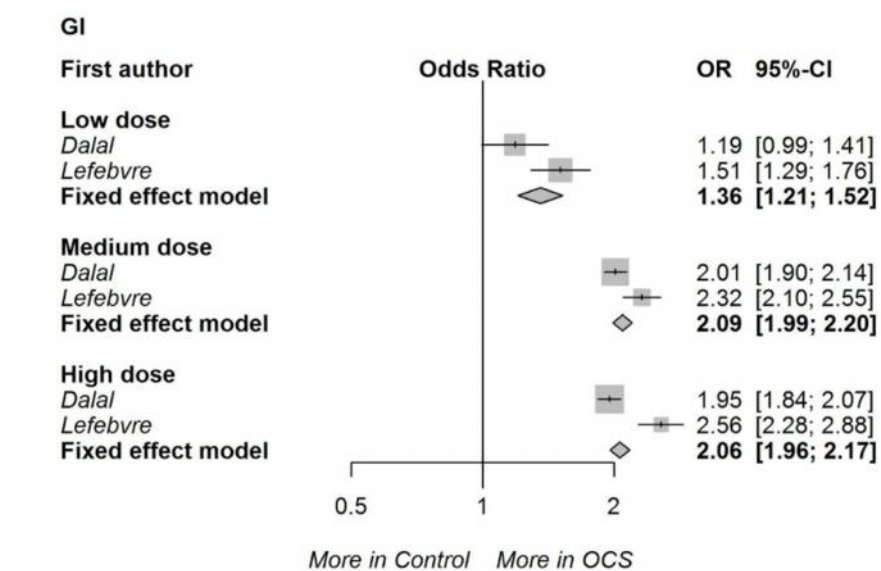


Figure S5: The risk of development of infections among different dose ranges of OCS compared with non-OCS users:

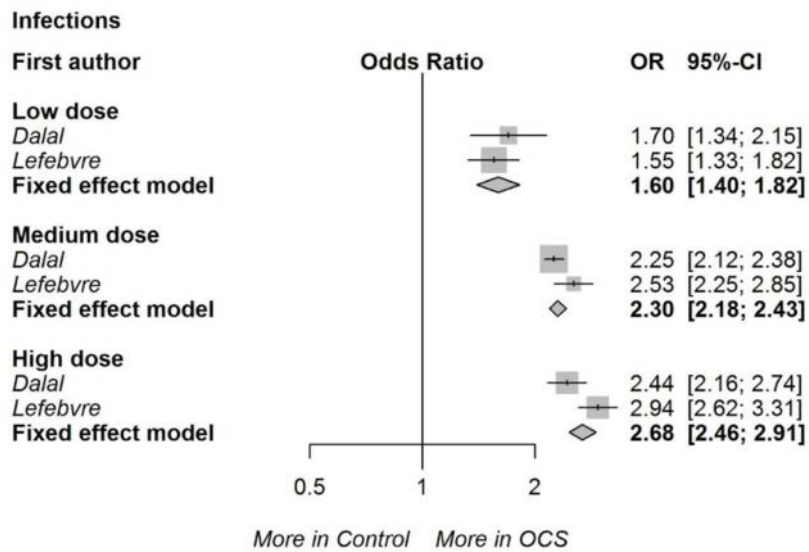
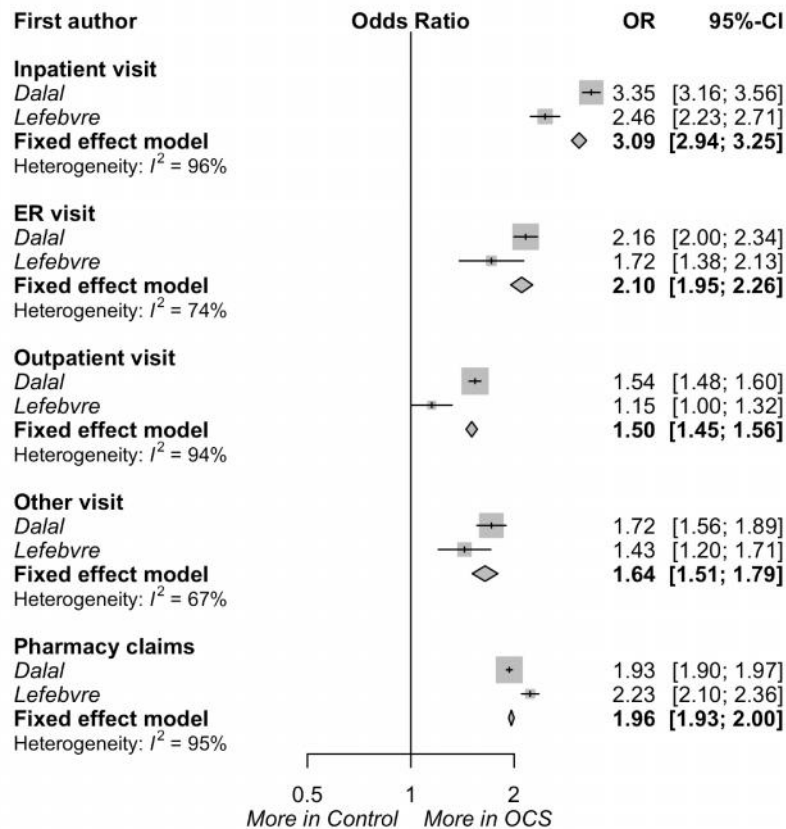


Figure S6: High dose OCS use and healthcare utilization because of OCS related complications compared with non-OCS users.



OR: Odds ratio, ER: emergency room

OCS use and healthcare utilization because of OCS related complications:

This study demonstrates higher rates of healthcare utilization as OCS dose increased. The adjusted OR of inpatients hospital admissions because of OCS related complications compared with non-OCS users, from the two studies that used regression modeling, was 1.71 (95% CI 1.59-1.83), 2.27 (95% CI 2.16-2.39), and 3.09

(95% CI 2.94-3.25) for low dose (< 6 mg), medium dose (5-12 mg) and high dose (>10 mg) respectively. As in supplementary file (table S4 and figure S5).

Healthcare cost of OCS related complications:

Six studies provided cost data. Although there are methodological limitations in terms of reporting these data we have included such data to provide a comprehensive overview. Upon individual study review, there was an increased cost difference of OCS related complications compared with non-OCS patients' healthcare cost across the different dose ranges as demonstrated in table S5. We adjusted the cost to the same currency and year.

Discussion:

This study also showed that higher cumulative doses of OCS significantly increased all types of OCS-related healthcare resource utilization with a significant dose-response relationship with an increase in IRR for inpatient visits to 3.09 compared to non-OCS using asthmatics. This is higher than that reported by Broder et al. where the all cause hospitalization risk was 1.81 (95% CI 1.25-2.62), which included patients with 6 or more courses of OCS or intake of OCS for more than 30 days compared with 1 course or less or no OCS intake for more than 30 days (28). Zeiger et al study showed that patients with severe asthma on chronic OCS with a dose 2.5mg or more per day are more likely to have asthma exacerbations, including ED visits and hospitalizations when compared with non-OCS dependent asthma patients.⁽³³⁾

While there are methodological issues in pooling health care costs described earlier, the studies reporting cost in this review have also shown that the annual healthcare costs associated with AEs from OCS is increased with increasing doses. Three studies showed that the cost of inpatient care accounted for the greater proportion of the total cost (11, 12). On the other hand, two other studies published in the UK showed that pharmacy costs accounted for most of the total cost (27, 34). Barry et al. study also demonstrated higher costs for OCS related complications compared to matched asthmatics with an estimated annual cost for prescription drugs and healthcare activity of £1310 "US\$2142" (£772 "US\$ 1262" plus £538 "US\$ 880") and £224 "US\$366" (£112 "US\$183" plus £112 "US\$183") respectively (27).