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POSITION PAPER

Meta-Analysis on the Harm of Systemic Glucocorticosteroids in Inflammatory Upper Airway Disease and Asthma: An EAACI Task Force

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ABSTRACT

Systemic glucocorticosteroids (sGCS) are widely used in the treatment of chronic inflammatory airway diseases such as rhinitis, rhinosinusitis and asthma. It is well-known that systemic use is linked to multiple adverse effects (AEs) both in the short- and the long-term. However, less is known about the safety of multiple short courses of sGCS. Currently there is no established agreement on the acceptable cumulative exposure to sGCS, considering the potential for various AEs. This systematic review and meta-analysis evaluated sGCS-related AEs in both upper and lower inflammatory airway disease, with a particular focus on short- and long-term risks. We further evaluated whether a dose–response relationship existed between the daily and cumulative dosages of sGCS and the occurrence of those AEs. Our meta-analysis confirmed that cumulative dosages between 500 mg and 1 g prednisolone-equivalent significantly increase the risk of most AEs, with risks increasing with incremental dose. These findings underscore the importance of: (a) judicious sGCS prescription and need for steroid stewardship, due to their potential for short- and long-term complications, occurring even with repeated short courses, and (b) prioritization of steroid-sparing approaches (e.g., biologicals) to avoid reaching a cumulative dose of 500 mg.

1 | Introduction

Chronic inflammatory airway diseases, including allergic rhinitis (AR), chronic rhinosinusitis (CRS), and asthma, are highly prevalent conditions worldwide [1] with a significant impact on quality of life and healthcare costs [2–5].

The first-line treatment typically involves local corticosteroids, often with bronchodilators in case of asthma [2, 6]. During exacerbations and for severe cases, systemic glucocorticosteroids (sGCS) are prescribed due to their potent anti-inflammatory properties [7–9]. Although sGCS are known to rapidly alleviate symptoms, their effects are usually transient [10], often

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Prof Dr Peter Valentin Tomazic passed away on 03-06-2024.
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necessitating repeated courses or even continuous use in severe patients. A recent systematic review demonstrated that 23%–92% of patients with severe asthma received a short course of sGCS for exacerbations and long-term sGCS were prescribed in 20%–30% of patients [11]. Even 28.5% of AR patients were prescribed sGCS [12].

In recent years, the arrival of biologics has revolutionized the management of airway disease and they have demonstrated significant corticosteroid-sparing effects [13, 14]. However, biologics are expensive, not universally accessible, and only indicated for patients with severe, type-2 mediated disease. As a result, a substantial group of patients continues to rely on sGCS for symptom management. Unfortunately, long-term exposure to sGCS is well-known to be associated with numerous adverse effects (AEs) [15–18]. While most data on these risks come from studies in conditions other than airway diseases, several studies have shown increased AEs from long-term sGCS use in chronic airway disease patients. Historically, physicians considered short courses of sGCS relatively safe, but recent research indicates that even short-term use may lead to AEs later in life [19]. This shift in understanding highlights a critical need for further investigation, particularly as repeated short courses of sGCS are often used in clinical practice without a consensus on the optimal dosing and treatment duration.

To bridge these gaps, a Task Force of the European Academy of Allergy and Clinical Immunology (EAACI) conducted a systematic review (SR) with meta-analysis focusing specifically on the sGCS-related AEs in patients with upper airway disease and asthma. The SR aimed to provide reliable data on dose-dependent associations for different AEs in order to propose recommendations for acceptable sGCS dosing regimens in clinical practice.

2 | Methods

The study protocol was registered on PROSPERO (registration number CRD42020155198) [20]. This systematic review and meta-analysis was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Harms [21].

2.1 | Study Inclusion Criteria and Outcomes

Peer-reviewed articles focusing on adults with upper airway disease (UAWD) or asthma were eligible for inclusion if they investigated immediate or delayed AEs in participants receiving sGCS (oral, intravenous or intramuscular) alone or as add-on therapy to standard of care (SOC) compared to no treatment, placebo, or SOC alone. As a primary outcome we analyzed the occurrence of any immediate or delayed AE that was linked to the use of sGCS in general. Secondary outcomes were the occurrence of serious AEs and the exploration of a dose-dependent association between either daily or cumulative sGCS dosages and the occurrence of related AEs. More details on the PICO questions and study inclusions are found in the supplement.

2.2 | Definitions of AEs

After a panel discussion immediate AEs were defined as any AE that occurred during a short course (≤21 days) of sGCS or within 3 weeks after the end of a short course. Delayed AEs were defined as AEs occurring during a long course (> 21 days) of sGCS or at least 3 weeks after the end of treatment.

2.3 | Search Strategy

EL and SS searched MEDLINE, EMBASE, and CENTRAL in October 2019, with an updated search in June 2023 and September 2025. Details on the search strategy are presented in the supplement annex 2.

2.4 | Study Selection

Titles and abstracts of the articles were screened, followed by the full-text study by at least two authors (SS, EL, MB, and MD). More information can be found in the supplement.

2.5 | Data Extraction Process

The data extraction form was designed in Covidence (Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) to retrieve specific information related to the PICO and items are listed in the Supplement. The data from each paper were independently extracted by two authors (EL, MB, MD or SS), and discrepancies were resolved after discussion with the senior author (VH).

2.6 | Assessment of Risk of Bias in Individual Studies

The quality assessment was completed independently by two reviewers per study (SS, EL, MD), and discrepancies were discussed in a consensus meeting with the senior author (VH). For randomized controlled trials, the Cochrane Risk-of-Bias (ROB) tool Version 2 (RoB 2) was used [22]. For non-randomized studies, the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I tool) [23] was used.

2.7 | Data Analysis

When possible, a meta-analysis was conducted to calculate the risk of AEs; otherwise, AE findings were summarized in a narrative synthesis. All statistical analyses were performed using RStudio. Because of the expected between-study heterogeneity, random effects meta-analysis was applied to combine estimated Odds Ratio's (ORs) of sGCS users versus non-sGCS users and their standard errors (SE). A two-sided p value < 0.05 was considered statistically significant. A more detailed explanation of the analysis is provided in the online supplement.

2.8 | Assessment of Heterogeneity

Information about the heterogeneity assessment can be found in the supplement. Statistically we examined both I^2 (a value above 50% indicates substantial heterogeneity) [24] as well as t^2, an estimate of the variance of the true effect sizes.

2.9 | Additional Analyses

The dose-dependent associations were assessed using either daily or total cumulative sGCS dose. For the daily dosages, we grouped our results into four dosing categories based on, and slightly adapted from a publication on sGCS AEs in lupus patients [25]: high exposure > 10 mg/d; medium exposure 5–10 mg/d; low exposure 1–5 mg/d; very low exposure 0.5–1 mg/d. We also used four categories for the assessment of the total cumulative sGCS dose-dependent associations: high dose > 10 g; medium dose 5–10 g; low dose 1–5 g; and very low dose 0.5–1 g. Information on sensitivity analyses can be found in the supplement.

3 | Results

3.1 | Description of Studies

3.1.1 | Search Results

The searches up to September 2025 retrieved 19,674 records. After removing duplicates, we screened 16,626 titles and abstracts and removed 16,382 irrelevant records. We assessed 244 records for eligibility and excluded 207 studies. Finally, 37 individual studies were included in the SR. The flow diagram of study retrieval and selection is provided in Figure 1.

3.1.2 | Included Studies

Twelve out of the fourteen prospective studies (eleven RCTs [26–36] and one prospective cohort study [37]) reported on immediate AEs. Two additional RCTs reported on AEs during or immediately after a sGCS course of 4 weeks [38] or 6 weeks [39]. Based on clinical judgment, these studies were added to the immediate AEs. Summarized characteristics of these studies can be found in Table 1. For delayed AEs, the SR included twenty-four large-scale retrospective cohort studies [40–62] The characteristics of these studies are summarized in Table 2.

3.2 | Synthesis of Results

3.2.1 | Primary Outcome: Occurrence of AEs in Patients Receiving sGCS vs. no sGCS

3.2.1.1 | Immediate AEs of Systemic GCS vs. no GCS

3.2.1.1.1 | Meta-Analysis. Five RCTs reported on the occurrence of sleep disturbances in the immediate setting [26, 27, 29, 34, 35]. Meta-analysis did not show a significant difference between patients treated with short courses of oral corticosteroids (OCS) compared to placebo [26, 29, 34] or nasal steroids [27, 35] (OR 1.41, 95% CI 0.52–3.83) (Figure 2). Three of these studies [29, 34, 35], together with two other RCTs [31, 36] investigated the presence of immediate gastrointestinal disturbances after a short course of sGCS. Meta-analysis did not demonstrate a significant difference between patients on sGCS compared to placebo [29, 31, 34] or nasal steroids [35, 36] (OR 1.24, 95% CI 0.60–2.60) (Figure 2).

3.2.1.1.2 | Narrative Synthesis. Four RCTs studied the occurrence of adrenal suppression after OCS use [33, 36, 38, 39]. Two of them showed a significant reduction in morning serum cortisol levels after a two-week treatment with OCS compared to local steroids in CRS and asthma respectively [33, 36]. Two other RCTs showed similar significant suppression of the hypothalamic–pituitary–adrenal (HPA) axis after a longer OCS course of four [38] and 6 weeks [39] by using the ACTH stimulation test in AR patients. Due to different assessment techniques, a meta-analysis was not possible.

Berthon and colleagues investigated changes in appetite, dietary intake, body weight or composition in a RCT in 60 asthma patients receiving ten days of 50 mg prednisolone [26]. Objective testing did not show significant differences compared to placebo. Three other RCTs in rhinosinusitis patients receiving short courses of OCS, did find a lack of loss in appetite or change in body weight, but did not use objective testing [27, 28, 34].

One prospective questionnaire-based cohort study studied immediate psychiatric symptoms in 32 asthma patients during a prednisolone course for at least 1 week [37]. Authors found a significant increase in mania, but not in depression, during the first week of treatment. Subjects with past or current symptoms of depression had a significant decrease in depressive symptoms during prednisone therapy compared with those without depression. Two RCTs in CRS patients also asked about self-reported mood swings after a short course of oral steroids and did not report any differences with the placebo group [27, 28].

Three RCTs demonstrated increased reporting of headaches by UAWD patients after a course of OCS compared to placebo [39] or nasal corticoid sprays [29, 35], but three other RCTs in CRS or asthma patients could not confirm this [27, 28, 33]. Chang and colleagues were unable to demonstrate differences in muscle weakness, blurred vision, diabetes type 2 control, blood pressure, nervousness and water retention in CRS patients receiving 12 days of postoperative prednisolone compared to placebo [27]. In the RCT performed by Zhang, two out of 31 CRS patients experienced elevated blood glucose levels and one patient reported hip pain, while no patients in the nasal steroids groups showed an AE [36]. McNamara found no difference in muscle pain in asthma patients who received intramuscular methylprednisolone compared to placebo [31], while the study by Berthon and colleagues did find mild muscle weakness in subjects taking OCS vs. placebo [26]. This last study also reported on a mild increase in urinary frequency in asthma patients on prednisolone compared to placebo [26].

3.2.1.2 | Delayed AEs of Systemic GCS vs. no GCS

3.2.1.2.1 | Meta-Analysis. Eleven studies investigated the link between sGCS use and the occurrence of overall

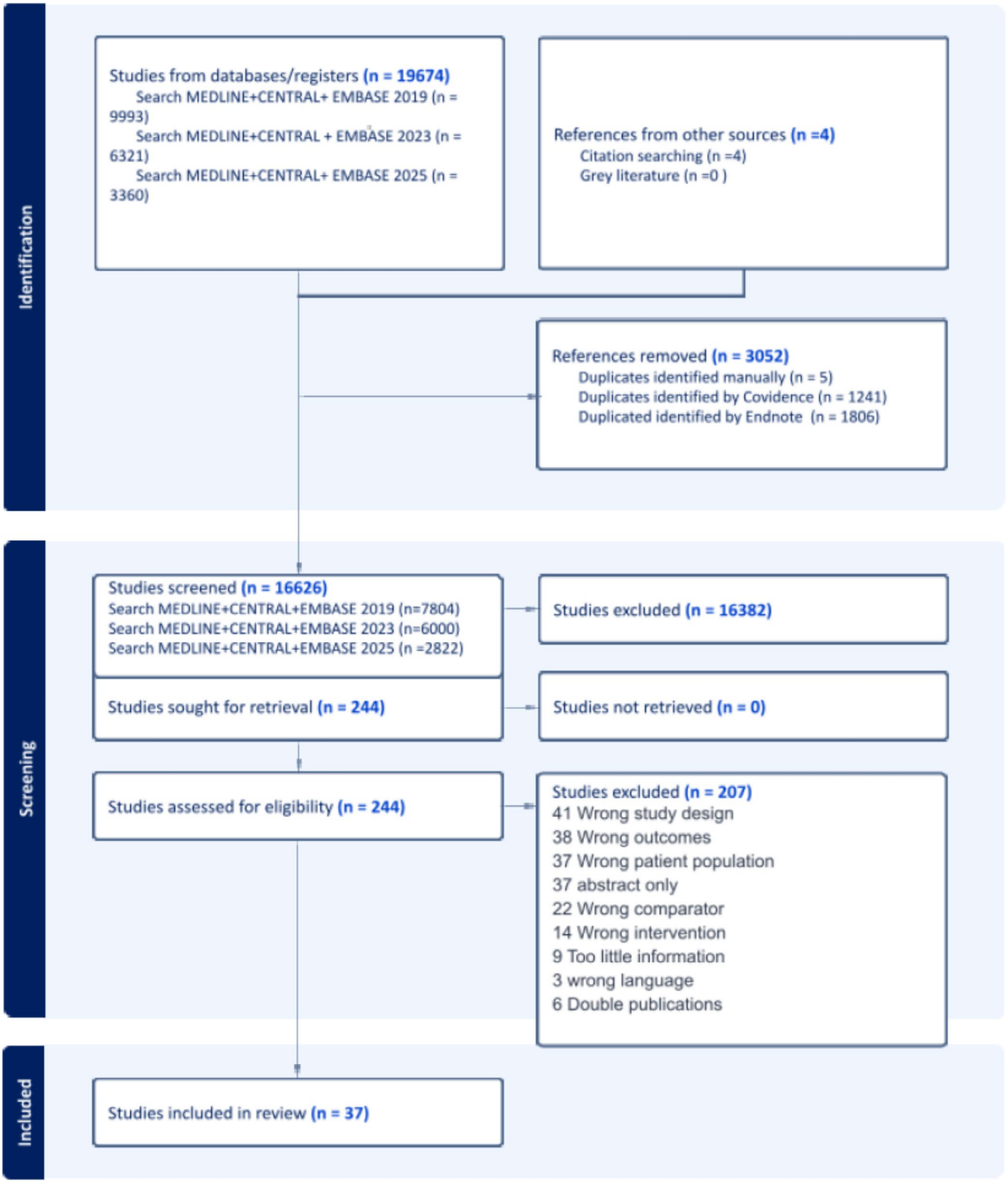

FIGURE 1 | Study selection flow chart. PRISMA flow chart on study identification and selection process.

cardiovascular problems [41, 42, 46, 48, 49, 51, 53, 56–58, 60] and analysis showed a significant risk increase in patients on sGCS compared to placebo or SOC (OR 1.53, 95% CI 1.25–1.87) (Figure S1). Five studies showed a significantly increased risk for acute myocardial infarction (AMI) in patients treated with sGCS (OR 1.30, 95% CI 1.19–1.42) [47, 53, 58, 60, 62] and five studies demonstrated an increased risk for arterial hypertension (OR 1.26, 95% CI 1.04–1.52) [53, 56, 58–62]. No significant differences were found for dyslipidemia [53, 56, 58–62] and stroke [47, 53, 58–60, 62] (Figure S1).

Regarding bone metabolism, analysis of 16 studies in asthma and UAWD patients showed a significantly increased risk for developing osteoporosis in patients exposed to sGCS (OR 1.36,

TABLE 1 | Summary of studies reporting on immediate AEs linked to sGCS use.

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Berthon et al. 2015	Asthma	Double-blinded, placebo-controlled RCT	Total number of participants randomized ($N = 60$). Total number of participants included in analysis ($N = 55$). Alternating treatment with OCS (prednisolone 50 mg) or placebo	Cross-over trial of 10 days prednisolone (50 mg) in adults with stable asthma Duration: ±48 days: 2 × 10 days treatment and wash-out 4 weeks Co-intervention: ICS: 78% of participants, mean (SD) 1025 (738) mcg/day	To determine whether 10-day OCS therapy in adults with asthma causes changes in leptin, appetite, dietary intake, body weight and body composition FU: 48 days	Adverse effects were assessed by questionnaires. Body composition was measured by dual-energy X-ray absorptiometry and bioelectrical impedance analysis, appetite mea-sured using a validated VAS and dietary intake assessed using 4-day food records. Leptin was measured as a biomarker of appetite	Short-term OCS in stable asthma did not induce significant changes in appetite, dietary intake, body weight or composition. Symptoms of sleep disturbances and gastrointestinal disturbance were reported significantly more often during prednisolone vs. placebo
Brown et al. 2002	Asthma	Prospective Cohort study	32 participants Age range 18–65	Oral prednisone course with an initial dose of at least 40 mg daily and a total duration of at least 7 days. Subjects scheduled to receive either abrupt steroid discontinuation or gradual tapers of steroids were included. ($N = 32$) Co-intervention: ICS 27/32, no dosages reported	To study sychiatric side effects of prednisone therapy FU: until 2 weeks after OCS completion	Assessed using Hamilton Rating Scale for Depression (HAM-D), Young Mania Scale (YMS), Brief Psychiatric Rating Scale (BPRS), and Internal State Scale (ISS)	Significant increases in mania observed during therapy (YMS score increased from 2.8 to 4.8, $p = 0.0054$) during the first 3 to 7 days of prednisone therapy. No increase in depression measures were seen during this period. In subjects with a history of depression, depressive symptoms decreased during treatment. All mood symptoms returned to baseline after discontinuation

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Chang et al. 2021	CRSsNP	RCT	81 participants (72 analyzed at 6 months) with clinician-diagnosed CRSsNP undergoing ESS Mean age (SD) of the overall population was 49.4 (14.9)	Post-operative oral prednisone 30 mg, 20 mg, 10 mg; each dose for 4 days ($n = 34$) vs. post-operative oral placebo ($n = 28$) for 12 days Co-intervention: ICS not reported	Effect of surgery on quality of life (SNOT-22) and Lund Kennedy endoscopy score FU: 6 months	Adverse events were assessed in both groups by means of an itemized questionnaire completed by patients to assess for symptoms potentially related to SCS adverse effects	1 month post-operatively there were no statistically significant differences between groups for all 14 symptoms; appetite, weight gain, gastrointestinal discomfort, mood swings, aggression, muscle weakness, blurred vision, worsened DM II, high blood pressure, nervousness, sleeping difficulty, water retention, easy bruising, Headache. *p*-value not reported
Hissaria et al. 2006	CRSwNP	RCT	41 Participants With symptomatic endoscopically diagnosed sinonasal polyposis Mean age (SD) for the treatment group was 49 (13). Mean age (SD) for the placebo group was 48 (12)	50 mg/d p.o. prednisolone ($n = 20$) vs. Placebo ($n = 20$) For 14 days Co-intervention: No ICS in both groups	Effect of prednisolone on the reduction in NP size on nasendoscopy & MRI and the reduction of symptom scores FU 2 weeks	Adverse effects in both groups were self-reported at study exit visit	At the end of a 14 days treatment, patients on GCS reported significantly more insomnia ($n = 8$) compared to placebo ($n = 2$; $p < 0.05$). No significant differences were demonstrated for the other AEs (mood disturbances, appetite, dyspepsia, acne, headache, fatigure, backache, feet oedema)

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Howland et al. 1996	AR	Double-blinded, placebo-controlled RCT	64 AR patients with a positive history confirmed by a positive skin prick test to seasonal or perennial allergens present in the patient's environment. Mean age: 33 years (19–50 years)	Oral prednisone 10 mg/d ($n = 16$) vs. Triamcinolone acetonide aqueous nasal spray 220 μg/d and 440 μg/d ($n = 32$) vs. Placebo ($n = 16$) for 6 weeks Co-intervention: No ICS in both groups	To study the effects of oral prednisolone and triamcinolone nasal spray on the adrenocortical function FU 6 weeks	Adrenocortical function was tested by using the cosyntropin stimulation test at baseline and after 6 weeks of treatment. The frequency and severity of AEs of the study treatments were recorded by each patient on diary cards. AEs were assessed by site investigators at patient interviews performed at the end of weeks 3 and 6 of the study	Prednisone produced statistically significant ($p < 0.001$) reductions in adrenocortical function compared with placebo. Reductions occurred in both the mean 6-h plasma cortisol levels and mean change in 6-h plasma cortisol levels from pretreatment Urinary free cortisol posttreatment was significantly higher for the OCS cohort compared to placebo: compared to placebo. The most frequently observed AE was headache, which occurred in 25.0% of patients who received placebo and 37.5% of those who received prednisone. No deaths, serious adverse clinical events, or clinically significant changes in physical examination results were noted during the study. No clinically significant laboratory abnormalities related to study medication were observed

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Karaki et al. 2013	Allergic Rhinitis	Non-randomized controlled interventional study	75 patients Mean (SD) age for the oral steroid group was 36.8 (12.5). Mean (SD) age for the nasal steroid group was 40.2 (16.2) Mean (SD) age for the non-steroid group was 38.1 (8.5)	Mometasone furoate NS + loratadine ($N = 25$) vs. Betamethasone p.o. + loratadine ($N = 23$) vs. Loratadine ($N = 24$) For 7 days FU 7 days Co-intervention: ICS not reported.	Reduction in nasal symptoms: sneezing, itching, discharge, obstruction	Adverse effects were self-reported, recorded in allergy diaries. Included stomachaches, sleepiness, hypersensitivity, and headaches	After 7 days, the oral corticosteroid group reported mild adverse events (e.g., stomachache, headache) with no major adverse events observed. The incidence of adverse events was lower in the nasal spray group (7.24%) compared to the oral corticosteroid group (exact % not specified). No statistics performed
Levy et al. 1996	Asthma	Double blind placebo controlled RCT	413 Adult asthmatic patients who presented with a mild exacerbation of asthma which, in the clinician's opinion was not considered severe enough to necessitate admission to hospital but which did require treatment with short course of oral corticosteroid. Mean age (SD) for the oral prednisolone group was 42 (15). Mean age (SD) for the fluticasone proprionate group was 43 (15)	Oral prednisolone for 16 days: starting at 40 mg and reducing by 5 mg every two days ($n = 207$ with 203 analyzed) vs. Fluticasone proprionate inhaler 2 mg/d ($n = 206$ with 200 analyzed) Co-intervention: All ICS were continued, but no dosages reported	To study whether a high dose of inhaled fluticasone propionate could be as effective as a short course of oral corticosteroid in the treatment of acute ex-acerbations of asthma which were not considered severe enough to necessitate admission to hospital. FU 16 days	At each visit (every 2 days during the first week and at 16 day) the physician recorded AEs	44% of patients in both treatment groups reported minor AEs, most of them being related to the digestive, nervous or respiratory systems. No difference between OCS and fluticasone inhaler was demonstrated, no comparison with placebo is mentioned

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
McNamara et al. 1993	Asthma	Single-blind, placebo-controlled RCT	70 asthma patients with acute exacerbations (peak expiratory flow rate measurement of 300 L/rain or less) and were judged by their treating physician to be sufficientlyimproved for discharge home were randomized, 56 included in analysis. Patients were approached for the study only after completion of their ED therapy Mean (SD) age SCS group: 27.9 (7.5) Mean (SD) age Placebo group: 30.1 (7.9)	Either an IM injection of 240 mg methylprednisolone acetate suspension vs. IM injection of saline as placebo Co-intervention: OCS group: ICS at discharge 6.7%, non-OCS group: ICS at discharge 7.7%	The main outcome measure of the study was relapse, defined as the need to seek nonroutine medical care for symptoms of asthma within seven days of study entry. For patients who did not return to the ED for this care, the treating facility or physician was contacted to verify that the visit was not of a routine nature. FU 7 days	At the time of follow-up, the patients were asked a series of questions about medication side effects	The reported side effects were similar between groups with one or more side effects reported by eight (27%) patients in the steroid group and 12 (46%) in the placebo group. The most common side effects reported in the steroid group were muscle pain in six (20%) and abdominal pain and nausea in four (13.3%) each. Muscle pain was also reported by six (23%) of the placebo group, whereas four (15%) had nausea, and there were three (11%) reports each of headache, irritability, and abdominal pain
Vaidyanathan et al. 2011	CRSwNP	RCT	60 participants With symptomatic endoscopically diagnosed bilateral moderate to large-sized NP. Mean age for the prednisolone group was 49 (24–70) years. Mean age for the prednisolone group was 52 (17–78) years.	Prednisolone p.o. 25 mg/d ($N = 30$) vs. Placebo ($N = 30$) For 2 weeks Co-intervention: ICS not reported	Reduction in NP size on nasendoscopy FU 28 weeks	Adverse effects assessed in both groups at baseline, week 2 and week 10 by means of: -laboratory analysis of bone turnover markers and adrenal function (urinary cortisol levels, serum cortisol, ACTH-stimulated cortisol) -measurement of FBG, BP and body weight - subjective reporting of other symptoms	After 2 weeks of prednisolone, transient adrenal suppression was observed, with overnight urinary cortisol dropping to 50% of baseline ($p < 0.001$) and ACTH-stimulated serum cortisol decreasing by 86% ($p < 0.001$). Increased bone turnover markers indicated transient bone activity changes, which returned to baseline by week 10 and were not significantly different at 28 weeks. No serious or lasting adverse effects were reported

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Van den Berge et al. 2009	Asthma	RCT	130 participants (127 analyzed) with a documented diagnosis of asthma with 'worsening of asthma' as measured by three predefined criteria Mean age (SD) of prednisolone group was 45 (12.9) years. Mean age (SD) of ciclesonide group was 45 (13.3) years	40 mg/day oral prednisone ($n = 62$) vs. Inhaled ciclesonide (800 mcg twice daily) ($n = 65$) For 14 days Co-intervention: Dose of ICS (μg/day): 1000 (range 800–2000)	Morning Peak expiratory Flow score FU 2 weeks	Secondary outcome: adverse events assessed in both groups by means of a question asked each visit by a research physician. Adrenal suppression was assessed by means of serum cortisol measurement	After 14 days of treatment morning serum cortisol levels were significantly reduced with oral prednisolone (mean reduction in serum cortisol: 67.3 nmol/L for ciclesonide and 338.5 nmol/L for prednisolone; $p < 0.0001$) compared to inhaled ciclesonide. For other adverse events (only reported if occurring in ≥ 3 patients during treatment) no differences were seen between groups (palpitations, nasopharyngitis, blood leucocytosis, headache, asthma aggravated, dyspnea)
Vargas et al. 1998	Allergic Rhinitis	RCT	105 patients with seasonal or perennial allergic rhinitis were randomized. Total number of patients included in analysis = 102. No differences between age groups from 29.7 (placebo) to 35.1 (prednisone 7.5)	Fluticasone propionate aqueous nasal spray (FP ANS) versus oral prednisone. —Prednisone 7.5 mg ($N = 20$)—Prednisone 15 mg ($N = 21$) - FP ANS 200 ($N = 20$) - FP ANS 400 ($N = 23$) - Placebo ($N = 21$) Duration: 28–30 days Co-intervention: ICS not reported	Safety evaluation of FP ANS by comparing its effects on the HPA axis with those of oral prednisone FU 51 days	Evaluation HPA axis by using the 6-h cosyntropin test	4 weeks of treatment with oral pred-nisone 7.5 or 15 mg once daily was associated with significant ($p < 0.05$ vs. placebo) reduction in HPA-axis function, as evi-denced by lower plasma cortisol concentrations after cosyntropin stimulation and reduced mean 24-h urinary cortisol excretion. Prednisone regimen was associated with a significant reduction in mean morning plasma cortisol concentrations compared to placebo ($p < 0.05$)

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Venekamp et al. 2012	Acute rhinosinusitis	Randomized Double Blind RCT	185 patients enrolled. 93 in SCS group (of which 88 included in analysis) and 92 in placebo group (of which 86 included in analysis) Age: for entire set of enrolled patients: Mean (SD) age SCS group: 43.9 (13.6) years. Mean (SD) age placebo group: 42.4 (13.7)	Either pred-nisolone 30 mg/d or placebo for 7 days Co-intervention: ICS not reported	The primary outcome measure was theproportion of patients with resolution of facial pain or pressure on day 7. FU 3 weeks	Adverse events reported by participants	Adverse events reported by participants were mild and did not differ between the groups. Not a single AE differed significantly between groups (gastric complaint, diarrhea, increased appetite, mood disturbance, sleep disturbance). Not in the first nor in the second week of follow-up
Xu et al. 2020	CRSwNP	RCT	127 patients with CRSwNP No differences between age groups: Oral methylprednisolone: 44.13 (12.03) Nasal drops: 48.06 (12.96) Nasal spray: 44.89 (14.67)	256 mg/day Budesonide NS ($N = 39$) vs. 256 mg/day Budesonide NS+ 1 mg/day Budesonide ND ($N = 38$) vs. 256 mg/day Budesonide NS + 24 mg/d methylprednisolone p.o. ($N = 40$) Co-intervention: ICS not reported	Reduction in Total Nasal Symptom Score (TNSS) and Sinonasal Outcome Test-22 (SNOT-22) FU 2 weeks	Adverse effects were self-reported, recorded by clinicians, including gastrointestinal discomfort, sleep disturbances, and skin rash	At the end of a 7-day treatment, patients in the oral steroid group reported significantly more adverse effects (6/40, 15%) compared to the nasal spray group (0/39; $p = 0.026$). Specific adverse events in the oral steroid group included headaches, gastrointestinal discomfort, and sleep disorders

(Continues)

TABLE 1 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Zhang et al. 2019	CRSwNP	RCT	Total number of participants rN = 91 patients of eosinophilic CRSwNP randomized 85 were included in analysis. Mean (SD) age OCS group: 43.42 (SD 12.22) Mean (SD) age nebulization group: 42.33 (SD 10.40) Mean (SD) age nasal spray group: 43.14 (SD 11.00)	Either oral methylprednisolone 24 mg once a day ($n = 26$) vs. budesonide inhalation suspension (BIS) via transnasal nebulization 1 mg/2 mL ($n = 30$) vs. budesonide nasal spray (BNS) (256 μg BID) for 2 weeks ($n = 29$) Co-intervention: ICS not reported	To compare the efficacy and safety of BIS administered via transnasal nebulization with budesonide nasal spray (BNS) and oral steroids in the management of patients with ECRSwNP. FU 2 weeks	Adrenal function was determined on the basis of changes in morning serum cortisol levels. The incidence of adverse events (AEs) experienced by individual patients was also recorded	Post-treatment serum morning cortisol levels were significantly decreased by oral methylprednisolone compared to BIS or BNS, which did not significantly alter the cortisol levels - Only 12.9% (4/31) patients in the OCS group demonstrated AEs, with 2 patients experiencing elevated blood glucose, 1 patient reporting hip pain and 1 patient reporting gastralgia. No AEs were reported in either group BIS or BNS during the study

95% CI 1.15–1.62) [40, 45, 47–50, 52–56, 58–62] (Figure S2). Additionally, the risk of bone fractures was significantly higher in patients using sGCS compared to non-sGCS users (OR 1.48, 95% CI 1.31–1.67) as documented in ten studies [42, 44, 45, 48, 51, 53, 56, 58, 60, 61] (Figure S2).

Regarding gastro-intestinal AEs, four studies showed a significant increase in dyspepsia in asthma patients that received sGCS (OR 2.68, 95% CI 1.13–6.36) [42, 56, 60, 62]. For peptic ulcers, seven studies (six in asthma [49, 53, 58, 60–62], one in CRSwNP [48]) showed that patients using sGCS have a significantly increased risk of developing peptic ulcers compared to no sGCS use (OR 1.28, 95% CI 1.15–1.41) (Figure S3).

Concerning ophthalmological complications, eight studies in asthmatics looked into the incidence of cataract [49, 53, 58, 60, 61, 62], while six of them reported also on glaucoma [49, 53, 58, 60, 61, 62]. Our analysis showed a significantly increased risk of developing cataract in patients on sGCS (OR 1.18, 95% CI 1.05–1.32), while the sGCS-related risk increase for glaucoma was not significant (OR 1.13, 95% CI 0.96–1.32) (Figure S4).

Eight studies in asthma patients were included in the meta-analysis on diabetes [42, 47, 50, 51, 56, 60–62], showing a significantly increased risk in patients that received sGCS (OR 1.20, 95% CI 1.08–1.33) (Figure S5). Five studies in asthmatics [49, 50, 53, 60, 62] and one study in CRSwNP [48] reported on pneumonia, showing a significantly higher risk in patients receiving sGCS than those who did not (OR 2.14, 95% CI 1.56–2.94) (Figure S5). Regarding psychological impact, we included six studies in asthmatics that reported on the occurrence of anxiety and depression [42, 51, 57, 58, 60, 62] and demonstrated a significantly increased risk in the sGCS group compared to no sGCS (OR 1.35, 95% CI 1.17–1.55) (Figure S5). Lastly, three studies also reported on sleep disorders (sleep apnoea/insomnia) [49, 56, 60], finding an increased risk in asthma patients that were treated with sGCS (OR 1.49, 95% CI 1.26–1.75) (Figure S5). Figure 3 depicts the summary of the results of the meta-analyses on the delayed AEs related to sGCS use.

3.2.1.2.2 | Narrative Synthesis. Eight studies looked at the occurrence of 'any sGCS-related AE' as a separate outcome and each of them showed a significant increase in this risk, both in asthma [46, 49, 51, 54, 55, 61, 62] and CRSwNP patients [48]. Because the types of AEs investigated were not consistent across studies, no meta-analysis was carried out.

Three studies also looked into the occurrence of osteopenia, but because of different read-out measures, could not be included in the meta-analysis. The studies by Barry and Li both identified a significantly higher level of osteopenia in patients on high dose of sGCS compared to no sGCS [42, 52]. Sweeney et al. confirmed this finding, but only in one out of two analyzed databases [56].

Four studies reported on the risk for developing 'infections' that were not specified as pneumonia and were addressed as either 'acute infections' [51, 60], 'severe infections' [43] or 'respiratory tract infections' [40]. The first three studies were in asthmatics and found a significantly higher occurrence in patients in

TABLE 2 | Summary of studies used for the analysis of delayed AEs linked to sGCS use.

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Aasbjerg et al. 2013	Allergic rhinitis	Retrospective Cohort	47,382 individuals with allergic rhinitis who completed the inclusion creteria Age range 18–45	≥1 Depot-steroid inj/y for three consecutive years ($N=26,428$) vs. immunotherapy ($N=17,798$) vs. immunotherapie + ≥1 Depot-steroid inj/y for three consecutive years ($N=3156$) Co-intervention: ICS not reported	Risk for developing diabetes and osteoporosis FU: Study period 1995–2011, with at least 3 years of continuous data on steroid injections	AEs assessed in the three groups included diabetes based on first prescription for diabetes, osteoporosis, respiratory tract infections and tendon rupture based on ICD codes.	In the depot-steroid treatment, patients showed a significantly increased risk of diabetes (RR = 1.5, 95% CI 1.3–1.8; $p<0.001$) and osteoporosis (RR = 1.2, 95% CI 1.0–1.5; $p=0.023$) compared to immunotherapy. No significant differences were observed for other side effects, including respiratory tract infections or tendon rupture
Ayodele et al. 2022	Asthma	Nested Case–Control	437,842 asthma patients aged 20–59 years	Systemic Glucocorticoid ($N=452$) vs. Inhaled glucocorticoids ($N=3329$) vs. Unexposed ($N=4724$) Co-intervention: ICS not reported	Risk of venous thromboembolism (VTE) FU: Patient study period between January 1, 1995, and December 31, 2015 (at least one steroid prescription) until time of AE	Assessed through conditional logistic regression	Current systemic glucocorticoid use significantly increases VTE risk (aOR = 3.5, 95% CI: 2.7–4.5) compared to unexposed and inhaled glucocorticoid use (aOR = 1.5, 95% CI: 1.3–1.8)
Barry et al. 2018	**Asthma**	Retrospective, matched patient cohort study	Total of patients randomized ($n=7195$) (1) Severe asthma group (High OCS exposure) ($n=808$) (2) Mild/moderate asthma group (Low OCS exposure) ($n=3975$) (3) Non-asthma group (no OCS exposure) ($n=2412$) Mean (SD) age Severe asthma: 59 years ±17 (95% CI 26–91) Mean (SD) age Mild asthma: 58 years ±16 (95% CI 26–90) Mean (SD) age Nonasthma: 58 years ±17 (95% CI 25–91)	High dose OCS exposure: >/=4 prescriptions for OCSs in each of 2 consecutive study years. Dosage intervention not reported for low or no OCS exposure Co-intervention: Baseline high OCS: Inhaled beclometasone diproprionate μg equivalence, mean ± SD: 1411 ± 846 ($n=738$), baseline low OCS: Inhaled beclometasone diproprionate μg equivalence, mean ± SD: 499 ± 323 ($n=3898$)	Explore associations between age, sex, comorbidity, and patterns of health care cost across groups differentiated by corticosteroid exposure. 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 FU: data were extracted between 2008 and 2013: At least 2 years of continuous medical records	Read codes in the data from the OPCRD	Younger subjects with severe asthma and high OCS exposure had greater odds of a number of recognized corticosteroid induced morbidities (osteopenia, osteoporosis, glaucoma, dyspeptic dis-orders, CKD, cardiovascular disease, cataracts, hypertension, andobesity) 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 ($p<0.01$), compared with age-matched subjects with mild/moderate asthma and low OCS exposure. Many corticosteroid-induced comorbidities have differential sex prevalence

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Bloechliger et al. 2018	**Asthma**	11 cohort analyses to assess incidence rates, followed by a series of 11 nested case–control analyses	Between 165,900 and 269,368 asthma patients were included in each of the 11 cohorts, of whom between 836 and 16,192 developed an outcome of interest Ever users: >=1 oral prednisolone prescription recorded at any time before the index date. Further categorized ever users into current, recent or past users. Sub-classified current oral prednisolone by cumulative dose prescribed before the index date, and average daily dose ever	Prednisolone: Dosage unclear for past and recent use, clear for current use (</=1 mg, >1–5 mg, >5 mg) vs. no oral prednisolone prior to the index date Co-intervention: *Cases*: 69%–76% ICS use, ICS + LABA 30%–38%; *Controls*: 73%–77% ICS use, ICS + LABA 27%–33%	To examine the risk of adverse events of oral prednisolone among adult asthma patients FU Between Jan 2000 and December 2015 cohort entry depending on asthma diagnosis timing, until the first record of an outcome of interest, death, loss to follow-up, the end of the study period	To evaluate the adverse events profile of oral prednisolone among adult asthma patients in the UK	Incidence rates per 1000 person-years of potential corticosteroid-related adverse events in patients with new current use of oral prednisolone ranged from 1.4 (95% confidence interval [CI], 1.0–1.8) for peptic ulcer to 78.0 (95% CI, 74.8–81.2) for severe infections. After adjusting for confounding, current oral prednisolone use was most strongly associated with an increased risk of severe infection, compared with non-use of prednisolone; OR 2.16 (95% CI, 2.05–2.27). There were smaller elevated risks of peptic ulcer, affective disorders, and cataract at higher doses, and marginally increased risks of herpes zoster, cardiovascular events, diabetes mellitus type 2, and bone related conditions, compared with non-use of prednisolone. We did not observe an association between oral prednisolone use and glaucoma, chronic kidney disease, or hypertension
Chalitsios et al. 2021	Asthma	Nested Case–Control	69,074 individuals with asthma Osteoporosis: $N=1564$ patients with asthma and osteoporosis and 3313 control subjects Fractures: $N=2131$ patients with asthma and fractures and 4421 control subjects Ages 18+	Oral Corticosteroids (OCS) vs. Inhaled Corticosteroids (ICS) vs. no OCS use Co-intervention: Cumulative dose before index date, *Cases* (mg) <40 13.4%, 41–80 14.8%, 81–120 11.5%, >120 23.7%; *controls (mg)* <40 13.1%, 41–80 10.1%, 81–120 8.5%, >120 14.7%	To study the risk of osteoporosis and fragility fractures related to OCS and ICS use FU: Between 1 April 2004–31 December 2017 patients were identified with an asthma diagnosis. FU until index date	Assessed through cumulative dose and number of corticosteroid prescriptions (OCS and ICS) using linked clinical data	OCS users with ≥9 prescriptions had a 4.50 times higher risk of osteoporosis (95% CI 3.21–6.11) and a 2.16 times higher risk of fragility fracture (95% CI 1.56–3.32). Higher ICS use also increased risk, though to a lesser extent (OR for ≥11 prescriptions: 1.60 for osteoporosis, 1.31 for fragility fracture)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Chang et al. 2024	Asthma	Cohort study	Korean adult asthma patients on ICS divided as OCS users (who initially used OCS more than once within 1 year from the first OCS prescription $n = 1593$) or only ICS users (who initially used ICS more than once within 1 year from the first ICS prescription $n = 3705$)	High-dose OCS group patients received the dose of OCS above the mean cumulative dose of OCS (> 904.1 mg/year) for 5 years vs. low-dose OCS group who received a dose below the OCS mean (< 904.1 mg/year) for 5 years. All OCS were recalculated as equivalent to prednisolone Co-intervention: ICS dose: average of 223.4 mg/y	To evaluate the long-term effect of ICS/OCS on osteoporosis, osteopenia, fractures, and bone metabolism in asthma patients in a real-world setting. FU until index date and 5 years after index date	Through OMOP disease Codes for osteoporosis, osteopenia and fractures. The major fracture outcomes included closed fractures of the vertebral column, pelvis, humerus, hip, forearm, and femur. Any fractures included all the closed and pathological fractures due to osteoporosis	The risk of osteoporosis/major fracture was higher (HR [95% CI], 2.00 [1.15–3.57]/3.03 [1.04–11.11]) in the high-dose OCS group (especially in females aged > 50 years) than in the low-dose OCS group
Dalal et al. 2016	Asthma	Cohort study	The matched asthma population included 12,697 SCS users and 12,697 SCS nonusers	SCS users were required to have ≥ 6 months of continuous chronic SCS use identified by claims with daily doses of at least 5 mg prednisone equivalent with no gap of ≥ 14 days between 2 SCS claims vs. No SCS use Co-intervention: ICS not reported	The risk of developing acute and chronic SCS-related complications and associated health care resource utilization and costs. FU: Study period between 2003 and 2014: from the index date to the earliest of disenrollment from health plan or data cutoff. The mean follow-up period duration for the * SCS Users group was 2.0 ± 1.9 years and for the *SCS Nonusers 1.1 ± 0.9 [1.1] years	ICD-9 codes for SCS-related complications and GPI (General Product Identifier) codes to identify medications used for SCS-related complications	The odds of developing associated complications increased significantly in a dose-dependent manner with systemic corticosteroid exposure: odds ratios were 2.50, 2.95, and 3.32 (p values < 0.05) for low (defined as < 5 mg/day), medium (≥ 5–10 mg/day), and high (> 10 mg/day) exposure, respectively, relative to no exposure (For individual outcomes: see paper)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Daugherty et al. 2018	Asthma	Cohort study	SCS arm: 35424 patients No SCS arm: 24994 patients Mean (SD) age in SCS arm: 54.77 (17.6) Mean (SD) age in non-SCS arm: 51.50 (18.7)	Prednisolone equivalent. Most patients were exposed to an average cumulative dosage of > 0– < 2.5 mg/day. Only 3%–4% of patients average cumulative dose > 2.5 mg/day. Co-intervention: ICS not reported	Incidence rate of AEs during the observation phase, the risk (HR) of SCS-related AEs and the dose-related risk of SCS-related AEs compared with non-SCS use FU: between Jan 2004 and March 2012 patients identified with asthma, FU until index date or end of study period, so variable time	An incident diagnosis of an AE was determined from patient medical records (CPRD database: read codes; HES database: ICD-10 codes)	The most frequent SCS-related AE during the observation phase was cataracts (1.26 events/1000 pt-[28 day]periods), followed by osteoporosis (1.13 events per 1000 pt-periods) and diabetes (1.04 per 1000 person-periods). The risk of diabetes (HR: 1.20 [95% CI: 1.11, 1.30]), MI (HR: 1.25 [95% CI: 1.09, 1.43]) and osteoporosis (HR: 1.64 [95% CI: 1.51, 1.78]) was increased at low SGC doses (0–2.5 mg/day), with further risk increases at doses > 2.5 mg/day versus no SGC use. Risk of cataracts was significantly increased with average daily doses > 2.5 mg/d, but not lower doses. Compared with no SGC use, SGC increased the risk of peptic ulcer in a non-dose-dependent manner, but the risk of stroke was unchanged
Davis et al. 2022	Retrospective observational cohort study from US database (Market Scan database)	CRSwNP	44.772 adult CRSWNP patients were included, defined as having either at least one claim (ICD-9-CM 471.0 and 471.9 or ICD-10-CM J33.0 and J33.9) from an allergist or otolaryngologist or at least two claims at different service dates from any other provider type. 33% had asthma. 37,740 were included in the SCS cohort, 7032 in the no SCS cohort Mean age of 48.1 for SCS cohort and 47.9 for the non SCS cohort	Outpatient prescription claim for an SCS or a medical claim for a physician-administered SCS within 1 year before or after the earliest NP diagnosis. The 12 months before the index date, and the follow-up period was of variable length (min 12 month), beginning at the index date and ending at the earlier of the end of continuous enrollment or of the end of the study period end of June 2019. Classified as 1–3/year (mean cumulative dose of 401 mg or 1.1 mg/d = very low daily and cumulative dose) or ≥ 4 claims/year (mean cumulative dose of 1087 mg or 3 mg/d = low daily and cumulative dose). Co-intervention: ICS not reported	Incidence of systemic GCS-related AEs during the follow-up period. FU follow-up period was of variable length (minimum of 12 months and maximum 16 years), beginning at the index date (starting from 2003) and ending at the earlier of the end of continuous enrollment or of the end of the study period (June 30, 2019)	An AE was identified by the presence of one or more claims with International Classification of Diseases codes ICD-9-CM and ICD-10-CM	SCS-users had a greater risk for any adverse outcome than controls (IRR = 1.10; 95% CI 1.05–1.16). For the following specific adverse events, IRRs with significantly higher among all SCS users vs. controls: anxiety and depression, fracture, hypertension, obesity, pneumonia and sleep apnoea

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Heatley et al. 2023	Asthma	Retrospective, observational, matched-cohort study from UK databases (OPCRD and PCRD)	952.334 patients (476.167 asthmatic in the OCS group and 476.167 matched astmatic and non-asthmatics in the Non-OCS group) Mean age for both groups = 38.1 years	Intermittent courses of any OCS classified according to frequency of prescriptions (all OCS were converted into prednisolone equivalents using the DDD) Co-intervention: ICS not reported	To assess the association between longitudinal patterns of intermittent OCS prescriptions, cumulative OCS dosages and OCS-related adverse outcomes FU: Study period between 2008 and 2019, median FU (IQR) was 8.3 (4.2–13.7) years for the OCS cohort and 9.0 (4.7–14.7) years for the non-OCS cohort; length of time in database preindex was 17.0 (7.5–31.1) and 16.8 (7.8–30.4) years, respectively	Adverse outcomes were defined according to International Classification of Diseases codes for diagnosis and—for some adverse outcomes—other criteria, such as disease-specific medication prescription and/or physiological biomarkers	Risk of any adverse outcome increased with increasingly frequent patterns of intermittent OCS versus non-OCS (HR; 95% CI: one-off 1.19 (1.18–1.20), less frequent 1.35 (1.34–1.36), frequent 1.42 (1.42–1.43)), and was consistent across age, GINA treatment step and ICS and SABA subgroups. The highest risks of individual OCS-related adverse outcomes with increasingly frequent OCS were for pneumonia and sleep apnoea
Kankaanranta et al. 2024	Asthma	Retrospective cross-sectional cohort study	193,730 Finnish asthma patients were included. Asthma was defined as continuously or transiently severe (13.7%) or non-severe (86.3%) based on annual dispensed ICS, OCS, and hospitalizations. 91.7% of patients were dispensed ICS and 54.7% were dispensed OCS at some point of the 1 year follow-up.	OCS use was classified based on annual use: 1–300 mg/year. 301-600 mg/year. 601-1200 mg/year. > 1200 mg/year. Co-intervention: ICS use ranged from 100 to > 1000 mg/day	To analyze the comorbidity burden in patients with severe asthma compared with non- severe asthma and investigated the role of corticosteroid use on the risk of comorbidities. FU: Any asthma diagnosis between Jan 2014-Dec 2017, FU until Dec 2018 for every patient	Comorbid conditions were based on International Classification of Diseases codes –10 codes	Excess prevalence of pneumonia was observed in continuously (22%) and transiently severe (14%) asthma patients compared with non-severe patients after adjusting for age and sex. Cataract, osteoporosis, obesity, heart failure, and atrial fibrillation were also more frequent in severe asthma patients. The use of OCS had a dose-dependent effect on the risk of pneumonia, cataract, osteoporosis, heart failure and atrial fibrillation

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Lefebvre et al. 2015	Asthma	Retrospective, open-cohort, observational study	3628 Severe asthma patients with more than 6 months of continuous SCS use Mean age (SD) overall study population 57.6 6 (16.3)	Prednisolone equivalent for at least 6 months High cumulative SCS exposure (daily doses of > 12 mg/d of prednisone equivalent) ($n = 1630$) Medium cumulative SCS exposure (daily doses of > 6–12 mg/d of prednisone equivalent) ($n = 1630$) Low cumulative SCS exposure (daily doses of ≤ 6 mg/d of prednisone equivalent) ($n = 368$) Co-intervention: ICS not reported	The risk of acute and chronic SCS adverse events and associated healthcare resource use and costs The risk of acute and chronic SCS adverse events and associated healthcare resource use and costs FU: study time was different for each US state: Florida (2001–2012), Iowa (1998–2013), Kansas (2001–2013), Missouri (1997–2013), Mississippi (2006–2013), and New Jersey (1997–2013)The mean follow-up period duration for the *low SCS* exposure group was 4.2 ± 3.4 years, for the *medium SCS* exposure group 3.9 ± 3.4 years	Primary outcome: adverse events were identified in both groups by means of ICD-9 diagnosis codes	A significant dose–response relationship was demonstrated between chronic SCS use and risk of SCS-related complications in patients with severe asthma. Patients with medium and high SCS exposure had significantly higher risks of infections, cardiovascular, metabolic, psychiatric, ocular, gastrointestinal, and bone-related complications versus those with low SCS exposure

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Li et al. 2011	Asthma	Retrospective chart review study	57 participants with a diagnosis of current moderate to severe asthma based on Canadian Thoracic Society guidelines and taking a regular minimum dose of 500 mcg/day of inhaled fluticasone propionate or equivalent. The mean age was not different between groups and the overall mean age (mean ± SD) was 50 ± 14.8 years	Group 1: $n = 15$ Daily SCS for ≥ 6 months in the previous year, cumulative SCS dose 12.5 mg/day (SD 9.5) Group 2: $n = 15$ Intermittent SCS with at least one adequate course of prednisone ≥ 40 mg/day for seven days but not exceeding 6 months, cumulative SCS dose 3.2 mg/day (SD 2.4) Group 3: $n = 27$ No SCS, only local corticosteroid Co-intervention: subjects were taking a regular minimum dose of 500 mcg/day of inhaled fluticasone propionate or equivalent	Prevalence and pattern of osteopenia/osteoporosis	Primary outcome: Bone mineral density in both groups was assessed by DEXA-scan results (lowest T-score results used)	Higher frequency of osteopenia/osteoporosis in daily vs. no OCS use ($p = 0.038$) was demonstrated No difference in osteopenia/osteoporosis between daily vs. intermittent use and intermittent vs. no OCS use were seen ($p = 0.46$ and $p = 0.21$ respectively)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Price et al. 2018	Asthma	Retrospective matchedCohort study	48,234 patients (24,117 matched pairs) SCS arm: mean age: 48.7y (SD 16.9) Non-SCS arm: mean age: 43.7y (SD: 18.1)	Any prescription for systemic prednisolone, methylprednisolone, prednisone, betamethasone, dexamethasone, hydrocortisone or cortisone acetate, either as monotherapy or combination therapy (98% oral, 2% parental) vs. No SCS use Co–intervention: *OCS group*: high-dose ics (mean dose > 500 μg/day): 1676 (7%), Fixed dose combination ICS/LABA: ICS daily dose (μg/day) * 0: 8692 (36%) *> 0–400: 12,792 (53%) * > 400–800: 2002 (8%) *> 800: 631 (3%); *No OCS group* high-dose ics (mean dose > 500 μg/day): 1029 (4%), Fixed dose combination ICS/LABA: ICS daily dose (μg/day) * 0: 7109 (30%) *> 0–400: 15,284 (63%) * > 400–800: 1357 (6%) *> 800: 367 (2%)	Impact of initiating SCS, and of SCS exposure, on the onset of known SCS-associated adverse outcomes FU between 1984 and 2017: Minimum FU of 3 years, median follow-up of 7.4 and 6.4 years in SCS and non-SCS arms, respectively	Adverse outcomes were evaluated by means of clinical diagnosis or other indications (medication use, laboratory measurement) specific to each given outcome	Patients in the SCS arm, irrespective of treatment regimen, had a significantly higher incidence of the study outcome compared with the non-SCS arm. Pneumonia had the greatest relative incidence (IRR 2.92). Osteoporosis diagnosis and fracture had the second highest relative incidence (IRR 2.84). The onset of type 2 diabetes was one of the most common adverse outcomes (IRR 1.70). For the SCS arm (vs non-SCS arm) the adjusted risk of the onset of an adverse outcome was significantly greater for 13 of 17 outcomes. The adjusted risk in the SCS arm compared with non-SCS arm ranged from 1.14 times greater for weight gain to 3.11 times greater for new osteoporosis diagnosis/osteoporotic fracture. Positive dose–response relationship was present between categorized, cumulative SCS exposure and adverse outcome in most risk cohorts. The relationship was evident at the lowest exposure categories, with increasing risk of most outcomes evident and becoming statistically significant when progressing from 0.5 to 1 g to a cumulative SCS exposure of 1.0 to < 2.5 g compared with the reference category (> 0 to < 0.5 SCS). A positive dose–response relationship between mean daily SCS exposure and each outcome studied was evident compared with the reference category of > 0 to < 0.5 mg day exposure. For every 5-mg increase in mean daily exposure, the adjusted risk of each outcome increased from 21% to 70%

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Skov et al. 2022	Asthma	Propensity score matched open cohort study	287,113 eligible patients, and 151,760 participants analyzed with > 2 asthma medication collections within 1 year median age in both groups 38 years [30–45]	30.352 all OCS users were classified according to cumulative dosages: Cumulative prednisolone equivalent ≤ 500 mg (low use) (n = 28,791) Cumulative prednisolone equivalent 500–2000 mg (medium use) (n = 10,679) Cumulative prednisolone equivalent > 2000 mg (high-use) (n = 4612) vs. No OCS Control (n = 121,408) Co-intervention: in budesonide equivalents in the year before index date, *OCS group*: No ICS 15.0%, low dose (< 400 mcg/day) ICS 55.7%, medium/high dose (> 400 mcg/day) ICS 29.2%; *no OCS group*: No ICS 14.6%, low dose ICS 55.9%, medium/high dose ICS 29.4%	Incident occurence of specific SCS-related comorbidities FU max 20 years from index dates from Jan 1999, until death, migration, first occurrence of disease commonly treated with OCS or end of study in Dec 2018	Primary outcome: adverse events in both groups identified by first occurence of a hospital-given diagnosis. For some comorbidities identification occured by dispensed prescriptions	OCS-users had, compared to non-users, an increased risk of all Outcomes (Ischemic heart disease, heart failure, peptic ulcer, osteoporosis, fractures, osteonecrosis, depression/anxiety, adrenal insufficiency) with evident dose–response relationships starting at cumulative doses of ≤ 500 mg prednisolone equivalents. The HR of having any SCS-related comorbidity was 1.40 (1.36; 1.45) for all SCS-use; 1.26 (1.21–1.31) for low SCS use, 1.59 (1.50–1.69) for Medium-use and 2.07 (1.92–2.23) for High-use. Hazard ratios for specific adverse events ranged from 1.24 (95% CI 1.18–1.30) for fractures to 8.53 (95% CI 3.97–18.33) for adrenal insufficiency. Depression/anxiety had the highest incidence rate difference at 4.3 (95% CI 3.6–5.0) per 1000 person years. Mortality rates and unscheduled hospital visits increased with increasing OCS exposure
Sullivan et al. 2008	Asthma	Retrospective cohort study	144,126 participants which had a ICD-9 diagnosis of asthma, at least 2 outpatient claims during baseline period Mean age after matching was 38.10 in the no SCS cohort and 38.04 in the SCS cohort	SCS use classified according to yearly prescriptions: SCS use (n = 72,063, high dose: ≥ 4 prescriptions in the current year low dose: 1–3 prescriptions in the current year) vs. no SCS use (n = 72,063) Co-intervention: ICS not reported	Incidence of any of prespecified SCS-related adverse Events FU Study period between 2000 and 2014: minimum 2 years of follow-up. Mean years of follow-up: No OCS cohort: 2.9; OCS cohort: 5.1	Adverse events were identified in both groups by means of ICD-9 diagnosis codes	Subjects taking 4 or more OCS prescriptions within the year had 1.29 (1.04) times the odds of experiencing a new AE within the year. Each year of exposure to 4 or more OCS prescriptions (current and past) resulted in 1.20 times the odds of having an AE in the current year. Exposure to 4 or more prescriptions was associated with significantly greater odds of AEs for osteoporosis, hypertension, obesity, type 2 diabetes, gastrointestinal ulcers/bleeds, fractures, and cataracts (odds, 1.21–1.44 depending on the AE)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Sweeney et al. 2016	Asthma	Cross-sectional Observational Study	7195 participants (808 severe asthmatics, 3975 mild/moderate asthma, 2412 non-asthmatic controls) Mean age (SD) was 58 ± 17 for the overall group. No difference was seen between groups	OCS prescriptions Severe asthma with >=4 prescriptions (medium daily OCS dose of 5 mg) (N = 442) vs. mild/moderate asthma (medium daily OCS dose 0-1 mg) (N = 3975) vs. non-asthmatic controls with No OCS use (N = 2412) Co-intervention: mean beclomethasone dipropionate equivalent dose 2000 mcg, IQR 1200–2000 mcg at initial clinical assessment	Prevalence of corticosteroid-induced morbidities in severe asthma; analyzed using odds ratios FU: Study period 1 April 2011–30 March 2013, cross-sectional design	Adverse effects were evaluated through medical records and questionnaires across two databases (OPCRD and BTS) with specific focus on comorbidities linked to corticosteroid use	At the end of the study period, 93% of patients on systemic corticosteroids had at least one comorbidity linked to OCS use, significantly higher than those with mild/moderate asthma (78%) and non-asthma controls (64%; p < 0.001). Significant differences included higher rates of osteoporosis (16% vs. 4%, p < 0.001), dyspeptic disorders (65% vs. 34%, p < 0.001), and cataracts (9% vs. 5%, p < 0.001). No significant difference in glaucoma (p = 0.58) or hypercholesterolemia (p = 0.21) compared to controls
Taube et al. 2019	Asthma	Cohort study	Total of 8524 asthmatic patients on high dose ICS plus LABA. Mean (SD) age: Total op patients: 61 (49–72)	Prednisolone equivalent Cumulative OCS dose (mg) per patient per year - Prednisolone equivalent cumulative OCS: Long-term > 180 days OCS dose mg/pt/year (N = 1417)—Prednisolone equivalent cumulative: Long-term > 90 to ≤ 180 days OCS dose mg/pt/year (N = 1184)—Prednisolone equivalent cumulative: Long-term > 20 to ≤ 90 days OCS dose mg/pt/year (N = 1871) Co-intervention: all asthma patients included with at least one ICS interval with a mean dosage above the upper threshold according to GINA	Prevalence rates of severe asthma and its OCS-associated comorbidities in patients on high-dosage (HD) inhaled corticosteroid (ICS) in combination with a long-acting β agonist (LABA) therapy were compared with those of patients who were also treated with OCS FU 1 year analysis in 2015. Only those insures who were continuously monitored in 2015 were included. Data from people who died in 2015 were also included if these data covered the previous period accordingly and were complete	Adverse effects were recorded on an outpatient basis (general practitioner (GP) or specialist diagnoses) or on an inpatient basis (discharge diagnoses) using the ICD-10 codes	Disorders of the heart (67.5%), metabolism/nutrition (51.4%), psychiatric disorders (36.0%), skeletal muscle/connective tissue and bone disorders (20.3%), and eye disorders (20.0%) were predominant comorbidities in asthma patients. The prevalence of these disorders increased for patients also receiving OCS therapy, depending on the length of treatment. The number of all OCS-associated comorbidities relative to group size increased from 1.87 to 2.76 with increasing treatment intensity (mean of 2.24)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
To et al. 2021	Retrospective observational Cohort study on a Japanese (MDV) database	Asthma	16.461 adults with at least 1 claim (ICD codes) with a confirmed asthma diagnosis and prescribed at least 1 asthma medication during the 12 months look-back period. There were 2406 patients in the OCS group and 14,055 in the non-OCS group There was a 12-month look-back period and 12 month follow-up period from index date, data were extracted during the study period from April 1, 2014, to March 31, 2018. Average age: 59.43 years	Oral corticosteroid use Patients were categorized in Long-term OCS users: > 180d Middle-term OCS users: 31–179 day Short-term OCS users: 1–30 days (no dosages reported) in the 12 month look-back period vs. no OCS users Co-intervention: ICS use 60%, well balanced across severe asthma/ mild/moderate asthma	To assess the cumulative incidence rate of OCS-related AEs. FU: Study period from April 1, 2014, to March 31, 2018. Twelve months FU period after index date	Claims containing International Classification of Diseases codes ICD 10 were used to identify AEs	Patients with long OCS use in the previous year had higher risks of secondary adrenal insufficiency (0.04% RR long-term vs. non-use: 25.9, 95% CI 5.23–127.80); osteoporosis (1.29% RR long-term vs. non-use: 2.64, 95% CI 1.31–5.30; RR mid-term vs. non-use: 2.22, 95% CI 1.05–4.68) and pneumonia (2.6% RR long-term vs. non-use: 2.09, 95% CI 1.40–3.11; RR mid-term vs. non-use: 2.79, 95% CI 1.78–4.36) in the following year. For the other AEs, differences were not significant between OCS and no OCS users: Myocardial infarction, Hypertension, Stroke, Gastrointestinal bleeding, Fractures, Depression, Sepsis, avascular necrosis, Glaucoma, Cataract et Hyperlipidemia

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Voorham et al. 2019	Asthma	Matched Cohort study	18,826 Asthmatics. (9413 in both SCS-arm and Non-SCS-arm). Ages: only numbers are reported for different age categories between 18 and > 80 years	Overall SCS: Mean average daily dose (mg): > 0– < 0.5: $n = 5152$ 0.5– < 2.5: $n = 3497$ 2.5– < 5.0: $n = 436$ 5.0– < 7.5: $n = 174$ 7.5– < 15.0: $n = 134$ ≥ 15.0: $n = 20$ Co-intervention: *OCS group*: only high-dose ICS (> 500 mcg/day fluticasone equivalent) use in the year prior was reported ($N = 582$, 6.2%). *No OCS group*: Only high-dose ICS use in the year prior was reported ($N = 365$, 3.9%)	Long-term incremental risks of AEs and their associated HCRU and costs for patients with asthma who did and did not initiate SCS. Furthermore, examined how healthcare costs changed over time FU: Study period 1994–2017. Minimum 2-year outcome (follow-up) period, starting from index date	ICD Codes	Regardless of SCS dosage, 15-year cumulative incidence was higher in the SCS arm than in the non-SCS arm (e.g., renal impairment: 27.9% vs. 12.5%; type 2 diabetes: 9.5% vs. 5.6%, respectively). Other adverse outcomes followed a similar trend. Greater SCS dosages were also correlated with greater cumulative incidence. For example, for type 2 diabetes, SCS patients with an average daily dosage of ≥ 7.5 mg had a 15-year cumulative incidence of 37.5%, which was 1.5–5 times greater than that of patients receiving < 0.5 mg/day, 7.0%, 0.5– < 2.5 mg/day (11.3%), 2.5– < 5.0 mg/day (16.3%), and 5.0– < 7.5 mg/day (25.0%)
Wu et al. 2025	Asthma	Retrospective cohort study	Asthmatic patients from which 55,363 were SCS non-users and 75,376 were SCS-users > 18 years of age, mean age was 49.6 years	Cumulative and mean daily exposure in prednisolone-equivalents reported. Patients divided into *high dose* mean cum 1328.9 mg (269.7), daily 38.6 mg (32.3) for mean 46.1 days, *medium dose* (mean cum 667.2 mg (137.6) and 34.4 mg (15.8) daily dose for 20.9 days) and *low dose* (mean cum 226 mg (111.4) and 29.0 mg (14.5) daily for 8.1 days) use within 12 months follow-up Co-intervention: ICS not reported	Incidence rate ratio and numbers of SCS-related predefined AEs. Study divides between acute and chronic AEs within 12 months of follow-up FU Study period spanned from January 1, 2016, through June 30, 2023, variable follow-up depending on index date, minimum of 12 months	ICD-10 code	Significant dose–response association between SCS dose exposure and the risk of AEs, all $p < 0.001$. New-onset SCS-related AEs (including both acute and chronic) were observed in 68.4%, 74.8%, and 76.5% of low-, medium-, and high-dose users, respectively, compared with 46.9% of non-SCS users throughout the first 12 months of follow-up Most prevalent acute AE's were infections (69.1% of SCS users vs. 44.5% of non-SCS users), gastritis/peptic ulcer/GI bleeds/perforations (22.8% vs. 18.6%), and anxiety (21.5% vs. 19.5%) (all $p < 0.001$)

(Continues)

TABLE 2 | (Continued)

Study	Disease studied	Study design	Population	Intervention	Primary study outcome	Assessment of adverse effects	Individual results
Zazzali et al. 2015	Asthma	Matched Cohort	7208 patients with asthma in a commercial health care claims data base Mean age (SD) after matching was 54.4 (12.7)	Oral Corticosteroids ≥30 days/year ($n=3604$) vs. no OCS ($n=3604$) Co-intervention: *OCS group* mean number of ICS canisters filled: 9.2 (SD 9.66); *no OCS group* mean number of ICS canisters filled: 7.0 (SD 7.79)	To study the incremental risk of corticosteroid-related AEs in high OCS users vs. non-users FU a 2-year observation period between 2008 and 2009	ICD-9 codes	High OCS users had a significantly higher prevalence of potential AEs (83.5%) compared to no-OCS users (78.1%), $p<0.001$. Specific AEs included pneumonia (28.4% vs. 10.9%) and diabetes (34.0% vs. 28.4%).
Zeiger et al. 2020	Asthma	Retrospective, observational, matched-cohort study (The MarketScan Commercial Database)	A total of 178.195 individuals were included with ≥1 nondiagnostic claim with a diagnosis of asthma between January 1,2003, and July 31, 2016. 86,786 SCS users and 91,409 non-SCS users were included Mean age of 41 years	≥1 medical or pharmacy claim for a SCS classified as 1–3/year (mean dose of 347 mg/year) or ≥4 claims/year (mean dose of 1110 mg/year) in the first year after the index date. Co-intervention: *OCS group*: ICS 25.9%; *no OCS group*: ICS 25.9%, no dosages reported	Burden of SCS use including AEs and AE-related health care costs FU: study period january 2002 to july 2017 inclusive of 1 year prior to index date and 1 year after index date, 37% 3 years FU of non- OCS group, OCS group 52% 3 years FU, others 2 or 1 year FU	By means of International Classification of Diseases codes ICD-9-CM and ICD-10-CM	In multivariate analysis, the 3-year risk of developing any chronic complication was 6% greater for those with 1–3 claims and 26% greater for those with ≥4 claims compared with non-systemic GCS users ($p<0.001$). Compared with controls, GCS users had significantly greater odds of developing diabetes, hypertension (12% for 1–3 claims and 32% for ≥4 claims), and obesity (35% for 1–3 claims and 70% for ≥4 claims) within 3 years of the index date compared with non-GCS users. For the other AEs (myocardial infarction, stroke, thromboembolism, dyspepsia, peptic ulcers, bone fracture, osteopororis, anxiety and depression, acute infections, sepsis, avascular necrosis, cataract, glaucoma, metabolic syndrome, dyslipidemia, renal disease) no significant differences were seen with the non-GCS group within ≥3 years of the index date

the high dose sGCS group [43, 51, 60], the last included AR patients and found no differences between the different treatment groups [40]. No meta-analysis was performed due to the different definitions of infections.

Two papers reported on a significantly increased incidence of sepsis [58, 62] and adrenal insufficiency [54, 58], and three papers on a significantly increased incidence of avascular necrosis [58, 62] and adrenal insufficiency [54, 58]. Single papers demonstrated significantly higher risks of tendon rupture [40], unspecified musculoskeletal/connective tissue problems [57], and nutritional issues [57]. One observational study in asthmatics found no reports of Cushing in all sGCS groups and controls. The same study also looked into skin problems and reported a significantly increased incidence with higher sGCS dose. One single nested case–control study from the UK found an increased risk of venous thromboembolism in asthma patients receiving sGCS compared to patients without sGCS treatment [41]. One Finnish database study in asthma patients reported on increased risks of heart failure and atrial fibrillation with all OCS dosages [50].

3.2.2 | Secondary Outcomes

3.2.2.1 | Serious AEs. No evaluation of serious AEs could be performed due to lack of reports in the prospective studies and lack of reporting on hospitalization or mortality due to AEs in the retrospective studies. This is explained in detail in the online supplement.

3.2.2.2 | Association Between sGCS Dosages and Adverse Event Risk

3.2.2.2.1 | Dosages Calculated as a Cumulative Dose. Nine retrospective studies reported on various cumulative sGCS dosage groups over longer time-spans; eight in asthmatics [43, 45, 49, 50, 53, 54, 56, 60] and one in CRSwNP patients [48]. A graphical summary of the results of the meta-analyses is provided in Figure 4. Table 3 presents ORs with 95% CI for each AE by dosage group.

We found an association between cumulative sGCS dosages and the risk of multiple AEs, evident even at the very low dose (0.5–1 g prednisolone-equivalent). Seven papers reported on cardiovascular diseases [43, 49, 53, 54, 56, 60] and analysis showed a significantly increased risk at the lowest dosage which gradually rose with higher dosages (Figure S6). This incremental dose-dependent association was also confirmed and even stronger for osteoporosis [43, 45, 49, 50, 53, 54, 60] and pneumonia [43, 48–50, 53, 60] (Figures S7 and S8). For diabetes [43, 49, 50, 53, 54, 60], renal complications [49, 53, 60], and cataract [43, 49, 50, 53, 56, 60], we found a dose-dependent association with increasing cumulative sGCS doses, already significant at the very low dose (Figures S9–S11).

Regarding anxiety/depression, we also found a significant association [43, 48, 49, 53, 56, 60], but only at the very low dose and the low dose of sGCS (Figure S12). For peptic ulcers, the risk in all dosage groups was significantly increased [43, 48, 49, 53, 60] with the exception of the high dose group (Figure S13). For both anxiety/depression and peptic ulcer, ORs increased at higher doses but were not significant, possibly due to heterogeneity between the two studies. For glaucoma, a dose-dependent risk was observed and was statistically significant across all dosages except the very low dose [43, 49, 53, 56, 60] (Figure S14).

For dyslipidemia, myocardial infarction, sleep disorders, and arterial hypertension, meta-analysis was not feasible for medium and high doses due to limited data. No significant risk increase was observed for dyslipidemia [53, 56, 60] or acute myocardial infarction [53, 60] at any dosage, whereas sleep disorders [49, 56, 60] and arterial hypertension showed a dose-dependent association at very low and low sGCS doses [43, 53, 56, 60] (Figures S15–S18).

3.2.2.2.2 | Dosages Calculated as a Mean Daily Dose. In a second dose–response analysis, results from fourteen studies across various outcomes were pooled to assess dose-dependent associations with (recalculated) mean daily sGCS doses [42, 44–48, 50, 51, 53, 56, 57, 60–62]. Results are discussed in the supplement.

3.3 | Risk of Bias Within Studies

The ROB assessment for the 12 RCTs revealed variability in methodological rigor. The ROB assessment for the 25 non-randomized studies revealed a serious ROB for the majority of the studies. This is because most of these studies were large-scale retrospective analyses involving thousands of patients from national databases. A more detailed discussion on ROB can be found in the supplement. Individual ROB results and summary plots are depicted in Figures 5 and 6.

3.4 | Subgroup and Sensitivity Analyses

Sensitivity analysis based on disease type and study quality did not significantly alter any of the results on immediate nor delayed AEs. We were unable to perform a sensitivity analysis based on administration route. Sensitivity analysis by study type was not indicated. These analyses are explained in depth in the supplement.

4 | Discussion

Due to their potent anti-inflammatory effects, sGCS are widely used in the management of inflammatory airway diseases. However, their use is associated with significant AEs. This SR with meta-analysis revealed a substantially increased risk for a broad range of sGCS-induced, predominantly delayed, AEs. Notably, our meta-analysis demonstrated that for several AEs, the risk became significantly elevated at cumulative dosages as low as 0.5–1 g prednisolone-equivalent. The risk escalated progressively with higher cumulative doses, indicating a dose-dependent association. Our findings underscore the urgent need for robust steroid stewardship in airway disease, ensuring that systemic corticosteroids are prescribed only when clearly indicated, at the lowest effective dose, and with careful monitoring of cumulative lifetime exposure.

4.1 | sGCS Use Associated With Diverse AEs

Regarding immediate AEs, adrenal suppression emerged as a significant concern. In our meta-analyses that included results from seven different studies, sleep and gastrointestinal disturbances in the immediate setting did not differ between patients on sGCS-treated and placebo/SOC. However, it should be noted that this was based on self-reporting or questionnaires and might therefore be underestimated. Immediate neuropsychiatric effects were also documented by one prospective cohort study. Individual studies anecdotally reported increases in blood glucose levels, self-reported headaches, loss of appetite, and hip pain.

Regarding delayed AEs, our meta-analysis revealed associations between sGCS exposure and the following AEs, when compared to placebo, no treatment or SOC: pneumonia, overall cardiovascular diseases, bone fractures, sleep disorders, osteoporosis, anxiety/depression, acute myocardial infarction, peptic ulcer, arterial hypertension, diabetes, and cataract. Although the risk was also increased for glaucoma, dyslipidemia, and stroke, it failed to reach statistical significance.

4.2 | Cumulative Dose–Response Effect of sGCS on AEs

This SR focused on the exploration of cumulative dose-dependent associations rather than dose-dependent associations for mean daily dosages due to the higher quality of the included studies and the higher relevance for our patient population. Remarkably, cumulative sGCS exposure was associated with a significantly increased risk of developing overall cardiovascular diseases, osteoporosis, pneumonia, diabetes, renal complications, cataract, anxiety/depression, peptic ulcer, sleep disorders, and arterial hypertension at cumulative sGCS doses as low as 0.5–1 g of prednisolone-equivalent. Translating the data from Voorham et al. the median prednisolone-equivalent dose per sGCS course in the UK was 200 mg per prescription [59]. This suggests that only two to five short sGCS courses

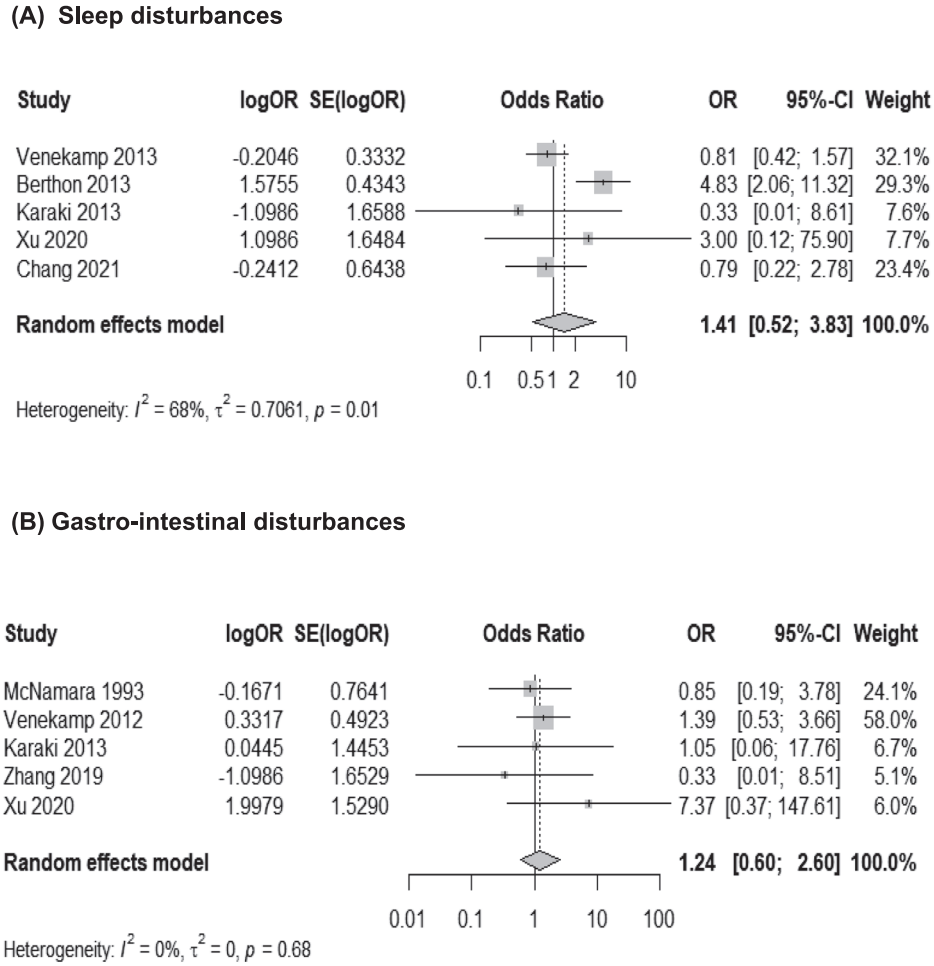

FIGURE 2 | Meta-analysis of immediate AEs associated with sGCS use. Meta-analysis of risk for immediate AEs associated with sGCS use. Forest plots of the study-specific odds ratios (ORs) for (A) sleep disturbances and (B) gastro-intestinal disturbance during or shortly after a short course of sGCS compared to placebo or no treatment. Each dot represents the OR of the respective study together with a 95% confidence interval (CI). The size of the box represents the weight of the study in the meta-analysis. Weights are from random effects analysis. The two larger diamonds represent the pooled effect estimate (+ 95% CI) for the 2 AEs.

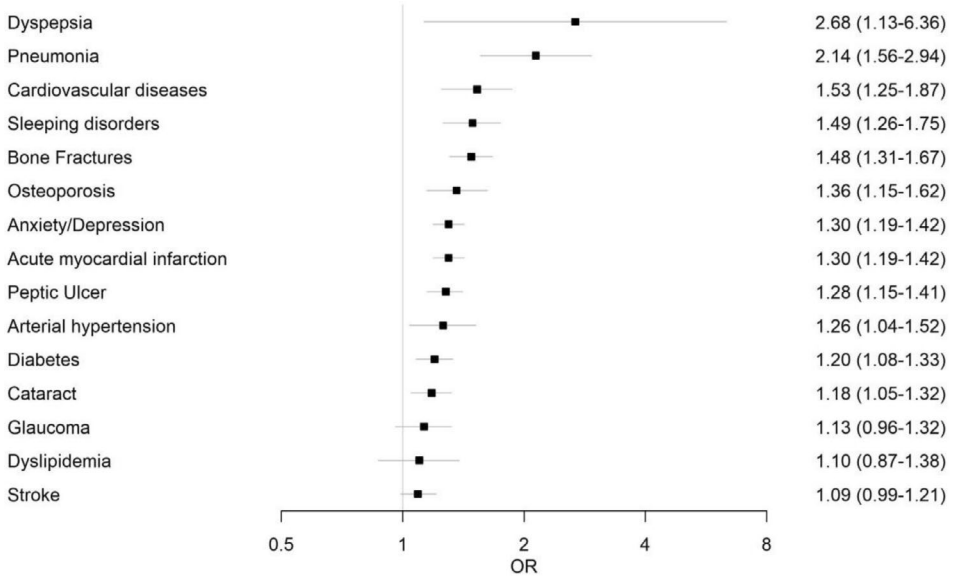

FIGURE 3 | Meta-analysis of delayed AEs associated with sGCS use. Summary of meta-analyses of delayed AEs associated with sGCS use compared with no sGCS use. Each dot represents the OR of the respective pooled effect estimate together with a 95% confidence interval (CI). The separate analyses are provided in the online supplement.

over a lifetime can be associated with a significantly increased risk for the above-mentioned AEs. Moreover, the ORs for these AEs increased with higher cumulative doses. These findings indicate a dose–response association between sGCS exposure and these outcomes, suggesting that even limited cumulative exposure may be associated with elevated risk. sGCS use was also associated with an increased risk of glaucoma from cumulative doses of 1–5 g onward, with progressively higher risk at greater cumulative doses, corresponding to 5–25 short sGCS courses over a lifetime.

4.3 | Comparison to Previously Published Work

A comparable meta-analysis was published by Al Efraij in 2019 which included 15 studies on asthma patients [63]. Similar to our results, they identified significantly increased risks for peptic ulcers, diabetes, cataract, arterial hypertension, and fractures in patients receiving sGCS compared to non-users. However, unlike us, they did not find a significantly increased risk for osteoporosis. This discrepancy can be attributed to the broader scope of our review, which included more than double the number of studies. While Al Efraij also reported a dose-dependent association for sGCS and "any AE," their data were insufficient to assess specific AEs. Additionally, their analysis used a daily dosage approach, as indicated by a "< 6 mg" threshold without any further specification, whereas our study calculated cumulative dosages. In 2020 the group from Price explored the real-world burden of sGCS use in asthma patients, synthesizing data from twelve studies [11]. Although they did not perform a meta-analysis, their findings mirror ours. Volmer and colleagues reviewed long-term chronic sGCS use in severe asthma patients in 2018, qualitatively assessing dose-dependent associations in nine retrospective cohort studies. However, only three studies provided relevant data, and no meta-analysis was conducted.

In UAWD, Tamene et al. reviewed sGCS use in CRS patients, identifying steroid-induced AEs in three of five included studies [64]. However, none of those were included in our meta-analysis due to methodological limitations, insufficient data on AEs, or lack of comparators. Two Canadian SRs compared sGCS-related risks with surgical risks in CRS patients [65, 66]. They concluded that frequent sGCS use (≥ 0.2–1.8 courses/year) posed higher risks than surgery for selected AEs (e.g., fractures, psychiatric issues, and cataracts). However, the included studies were limited by their focus on non-respiratory GCS indications and a lack of clarity in study selection processes. Other reviews analyzing sGCS-related AEs have included studies looking at other disease types, such as rheumatologic, neurological, oncological, and pulmonary conditions like COPD. Unlike these reviews, we specifically focused on the rhinitis, rhinosinusitis, and asthma population to exclude conditions where the disease itself may contribute to the observed AEs. This approach strengthens the suspicion of a causal link between sGCS use and the identified AEs, enhancing the validity of our findings.

4.4 | Strengths and Limitations of Our Work

This SR has several strengths, including a comprehensive assessment of both immediate and delayed AEs, and the use of rigorous meta-analytic techniques to address our primary and secondary outcomes. To our knowledge, this is the first SR on AEs focusing on inflammatory upper airway disease and asthma that includes a cumulative dose–response meta-analysis for individual AEs, showing that lifetime cumulative sGCS dosages as low as 0.5–1 g were significantly associated with an increased risk of a wide range of sGCS-related AEs. Given the frequent prescription of sGCS in airway disease, these findings are highly relevant to both patients and public healthcare systems worldwide. Our data suggest that reducing sGCS prescriptions could

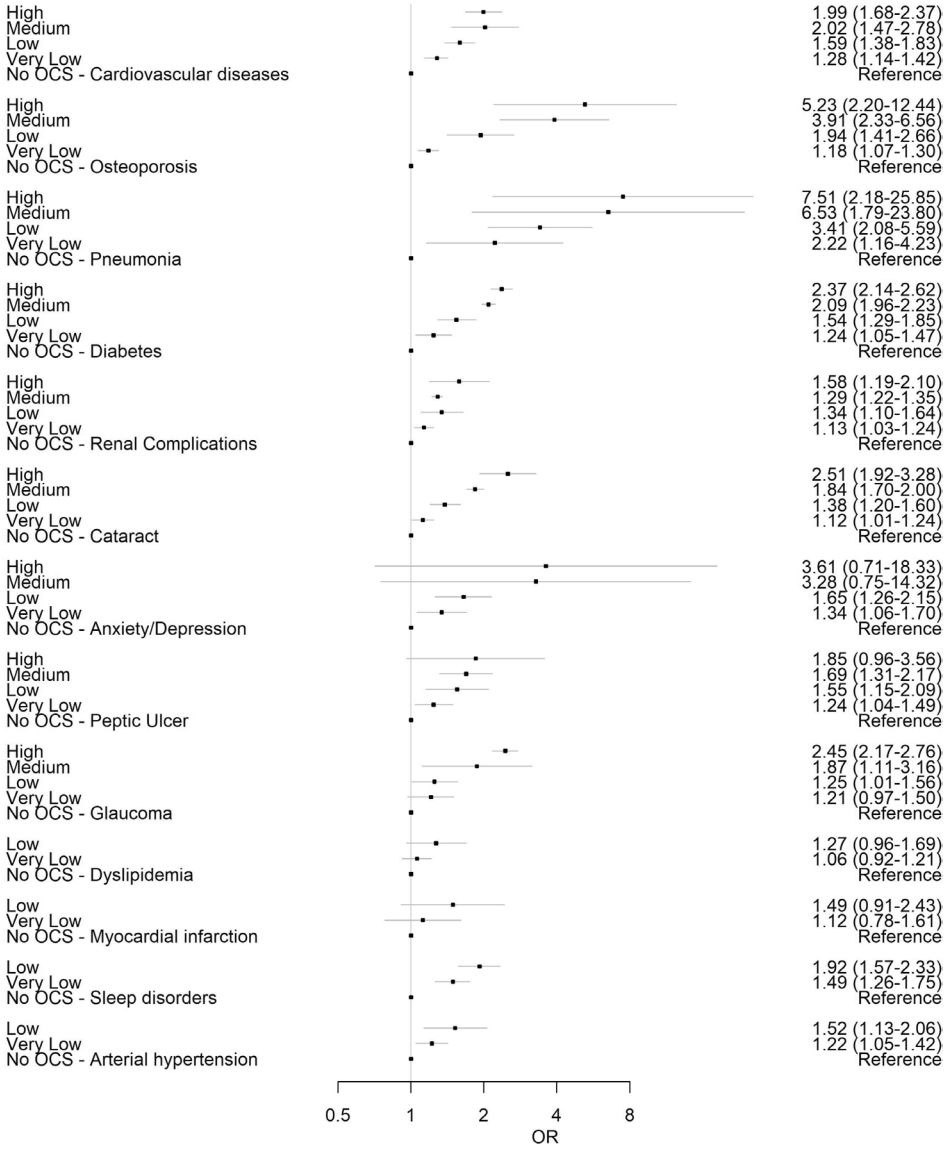

FIGURE 4 | Meta-analysis exploring the dose-dependent associations between cumulative sGCS dosages and adverse event risk. Summary of meta-analyses evaluating cumulative dose-dependent associations between sGCS use and adverse event risk. Each dot represents the OR of the respective pooled effect estimate together with a 95% confidence interval (CI). The separate analyses are provided in the online supplement. High dose > 10 g cumulative prednisolone equivalent; medium dose 5–10 g cumulative prednisolone equivalent; Low dose > 1–5 g cumulative prednisolone equivalent; Very low dose 0.5–1 g cumulative prednisolone equivalent.

lower the incidence of chronic diseases such as diabetes, osteoporosis, and cardiovascular complications, which all significantly impact patients' quality of life and impose an enormous socioeconomic burden in the western world.

To ensure robust findings, we only included studies that compared AEs to either placebo, SOC, or no treatment. This improved the quality of the included studies compared to previous SRs and enabled the dose–response calculation. However, most of the retrospective studies used for these calculations had a serious ROB, primarily due to confounding factors and outcome measurement issues, which are common in large-scale registry studies. So, a key limitation of our meta-analysis is the inherent susceptibility to residual confounding in these included observational registry studies. Although all studies employed statistical methods to control for confounding—including multivariable Cox proportional hazards models and propensity score matching—these techniques can only adjust for measured confounders that were recorded in the respective databases. Unmeasured confounders may still influence both the likelihood of receiving sGCS and the risk of developing adverse events. The specific confounders adjusted for varied across studies, and the adequacy of adjustment depends on the completeness and accuracy of registry data. Yet, only three out of thirty-seven studies were classified as critically biased [29, 43, 52] and sensitivity analysis confirmed that they did not influence our results.

We focused solely on studies involving patients with inflammatory upper airway disease or asthma. Rhinitis, rhinosinusitis, and asthma share common pathophysiological pathways and frequently co-exist in the same patient [67]. Thus, we considered the results in these populations comparable and combined them in our

TABLE 3 | Meta-analysis exploring the association between cumulative sGCS dosages and adverse event risk, reported as odds ratios (ORs) with 95% confidence intervals (95% CI).

	Very low (0.5–1 g) OR (95% CI)	Low (>1–5 g) OR (95% CI)	Medium (5–10 g) OR (95% CI)	High (>10 g) OR (95% CI)
Cardiovascular disease	1.28 (1.14–1.42) [48, 49, 53, 54, 60]	1.59 (1.38–1.83) [43, 48, 49, 53, 54, 56, 60]	2.02 (1.47–2.78) [49, 53, 54]	1.99 (1.68–2.37) [49, 53]
Osteoporosis	1.18 (1.07–1.30) [49, 50, 53, 54, 56, 60]	1.94 (1.41–2.66) [43, 49, 50, 53, 54, 56, 60]	3.91 (2.33–6.56) [45, 49, 53, 54]	5.23 (2.20–12.44) [49, 54, 56]
Pneumonia	2.22 (1.16–4.23) [48–50, 53, 60]	3.41 (2.08–5.59) [48–50, 53, 60]	6.53 (1.79–23.80) [49, 53]	7.51 (2.18–25.85) [49, 53]
Diabetes	1.24 (1.05–1.47) [49, 50, 53, 54, 60]	1.54 (1.29–1.85) [43, 49, 50, 53, 54, 56, 60]	2.09 (1.96–2.23) [49, 53, 54]	2.37 (2.14–2.62) [49, 53]
Renal complications	1.13 (1.03–1.24) [49, 53, 60]	1.34 (1.10–1.64) [49, 53, 60]	1.29 (1.22–3.35) [49, 53]	1.58 (1.19–2.10) [49, 53]
Cataract	1.12 (1.01–1.24) [49, 50, 53, 60]	1.38 (1.20–1.60) [43, 49, 50, 53, 56, 60]	1.84 (1.70–2.00) [49, 53]	2.51 (1.92–3.28) [49, 53]
Anxiety/depression	1.34 (1.06–1.70) [48, 49, 53, 60]	1.65 (1.26–2.15) [43, 48, 49, 53, 56, 60]	3.28 (0.75–14.32) [49, 53]	3.61 (0.71–18.33) [49, 53]
Peptic Ulcer	1.24 (1.04–1.49) [48, 49, 53, 60]	1.55 (1.15–2.09) [43, 48, 49, 53, 60]	1.69 (1.31–2.17) [49, 53]	1.85 (0.96–3.56) [49, 53]
Glaucoma	1.21 (0.97–1.50) [49, 53, 60]	1.25 (1.01–1.56) [43, 49, 53, 56, 60]	1.87 (1.11–3.16) [49, 53]	2.45 (2.17–2.76) [49, 53]
Sleep disorders	1.49 (1.26–1.75) [49, 53, 60]	1.92 (1.57–2.33) [49, 53, 60]	No meta-analysis possible	No meta-analysis possible
Dyslipidemia	1.06 (0.92–1.21) [53, 60]	1.27 (0.96–1.69) [53, 56, 60]	No meta-analysis possible	No meta-analysis possible
Myocardial infarction	1.12 (0.78–1.61) [53, 60]	1.49 (0.91–2.43) [53, 60]	No meta-analysis possible	No meta-analysis possible
Arterial hypertension	1.22 (1.05–1.42) [53, 56, 60]	1.52 (1.13–2.06) [43, 53, 56, 60]	No meta-analysis possible	No meta-analysis possible

meta-analysis, thus increasing the available data. Sensitivity analysis by disease type confirmed consistency even after excluding one disease category. Among the prospective studies evaluating immediate AEs, there was a balanced representation of both studies on UAWD and asthma. However, for delayed AEs and dose–response calculations, 90% of included studies focused on asthma patients, which precluded separate subgroup analysis for UAWD due to the limited number of studies. This limitation may raise the question about the generalizability of our findings to patients with rhinitis or rhinosinusitis without asthma.

Theoretically, this study might overrate the risk for pneumonia by sGCS use in asthma patients, since asthma exacerbations could have been misclassified to some extent as pneumonia by health care practitioners. Although diagnostic misclassification between asthma exacerbations and pneumonia may occur in real-world datasets, especially in first-line care, such misclassification would likely be non-differential across exposure groups and therefore bias results toward the null; the consistent dose-dependent increase in pneumonia and other infection-related outcomes across studies suggests that systemic immunosuppression from sGCS remains the most plausible explanation for the observed associations.

The most important limitation of our study is that our cumulative dose–response analyses often relied on a limited number of studies. Certain analyses were largely based on two registry studies from the same British research group, using overlapping patient databases [49, 53]. For all AEs with dose-dependent associations, these two studies provided the only data on the highest sGCS dosage group. For six specific AEs (renal complications, glaucoma, cataract, anxiety/depression, peptic ulcer, and pneumonia), they were also the sole source of data for medium doses. While the populations and timings differed between these studies, some overlap exists as can be interpreted from the low or absent heterogeneity values for certain AEs. This should be considered when interpreting our results. For other meta-analyses relying on a higher number of papers, heterogeneity was substantial/considerable, which is common for analyses of large-scale retrospective database studies that yield a high amount of data. Substantial or considerable between-study heterogeneity has a large effect on the width of the confidence interval of the overall effect estimate. However, our applied random-effects model accounts for between-study variance, ensuring that the confidence interval width of the overall effect estimate remains appropriate, even in cases of high between-study variance.

A second important limitation is the fact that our included studies do not take into account the potential systemic absorption of inhaled corticosteroids (ICS) when administered in high doses or due to incorrect inhaler technique that might contribute to CS-induced AEs [68]. Since asthma patients needing more sGCS are also likely to be treated by high-dose ICS, this phenomenon might lead to an overestimation of our results, especially for the high-dose sGCS data.

A final limitation of the study is our inability to fully separate delayed from immediate AEs. This is due to the retrospective nature of the majority of the included studies, which often did not specify the timing of AEs relative to sGCS courses. As a result, some data categorized as delayed AEs (e.g., pneumonia, fractures, dyspepsia) may actually reflect immediate

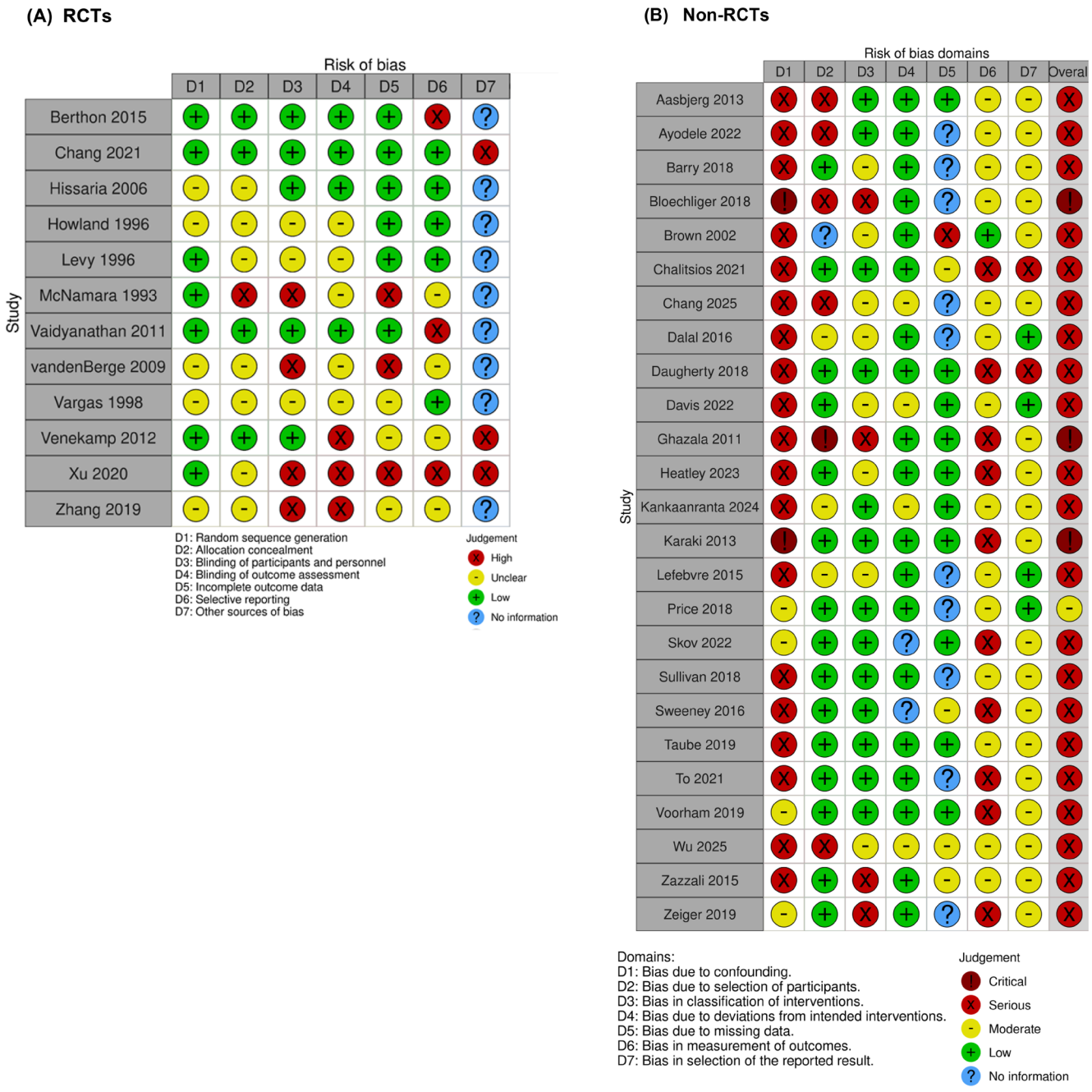

FIGURE 5 | Risk of bias analysis of individual studies. Review authors' judgments about each risk of bias item for (A) RCTs, evaluated by the Cochrane Risk-of-Bias tool Version 2; and (B) non-RCTs, evaluated by the Risk of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool.

outcomes. Additionally, while these registry-based studies provided valuable information, they hindered subgroup analysis by administration route (injected vs. OCS) and prevented distinguishing serious AEs (leading to hospitalization or death) from less severe ones.

4.5 | Impact on Clinical Practice

The findings of this SR highlight the importance of steroid-stewardship in patients with chronic airway diseases. While sGCS remain indispensable for managing severe inflammatory airway conditions, their use must be carefully weighed against their potential risks. Clinicians should firstly focus on optimizing (adherence to) local treatments, and secondly consider alternative step-up therapies like biologics or surgery when deemed appropriate, well before reaching an at-risk cumulative dose of 0.5–1 g of prednisolone-equivalent.

Raising awareness among patients about the dangers of self-medication is crucial, as is educating health care practitioners (HCPs) on the importance of monitoring total cumulative sGCS exposure, even for non-respiratory indications. HCPs should also bear in mind that sGCS add to the steroid burden that could be already high given the use of potent ICS. When sGCS are necessary, clinicians should aim to prescribe the lowest effective dose for the shortest possible duration. For high-risk patients, prophylactic measures such as

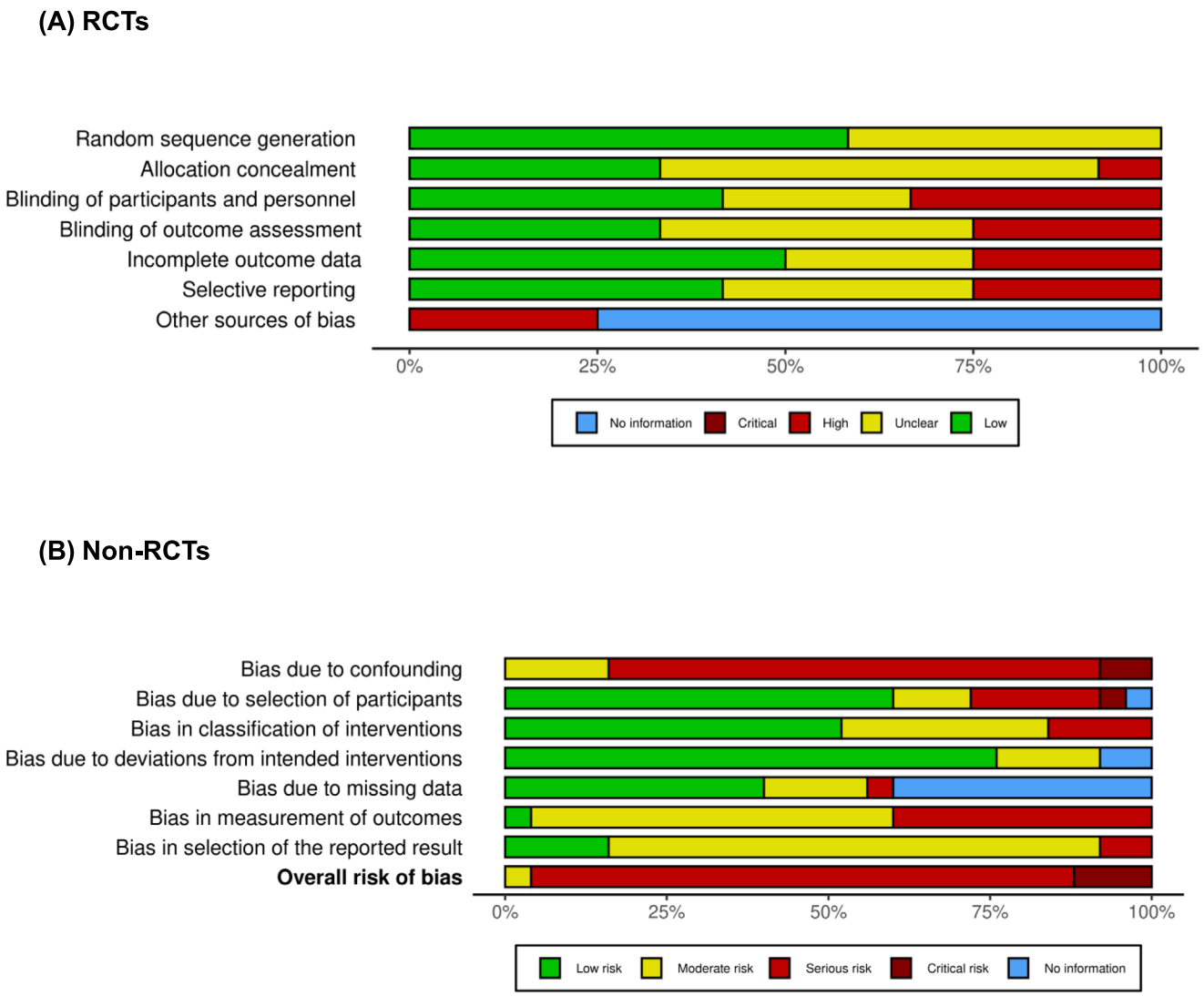

FIGURE 6 | Summary plots of Risk of bias analysis. Review authors' judgments about each risk of bias presented as percentages across all included studies separated in (A) RCTs, evaluated by the Cochrane Risk-of-Bias tool Version 2; and (B) non-RCTs, evaluated by the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.

bone-protective agents and metabolic monitoring should be implemented to mitigate the long-term complications associated with sGCS use.

Future research should focus on standardizing AE assessments and investigating the long-term impact of sGCS-sparing strategies. Also, studies that quantify combined ICS and sGCS exposure—preferably through detailed inhaler technique assessment and pharmacokinetic markers—could help us in accurately distinguishing their individual contributions to systemic AEs.

In addition, an investigation of AEs associated with sGCS use specifically in pediatric populations is needed. Children may exhibit different susceptibility to corticosteroid-related complications such as growth suppression and bone density reduction. Current evidence on corticosteroid safety in children is limited, and pediatric patients are often underrepresented or excluded from large registry studies. Dedicated research is essential to inform evidence-based prescribing practices and risk–benefit considerations in children. Such efforts will be critical to improve patient outcomes while minimizing the burden of sGCS-related complications.

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** all70332-sup-0001-Supinfo1.docx. **Data S2:** all70332-sup-0002-Supinfo2.docx. **Figure S1:** all70332-sup-0003-Figures.docx.