Impact of Inhaled and Intranasal Corticosteroids Exposure on the Risk of Ocular Hypertension and Glaucoma: A Systematic Review and Meta-Analysis

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Purpose: Starting in 2019, the Global Initiative for Asthma recommended the use of inhaled corticosteroids (ICS) as part of reliever combination therapy in patients 12 years of age and older, thus dramatically increasing the population exposure to ICS. ICS and intranasal corticosteroids (INS) are commonly used for a variety of respiratory diseases. Chronic steroid use is a well-known risk factor for elevated intraocular pressure (IOP) and glaucoma regardless of route of administration. This study aimed to determine the reported risk of glaucoma, ocular hypertension (OHT) and IOP elevation associated with ICS and INS use.

Materials and Methods: Systematic literature search in MEDLINE, EMBASE, Cochrane, CINAHL, BIOSIS, and Web of Science databases from the date of inception identified studies that assess ocular outcomes related to glaucoma in ICS and INS users. Study selection, risk of bias assessment and data extraction were done independently in duplicate. Meta-analysis assessed glaucoma incidence, OHT incidence and IOP changes in patients using ICS and INS. Study adhered to PRISMA guidelines. Study protocol was registered with PROSPERO: CRD42020190241.

Results: Qualitative and quantitative analyses included 65 and 41 studies, respectively. Incidence of glaucoma was not significantly different in either ICS or INS users compared to control over 45,457 person-years of follow-up. Similarly, no significant difference in OHT incidence over 4431 person-years was detected. In studies reporting IOP, a significantly higher IOP was observed (0.69 mmHg) in 857 ICS or INS users compared to 615 controls. However, no significant increase in IOP was observed within ICS or INS users when compared to pre-treatment baseline.

Conclusion: Overall, use of ICS or INS does not significantly increase the incidence of glaucoma or OHT. However, ICS and INS patients had significantly higher IOPs compared to untreated patients. Awareness of these findings is significant in care of patients with additional risk factors for glaucoma.

Keywords: corticosteroids, asthma, glaucoma, intranasal, inhalation

Introduction

In 2019, the Global Initiative for Asthma (GINA) introduced what is described as the most radical change to the asthma treatment paradigm of the last 30 years.1 Previously, for patients with mild intermittent asthma, short-acting beta-agonists (SABA) alone were used as first-line therapy. The addition of inhaled corticosteroids (ICS) was reserved for more severely symptomatic cases.1 The new report from GINA recommended using SABA + ICS combination for both maintenance and relief therapy in patients of 12 years of age or older,2 affecting the patients with mild intermittent asthma who are not currently adherent to regular ICS treatment, thus increasing the population’s exposure to corticosteroids. These recommendations influence clinical decision-making and treatment guidelines throughout the world and these changes continue to be reflected in the 2020 and 2021 GINA reports.3,4
Asthma affects over 272 million people worldwide based on a 2017 report by Global Burden of Disease Study, which includes 3.8 million or 10.2% of Canadians. The new treatment paradigm exposes an entire new cohort of the patient population to ICS. In addition, many asthma patients are concurrently affected by rhinitis, conjunctivitis, rhinosinusitis and nasal polyps. Management of these conditions often warrants intranasal corticosteroid (INS) use, increasing patient exposure to corticosteroids even further. ICS are also extensively used for medical management of chronic obstructive pulmonary disease (COPD), another disease with significant health burden affecting over 251 million people worldwide, including 2.0 million Canadians. Corticosteroid use has been previously linked to increased intraocular pressure (IOP). When IOP rises beyond a certain threshold, typically defined as 21 mmHg, the condition is defined as ocular hypertension (OHT). Glaucoma is a disease defined by progressive damage of the optic nerve, and is the leading cause of irreversible blindness worldwide. OHT and glaucoma are closely related, and are often identified concurrently, as studies have shown that OHT is a major risk factor for development and progression of glaucoma. Anatomic proximity of the administration routes of ICS and INS, in addition to documented systemic effects, may increase exposure of ocular structures to corticosteroids.

To date, multiple studies of various methodology, including randomized control trials (RCTs), prospective and retrospective studies, have looked at corticosteroid exposure via inhalation or intranasal routes, assessing systemic adverse effects, including ocular outcomes. As a result, some studies suggest increased incidence of ocular hypertension or glaucoma while others do not observe such an effect. However, systematic reviews on the topic tend to focus on ocular administration of corticosteroids, and there is a lack of recent syntheses appraising IOP elevation or glaucoma incidence in patients exposed to ICS/INS. The purpose of the current systematic review and meta-analysis is to analyze all available data on incidence of glaucoma, OHT and IOP elevation in ICS and INS users, as well as to summarize and quantify the effects ICS and INS have on IOP.

Materials and Methods
Literature Search Strategy
Details of the protocol for this systematic review and meta-analysis were registered with PROSPERO (registration number CRD42020190241) and can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42020190241. A predefined search strategy was used to obtain relevant literature from the following databases: MEDLINE, EMBASE, Cochrane, CINAHL, BIOSIS, and Web of Science. Databases were first searched on May 23, 2020 using key terms and subject headings related to 1) corticosteroids 2) inhalational and intranasal administration routes and 3) glaucoma and relevant clinical findings such as IOP or OHT. Additional records were identified through screening of relevant studies’ citation lists. References were managed in Mendeley (Mendeley Ltd, Version 1.19.8, London, England) and Zotero software (Version 5.0.96.2, Virginia, US), deduplicated and entered into Covidence software (Veritas Health Innovation, Melbourne, Australia). Database searches were rerun on August 31, 2021, to retrieve any further studies for inclusion before final analyses. This work adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Supplementary Material, Table 1).

Study Selection
References imported into Covidence software first underwent level 1 screening based on title and abstract using predefined criteria. Studies advanced to level 2 screening if they 1) involved human patients; 2) were published in the English language; 3) involved administration of pre-defined corticosteroid drugs through inhalational or intranasal route; 4) measured an ocular outcome. Case reports, reviews, editorials, posters, abstracts, non-English language studies, and studies involving corticosteroids use through any other route than inhalation or intranasal were excluded. Full-texts were obtained. In level 2 screening, studies were selected for inclusion if they 1) reported IOP or any other clinical diagnostic features indicating glaucoma diagnosis or progression; 2) involved administration of corticosteroids through inhalational or intranasal routes; 3) possessed a sample size of at least 10 participants. All studies were screened by at
least two independent reviewers and conflicts were resolved through consensus, and all studies passing level 2 screening were included in qualitative review.

**Data Collection and Quality Assessment**

The following information was extracted from included studies for input into quantitative and qualitative analyses: first author, publication year, study design, study location, funding sources, medication used, dose, route and indication, patient age (mean ± standard deviation (SD) when available, or derived from available data, and range as reported by the authors), follow-up duration, sample size at the study conclusion, and reported ocular outcomes such as IOP change, glaucoma or OHT diagnosis in ophthalmological assessment during study follow-up.

Methodological quality of the studies included after level 2 screening was assessed independently and in duplicate by two reviewers using Cochrane RoB-2 Risk of Bias tool for randomized trials and Cochrane ROBINS-I Risk Of Bias In Non-randomized Studies – of Interventions tool for non-randomized studies of interventions (NRSIs). Any discrepancies were resolved by consensus. Summary of the results of the risk of bias was presented using the robvis tool.

**Data Analysis and Synthesis**

Meta-analysis was completed using Review Manager (RevMan, version 5.4; The Nordic Cochrane Center, Copenhagen). Among the studies that passed inclusion criteria for qualitative review, studies were included in the meta-analysis if they reported data on the outcomes of interest as described below. Studies were excluded from quantitative meta-analysis and remained in qualitative review only, if their results did not provide sufficient detail regarding ocular outcomes, lacked quantitative outcomes, or did not have a clear control group. The main outcomes of interest were incidence of glaucoma and OHT, as well as mean ± SD of IOP in controls and patients before and after ICS or INS use. Incidence of new glaucoma diagnoses, OHT and IOP increase was expressed as number of cases per person-years (PPY) based on study follow-up, in order to allow weighted measurement of the incidence rate, and was used to calculate risk differences. For incidence of OHT, the clinical threshold chosen by each study was accounted for in subgroup analysis. For IOP, reported mean ± SD of ICS users, INS users, and controls before and after medication use were pooled for meta-analysis. For all outcomes, subgroup analyses pooled studies based on study methodology, separating RCT and NRSI to account for the different strength of evidence each design provides in summary estimates, and drug administration route, to examine whether proximity to ocular tissues could influence ophthalmic outcomes. Heterogeneity was tested by computing I² value and for low-heterogeneity studies (I² value <50%), the fixed-effect model was used, while for high-heterogeneity studies (I² value ≥50%), the random-effect model was used. Sensitivity analyses were performed for large studies (>1000 participants/person-years) and for studies with pediatric populations (<18 years of age) versus adult population.

**Results**

**Search Results**

The study selection process is outlined in the PRISMA flow diagram (Figure 1). The chosen search strategy yielded 2381 references, including 1764 from EMBASE, 205 from MEDLINE, 59 from CINAHL, 102 from Cochrane Library, 210 from Web of Science, and 41 from BIOSIS databases. An additional 7 studies were identified through a hand search of reference lists. After deduplication, 1805 references remained. The agreement between the reviewers was substantial – 0.79 for level 1 and 0.84 for level 2. After level 1 screening, 132 references remained. During level 2 screening, 67 references were excluded, while the remaining 65 studies met our inclusion criteria and thus were included in qualitative synthesis. Out of these 65, 24 studies were included only in qualitative synthesis because their results did not provide sufficient detail regarding ocular outcomes, lacked quantitative outcomes, or did not have a clear control group. The remaining 41 studies were included in quantitative meta-analysis.

**Study Characteristics**

Characteristics of the included studies are summarized in Table 1. A total of 536,412 patients participated in the included studies, aged 0 to 97 years of age. Follow-up period varied between 1 week and 2 years. Number of patients enrolled per study varied between 10 and 459,795. Main indications for inhaled corticosteroids were asthma and COPD, while
intranasal corticosteroids were mainly indicated for allergic rhinitis, and rhinosinusitis with or without nasal polyps. For both administration routes, a wide range of corticosteroids doses has been used, with a comparable spread. Methodological quality of the included studies was good overall, with RCTs having a lower risk of bias compared to NRSIs (Supplementary Material, Figure 1).³⁴

Publication Bias Funnel Plots
Funnel plots did not display asymmetry for glaucoma incidence, OHT incidence, differences in IOP between ICS/INS users versus non-users, nor IOP elevation after corticosteroid use compared to pre-treatment baseline (Figure 2).
| Reference | Study Design | Study Location | Funding Sources | Indication | Drug | Dose | N (Original) | Follow-Up | Mean Age | Age (SD) | Age Range |
|-----------|--------------|----------------|----------------|------------|------|------|--------------|-----------|----------|----------|-----------|
| Dereci (2015) | Cross-Sectional | Turkey | ND | Asthma | Fluticasone | 250 ug/day | 78 | 1 Year | 10.0* | 2.7* | 6–13 |
| Emin (2011) | Cross-Sectional | Turkey | ND | Asthma | Fluticasone | 323 ug/day | 426 | 3–6 Years | 8.3* | 22.4* | 7–11 |
| Mitchell (1999) | Cross-Sectional | Australia | Australian Department Of Health And Family Services and The Save Sight Institute, | NI | NI | NI | 3654 | NI | — | — | 49–97 |
| Alsaadi (2012) | Prospective Cohort | Saudi Arabia | ND | Asthma | Fluticasone | 250 ug | 93 | >6 Mo | 8.3 | 2.6 | 5–15 |
| Behbehani (2005) | Prospective Cohort | Kuwait | ND | Asthma | Budesonide / Beclomethasone | 50 ug / 100 ug | 95 | 2 Years | 7 | 3 | 1.5–12 |
| Gunay (2019) | Prospective Cohort | Turkey | ND | Asthma | Fluticasone | 250 ug | 53 | NI | 9.5 | 1.9 | 6–14 |
| Marcus (2012) | Prospective Cohort | Netherlands | ** | NI | NI | NI | 1193 | 9.8 Years | 65.8* | 6.8* | 55+ |
| Nath (2017) | Prospective Cohort | India | ND | COPD | Fluticasone | 250–1000 ug/day | 357 | 4–6 Months, 6 Months To 1 Year, 1 Year + | 64.1* | 8* | 50+ |
| Boulet (2004) | RCT | Canada | 3M Pharmaceuticals Claimed Unbiased Study | Asthma | Beclomethasone | 800/1500 ug/day | 141 | 6 Mo | 41.3 | 16.2 | 14+ |
| Busse (2013) | RCT | US | GSK | Asthma | Fluticasone | 100/200/500 ug | 503 | 52 Wks | 39* | 15.8* | 12+ |
| Chylack (2008) | RCT | US | Sanofi-Aventis US And Nycomed | Asthma | Ciclesonide / Beclomethasone | 640 ug/day / 640 ug/day | 1568 | 12 Months | 43.1* | 12.8* | 18+ |

(Continued)
| Study                     | Design | Country          | Brand/sponsor            | Disease                  | Treatment  | Dose    | Duration  | Effect | Safety |
|--------------------------|--------|------------------|--------------------------|--------------------------|------------|---------|-----------|--------|--------|
| Covelli (2015)           | RCT    | Canada, Czech Republic, Germany, Poland, Romania, US | GSK                      | COPD                     | Fluticasone | 100 ug  | 12 Weeks  | 623    | 40–86  |
| Duh (2000)               | RCT    | US               | Astra Pharma-Geuticals, LP And AstraZeneca R&D Lund. | Asthma                   | Budesonide | 200/400/800 ug | 976    | 12–20 Weeks | — | 6–70  |
| Ferguson (2017)          | RCT    | US, UK           | AstraZeneca              | COPD                     | Budesonide | 320 ug   | 26 Weeks  | 1218   | 40–87  |
| Gelfand (2006)           | RCT    | US               | Aventis Pharmaceuticals  | Asthma                   | Ciclesonide | 40/80/160 ug | 1018   | 12 Weeks  | 8.2* 0.1* | 4–11  |
| Kemp (2004)              | RCT    | US               | CoI Acknowledged For GlaxoSmithKline, Aventis, And AstraZeneca. | Asthma                   | Fluticasone | 88/440 ug | 160     | 2 Years  | 29.7* | 18–50 |
| Kerwin (2019)            | RCT    | US               | AstraZeneca              | COPD                     | Budesonide | 320 ug   | 52 Weeks  | 531    | 40–80  |
| Li (1999)                | RCT    | US               | Glaxo Wellcome Inc.     | Asthma                   | Fluticasone | 500 ug   | 104 Weeks | 64     | 18+    |
| Maspero (2010)           | RCT    | US               | Merck & Co.              | Asthma                   | Mometasone | 200/250 ug/400/500 ug | 404    | 52 Wks   | 35.5* 15.2* | 12+   |
| Moss (2017)              | RCT    | Canada           | Internal Funding         | NI                       | Fluticasone | 500 ug/day | 20     | Twice Daily, 6 Weeks | 65.7* 10* | 18–85 |
| Novak-Laus (2003)        | RCT    | Croatia          | ND                       | Asthma                   | Beclomethasone Fluticasone | 800 ug/day/100 ug/day | 60     | 4 Years  | 41.5 | 19–65 |
| Ratner (2006)            | RCT    | US               | ALTANA Pharma US Inc.   | Allergic Rhinitis        | Ciclesonide | 25/50/200 ug | 581    | 14 Days  | — | 18–65 |
| Reed (1998)              | RCT    | US               | Grant From Allen And Hanburys, Research Triangle Park, N.C., To The American Academy Of Allergy, Asthma And Immunology | Asthma                   | Beclomethasone | 42 ug | 771     | 1 Year | — | 6–65  |
| Sheffer (2005)           | RCT    | US               | AstraZeneca R&D.         | Asthma                   | Budesonide | 200/400 ug/day | 7221   | 3 Yr     | — | 5–66  |
| Reference           | Study Design     | Study Location                           | Funding Sources                                                                 | Indication      | Drug                      | Dose                  | N (Original) | Follow-up | Mean age (SD) | Age Range |
|---------------------|------------------|------------------------------------------|--------------------------------------------------------------------------------|----------------|---------------------------|----------------------|--------------|-----------|----------------|-----------|
| Tinkelman (1993)    | RCT              | US                                       | American Academy Of Allergy And Immunology And Glaxo Inc, Allen And Hanburys (Research Triangle Park, NC) | Asthma          | Beclomethasone            | 42 ug                | 195          | 1 Year   | 11.9*          | 6–17      |
| Garbe (1997)        | Retrospective Case-Control | Canada (QC)                                | ND                                                                             | NI              | NI                        | NI                   | 25545        | Nil       | —         | —         | 66+      |
| Gonzalez (2010)     | Retrospective Case-Control | Canada                                    | ND                                                                             | NI              | Fluticasone               | 500–1000 ug          | 15,736       | 1 Year   | 75         | 4.2       | 66+      |
| Miller (2011)       | Retrospective Case-Control | US                                       | GSK                                                                            | COPD            | Fluticasone               | 250–1000 ug/day      | 976          | 1–381 Days | —         | —         | 45+      |
| Shroff (2018)       | Retrospective Case-Control | India                                     | ND                                                                             | NI              | Budesonide                | 800 ug/day           | 400          | At Least 6 Mo | 53.9*     | 15*       | 18–89    |
| Baan (2020)         | Retrospective Cohort | Netherland/ Belgium                        | ND                                                                             | Asthma          | Fluticasone               | NI                   | 565          | Nil       | —         | —         | 0–17     |
| Chang (2017)        | Retrospective Cohort | China                                     | National Science Council, Chang Gung Memorial Hospital, Ministry of Science and Technology, Taiwan | Asthma          | NI                        | NI                   | 5380         | 4 years   | —         | —         | <6       |
| Johnson (2012)      | Retrospective Cohort | US                                       | Unrestricted Grant From Research To Prevent Blindness.                      | Asthma          | NI                        | NI                   | 42           | 2–6 Years | —         | —         | NI       |

| Reference           | Study Design     | Study Location                           | Funding Sources                                                                 | Indication      | Drug                      | Dose                  | N (Original) | Follow-up | Mean age (SD) | Age Range |
|---------------------|------------------|------------------------------------------|--------------------------------------------------------------------------------|----------------|---------------------------|----------------------|--------------|-----------|----------------|-----------|
| Manji (2017)        | Cross-sectional  | Canada, Australia, Mexico, Chile         | ND                                                                             | CRS             | Budesonide                | 600 ug/day           | 100          | 23.5 months | 61.8*     | —         | 51–68    |
| Mohd Zain (2019)    | Cross-sectional  | Malaysia                                  | ND                                                                             | Allergic Rhinitis | Mometasone Fluticasone Budesonide | 95 | 5.42 ± 3.22 years | 24.5*     | 9.4*      | 10–40    | (Continued) |
Table 1 (Continued).

| Study             | Design | Country | Site                        | Diagnosis | Medication | Dose | Duration | Efficacy | Adverse Reactions |
|-------------------|--------|---------|-----------------------------|-----------|------------|------|----------|-----------|-------------------|
| Ozkaya (2011)     | Cross-sectional | Turkey | ND                          | PAR       | Budesonide | 93.3 ug/day | 240       | 25–76 months | 11.2*     | 8.2*              | 8–15              |
| Douglas (2019)    | Prospective Cohort | New Zealand, Australia | ND            | CRSwNP, CRSsNP | Mometasone | 2500 ug/packing | 20       | 24 wks   | 39.9      | 23.5–66.9         |
| Forwith (2011)    | Prospective Cohort | US | Intersect ENT               | CRS        | Mometasone | 370 ug | 89       | 30 days   | 44.2*     | —                 | 20–72             |
| Man (2013)        | Prospective Cohort | US | Richie's Specialty Pharmacy | CRS        | Fluticasone | 3 mg/irrigation | 23       | 6 weeks  | 53.3*     | 13.7*             | 18+               |
| Ozturk (1998)     | Prospective Cohort | Turkey | ND                          | ESS       | Budesonide | 200 ug/200 ug | 26       | 3–19 months | 40.3*     | 13*               | 18–66             |
| Seiberling (2013) | Prospective Cohort | US | ND                          | CRSwNP, post-ESS | Budesonide | 0.5 mg/day/irrigation | 10       | 4 wks    | 57.2*     | 14.1*             | 36–83             |
| Simsek (2016)     | Prospective Cohort | Turkey | ND                          | Allergic rhinitis | Fluticasone | 100 ug/day/200 ug/day | 100      | 24 weeks | 47.9*     | 18.9*             | 18+               |
| Spiliotopoulos (2007) | Prospective cohort | Greece | ND                          | Allergic Rhinitis | Dexamethasone | 20 ug/day  | 54       | 27–35 days | 47        | —                 | 22–55             |
| Yenigun (2018)    | Prospective cohort | Turkey | ND                          | AR and dry eye | Beclomethasone | 400 ug/day | 29       | 6 wks     | 30.8*     | 4.6               | 17–43             |
| Adriaensen (2017) | RCT    | Holland | BiolInspire Technologies, Inc. | Post-ESS wound healing | Fluticasone | 160 ug/packing | 202      | 30 days  | 49        | 24–80             |
| Berger (2014)     | RCT    | US, UK, India, Germany | Meda Pharmaceuticals, | Chronic rhinitis | Fluticasone | 200 ug | 612      | 1 year   | 33.6*     | 11.5*             | 12–80             |
| Bross-Soriano (2004) | RCT    | Mexico | ND                          | Chronic rhinitis | Fluticasone | 200 ug/200 ug/400 ug | 360      | 1 year   | —         | —                 | 18–60             |
| Chervinsky (2007) | RCT    | US | Altana Pharma US, a Nycomed company | Allergic rhinitis | Ciclesonide | 200 ug | 663      | 52 weeks | 36.5      | 12–73             |
| Han (2014)        | RCT    | US | Intersect ENT               | CRSwNP     | Mometasone | 100 ug | 100      | 90 days  | 49.6*     | —                 | 19–80             |
| Study                                    | Study Design | Country | Funding | Condition                  | Treatment | Duration | Endpoint | Comparison 1 | Comparison 2 | Comparison 3 |
|-----------------------------------------|--------------|---------|---------|-----------------|-----------|----------|----------|-------------|-------------|-------------|
| Howland (1996)                          | RCT          | US      | ND      | Seasonal allergic rhinitis | Fluticasone 200 ug | 1 year   | —        | —           | —           | 18–40       |
| Igarashi (2012)                         | RCT          | Japan   | ND      | Seasonal allergic rhinoconjunctivitis | Mometasone 200 ug | 4 wks    | 44.6*    | 6.9*        | 15+         |
| Kim (2007)                              | RCT          | US      | Alfara Pharma | Ciclesonide 25/100/200 ug | 6–12 wks | —        | —        | 2–6         |
| Kothiwala (2021)                        | RCT          | India   | ND      | CRSwNP, CRSsNP | Budesonide 1 mg/irrigation | 12 weeks | 33       | 33          | 15–68       |
| LaForce (2013)                          | RCT          | US      | GlaxoSmithKline | Allergic rhinitis | Fluticasone 110 ug | 2 yr     | 37.3*    | —           | 12+         |
| Marple (2012)                           | RCT          | US      | Intersect ENT | CRSwNP, CRSsNP, ESS | Mometasone 370 ug/packing | 30 days  | 46.5     | 18–76       |
| Maspero (2008)                          | RCT          | Chile, US | GSK assistance though unclear if funds were involved | Fluticasone 55/110 ug | 12 weeks | 7.7      | —        | 2–12        |
| Rotenberg (2011)                        | RCT          | Canada  | ND      | CRSwNP, ESS | Budesonide 256/1000 ug/day | 1 year    | 47.5*    | —           | 21–78       |
| Weinstein (2014)                        | RCT          | US      | Teva Branded Pharmaceutical Products R&D. | Beclomethasone 320 ug | 52 wks   | 37.0*    | 13.5*    | 12+         |

(Continued)
Table 1 (Continued).

| Study          | Design        | Country | Funding Source | Treatment                      | Duration | Follow-Up | Worsened (%) | 50%* | 90%* | 100%* |
|----------------|---------------|---------|----------------|--------------------------------|----------|-----------|---------------|------|------|-------|
| Yuen (2013)    | RCT           | Canada  | Internal department funding | Beclomethasone 400 ug/day | 19       | 6 wks     | 62.7*         | 12*  | 18–85|
| Soudry (2016)  | Retrospective case series | Canada | ND | post-ESS Budesonide 0.75 mg/day/irrigation | 48       | 6–66 mo   | 54.5          | —    | 27–77|
| Bui (2005)     | Retrospective Cohort | US     | Supported by Olive Lewellyn Glaucoma Research Fund and a ChallengeGrant from Research to Prevent Blindness, Inc, NY | Nil     | 36       | 16 months    | 66.2* | 14.4* | 35–83|
| Davis (2016)   | Retrospective Cohort | US     | GSK             | Nil Fluticasone 459,795 | 459,795 | Nil       | —             | —    | —    | —     |
| Martino (2015) | Retrospective Cohort | US     | ND | CRSwNP Dexamethasone 800 ug/day | 28       | 6–104 weeks | 60*          | 16.4* | 15–85|

Notes: In studies where funding sources were not clearly disclosed, an attempt was made to contact the authors for further information. *Derived from reported data. **Krimpen Aan De Lek; MD Fonds, Utrecht; Rotterdamse Vereeniging Blindenbelangen, Rotterdam; Stichting Oogfonds Neder-Land, Utrecht; Blindenpenning, Amsterdam; Blindenhulp, The Hague; Algemene Nederlandse Vereniging Ter Voorkoming Van Blindheid (ANVVB), Doorn; Landelijke Stichting Voor Blinden En Slechtzien-Den, Utrecht; Swart Van Essen, Rotterdam; Stichting Wincel-Sweep, Utrecht; Henkes Stichting, Rotterdam; Professor Mulder Stichting, Groningen; Stichting Nederlands Oogheelkundig Onderzoek, Rotter-Dam; Lane's Ootech BV, Nieuwegein; Medical Workshop, De Me-Ern; Topcon Europe BV, Capelle Aan De IJssel, All In The Netherlands and Heidelberg Engineering, Dossenheim, Germany.

Abbreviations: RCT, randomized controlled trial; NI, not indicated; ND, none disclosed; PAR, Perennial Allergic Rhinitis; CRS, Chronic Rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with Nasal Polyps; CRSSNP, Chronic Rhinosinusitis without Nasal Polyps; ESS, Endoscopic Sinus Surgery.
Figure 2 Continued.
Main Outcomes

Main outcomes of this study were glaucoma and ocular hypertension incidence, as well as differences in IOP between ICS/INS users and controls, and change in IOP in corticosteroid users compared to pre-treatment baseline.
Glaucoma Incidence

There was no statistically significant risk difference in glaucoma incidence identified between corticosteroid users and non-users (Figure 3A). Subgroup analyses of both RCT and NRSI revealed no significant increase in glaucoma incidence for ICS or INS users. Sensitivity analysis (Supplementary Material, Figure 2) did not reveal significant influence of large studies by Sheffer\(^26\) or Chang\(^37\) on subgroup or overall risk difference, or heterogeneity. No significant differences were identified between adult and pediatric populations (Supplementary Material, Figure 3).

OHT Incidence

Studies reported different thresholds for classification of OHT, beginning at IOP above 20 mmHg, 21 mmHg, or 22 mmHg. Many authors reported only occurrence of IOP elevation, without specifying the magnitude. Overall, there was no statistically significant risk difference in OHT incidence or incidence of IOP elevation between corticosteroid users and non-users (Figure 3B). Subgroup analysis accounting for different reporting styles was overall consistent with the summary analysis, revealing two subgroups slightly favoring control. Both of these subgroups included RCT studies that used >22 mmHg as an IOP threshold for OHT, with one of these reporting a 27% increased risk with ICS use in a sample of 30 patients over 30 person-years,\(^18\) and the other reporting a 2% risk increase with INS use in a sample of 806 patients over 806 person years.\(^19\) In the latter subgroup, a 2% risk increase persisted despite a study that included 66 patients over 16 person years reporting 0% increased risk. Sensitivity analysis (Supplementary Material, Figure 2) did not reveal

| Study or Subgroup | Corticosteroids | Control | Risk Difference M-H, Fixed, 95% CI | Risk Difference M-H, Fixed, 95% CI |
|-------------------|----------------|---------|-----------------------------------|-----------------------------------|
| 1.1.1 RCT ICS     |                |         |                                   |                                   |
| Covelli 2015      | 0              | 71      | 1 72 0.4% -0.01 [-0.05, 0.02]      |                                   |
| Gefand 2005       | 0              | 176     | 0 58 0.4% 0.00 [0.02, 0.02]        |                                   |
| Li 1999           | 0              | 64      | 0 64 0.3% 0.00 [0.03, 0.03]        |                                   |
| Novak-Laus 2003   | 0              | 15      | 0 15 0.1% 0.00 [-0.12, 0.12]       |                                   |
| Reed 1989         | 0              | 384     | 0 363 1.9% 0.00 [0.01, 0.01]       |                                   |
| Sheffer 2005      | 2              | 10890   | 2 10773 55.5% -0.00 [-0.00, 0.00]  |                                   |
| Tinkelman 1993    | 0              | 102     | 0 93 0.5% 0.00 [-0.02, 0.02]       |                                   |
| Subtotal (95% CI) | 11702          | 11438   | 59.1% -0.00 [-0.00, 0.00]          |                                   |
| Total events      | 2              | 3       |                                   |                                   |
| Heterogeneity: Ch\(^2\) = 0.71, df = 6 (P = 0.99); I\(^2\) = 0% |
| Test for overall effect: Z = 0.30 (P = 0.76) |
| 1.1.2 RCT INS     |                |         |                                   |                                   |
| Howland 1996      | 0              | 77      | 0 77 0.4% 0.00 [-0.03, 0.03]       |                                   |
| Maspero 2008      | 0              | 85      | 0 43 0.3% 0.00 [-0.04, 0.04]       |                                   |
| Subtotal (95% CI) | 162            | 120     | 120 0.7% 0.00 [-0.02, 0.02]        |                                   |
| Total events      | 0              | 0       |                                   |                                   |
| Heterogeneity: Ch\(^2\) = 0.00, df = 1 (P = 1.00); I\(^2\) = 0% |
| Test for overall effect: Z = 0.00 (P = 1.00) |
| 1.1.3 NRSI ICS    |                |         |                                   |                                   |
| Chang 2017        | 12             | 4928    | 76 16592 38.9% -0.00 [-0.00, -0.00] |                                   |
| Subtotal (95% CI) | 4928           | 16592   | 38.9% -0.00 [-0.00, -0.00]         |                                   |
| Total events      | 12             | 76      |                                   |                                   |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.45 (P = 0.01) |
| 1.1.4 NRSI INS    |                |         |                                   |                                   |
| Mohd Zain 2019    | 16             | 271     | 7 244 1.1% 0.03 [-0.00, 0.07]      |                                   |
| Subtotal (95% CI) | 271            | 244     | 1.1% 0.03 [-0.00, 0.07]            |                                   |
| Total events      | 16             | 7       |                                   |                                   |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.70 (P = 0.09) |
| Total (95% CI)    | 17063          | 28394   | 100.0% -0.00 [-0.00, 0.00]         |                                   |
| Total events      | 30             | 86      |                                   |                                   |
| Heterogeneity: Ch\(^2\) = 14.00, df = 10 (P = 0.17); I\(^2\) = 29% |
| Test for overall effect: Z = 1.07 (P = 0.28) |
| Test for subgroup differences: Ch\(^2\) = 7.91, df = 3 (P = 0.05), I\(^2\) = 62.1% |

Figure 3 Continued.
### Figure 3 Continued.

| Study or Subgroup | Corticosteroids | Control | Risk Difference M-H, Fixed, 95% CI |
|-------------------|-----------------|---------|----------------------------------|
| **1.2.1 RCT ICS IOP increase** |
| Duh 2020          | 10              | 311     | 2 81 6.2% 0.02 [-0.02, 0.06] |
| Ferguson 2017     | 0               | 303     | 1 307 15.8% -0.00 [-0.01, 0.01] |
| Kerwin 2019       | 7               | 186     | 3 125 7.7% 0.01 [-0.02, 0.05] |
| Moss 2017         | 0               | 1       | 0 1 0.1% 0.00 [-0.85, 0.85] |
| **Subtotal (95% CI)** | 721             | 514     | 297 18.4% 0.01 [-0.01, 0.02] |
| Total events      | 17              |         | 6                                |
| **Heterogeneity:** | Chi² = 4.30, df = 3 (P = 0.23); I² = 30% |
| **Test for overall effect:** | Z = 0.77 (P = 0.44) |

| **1.2.2 RCT ICS IOP >21** |
| Kemp 2004          | 0               | 212     | 1 108 7.4% -0.01 [-0.03, 0.01] |
| Kerwin 2019        | 5               | 186     | 4 125 7.7% -0.01 [-0.04, 0.03] |
| Li 1999            | 2               | 64      | 3 64 3.3% -0.02 [-0.08, 0.05] |
| **Subtotal (95% CI)** | 462             | 297     | 18.4% -0.01 [-0.03, 0.01] |
| Total events       | 7               |         | 8                                |
| **Heterogeneity:** | Chi² = 0.08, df = 2 (P = 0.96); I² = 0% |
| **Test for overall effect:** | Z = 0.77 (P = 0.44) |

| **1.2.3 RCT ICS IOP >22** |
| Novak–Laus 2003    | 4               | 15      | 0 15 0.8% 0.27 [0.03, 0.50] |
| **Subtotal (95% CI)** | 15              | 15      | 0.8% 0.27 [0.03, 0.50] |
| Total events       | 4               |         | 0                                |
| **Heterogeneity:** | Not applicable |
| **Test for overall effect:** | Z = 2.21 (P = 0.03) |

| **1.2.4 RCT INS IOP increase** |
| Adriaensen 2017    | 0               | 1       | 0 1 0.1% 0.00 [-0.85, 0.85] |
| Han 2014           | 0               | 13      | 0 12 0.6% 0.00 [-0.14, 0.14] |
| Igarashi 2012      | 0               | 1       | 0 1 0.1% 0.00 [-0.85, 0.85] |
| LaForce 2012       | 7               | 734     | 1 362 25.1% 0.01 [-0.00, 0.02] |
| Marhold 2011       | 1               | 26      | 0 26 1.3% 0.04 [-0.06, 0.14] |
| Rosenwasser 2008   | 0               | 1       | 1 1 0.1% -1.00 [-1.85, -0.15] |
| Rotenberg 2011     | 0               | 21      | 0 39 1.4% 0.00 [-0.07, 0.07] |
| Weinstein 2014     | 1               | 197     | 0 48 4.0% 0.01 [-0.03, 0.04] |
| **Subtotal (95% CI)** | 994             | 490     | 32.6% 0.01 [-0.01, 0.02] |
| Total events       | 9               |         | 2                                |
| **Heterogeneity:** | Chi² = 5.88, df = 7 (P = 0.55); I² = 0% |
| **Test for overall effect:** | Z = 1.04 (P = 0.30) |

| **1.2.5 RCT INS IOP >20** |
| Ratner 2006        | 6               | 17      | 3 6 0.5% -0.15 [-0.61, 0.31] |
| **Subtotal (95% CI)** | 17              | 6       | 0.5% -0.15 [-0.61, 0.31] |
| Total events       | 6               |         | 3                                |
| **Heterogeneity:** | Not applicable |
| **Test for overall effect:** | Z = 0.63 (P = 0.53) |

| **1.2.6 RCT INS IOP >22** |
| Kothiwala 2021     | 0               | 8       | 0 8 0.4% 0.00 [-0.21, 0.21] |
| Rosenblut 2007     | 12              | 605     | 0 201 15.6% 0.02 [0.01, 0.03] |
| **Subtotal (95% CI)** | 613             | 209     | 16.0% 0.02 [0.00, 0.03] |
| Total events       | 12              |         | 0                                |
| **Heterogeneity:** | Chi² = 0.04, df = 1 (P = 0.85); I² = 0% |
| **Test for overall effect:** | Z = 2.64 (P = 0.008) |

| **1.2.7 NRSI ICS IOP increase** |
| Dereci 2015        | 0               | 38      | 0 40 2.0% 0.00 [-0.05, 0.05] |
| **Subtotal (95% CI)** | 38              | 40      | 2.0% 0.00 [-0.05, 0.05] |
| Total events       | 0               |         | 0                                |
| **Heterogeneity:** | Not applicable |
| **Test for overall effect:** | Z = 0.00 (P = 1.00) |

| **Total (95% CI)** | 2860            | 1571    | 100.0% 0.01 [-0.00, 0.01] |
| Total events       | 55              |         | 19                                |
| **Heterogeneity:** | Chi² = 22.44, df = 19 (P = 0.02); I² = 15% |
| **Test for overall effect:** | Z = 3.06 (P = 0.001) |
| **Test for subgroup differences:** | Chi² = 9.95, df = 6 (P = 0.13), I² = 39.7% |
Figure 3 Forest plots for reported (A) glaucoma incidence; (B) OHT incidence; (C) endpoint IOP difference between ICS or INS users and controls; (D) change in IOP after ICS or INS use compared to pre-treatment baseline.

Abbreviations: CI, confidence interval; OHT, ocular hypertension; IOP, intraocular pressure; ICS, inhalational corticosteroids; INS, intranasal corticosteroids; RCT, randomized control trial; NRSI, non-randomized study of interventions.
significant influence of the large study by LaForce on the analysis. Pediatric and adult populations did not display significantly different trends (Supplementary Material, Figure 3).

Differences in IOP Between Corticosteroid Users and Controls
Among 857 ICS/INS users and 615 non-user controls (Figure 3C), corticosteroid users had significantly higher IOP with a mean difference of +0.69 mmHg (95% CI: 0.15, 1.23; \( p < 0.01 \)) compared to controls. In a subgroup analysis of RCTs, ICS users were statistically indistinguishable from controls with a mean difference in IOP of −0.10 mmHg (95% CI: −2.89, 2.69; \( p = 0.94 \)). In NRSIs, ICS users had a higher mean IOP compared to controls by 0.70 mmHg (95% CI: −0.21, 1.61; \( p = 0.13 \)). In a subgroup analysis of RCTs, INS users had a higher mean IOP compared to controls (+0.06 mmHg; 95% CI: −0.85, 0.98; \( p = 0.89 \)). In NRSIs, INS users had significantly higher mean IOP than controls by 1.21 mmHg (95% CI: 0.57, 1.85; \( p < 0.0002 \)). There was significant heterogeneity between the studies (\( I^2 = 75\% \)), however no large studies were identified to explain the large heterogeneity. Largest effect was noted by the study by Shroff (Supplementary Material, Figure 2), however overall result remained consistent even with this study excluded. Both adult and pediatric populations have displayed these statistically significant trends (Supplementary Material, Figure 3). However adult studies showed a higher mean IOP by 0.90 mmHg (95% CI: 0.08, 1.73, \( p < 0.02 \)) in ICS/INS users compared to controls, while in pediatric population, this difference was smaller at 0.45 mmHg (95% CI: 0.33, 0.57, \( p < 0.00001 \)).

Change in IOP from Pre-Treatment Baseline
Collectively, 1360 patients had IOP measurements reported prior to initiating ICS/INS use, as well as at the end of follow-up. These data are summarized in Figure 3D. Overall, there was a 0.25 mmHg (95% CI: −0.85, 0.34, \( p = 0.41 \)) nonsignificant increase in IOP following corticosteroid use. Subgroup analysis of RCTs showed a significant increase in mean IOP after ICS use of 1.09 mmHg (95% CI: 0.18, 1.99; \( p < 0.05 \)). In NRSIs, IOP increased after ICS use by 0.04 mmHg (95% CI: −0.65, 0.74; \( p = 0.90 \)). Within RCTs, IOP increased after INS use by 0.18 mmHg (95% CI: −0.20, 0.56; \( p = 0.36 \)). In NRSIs, IOP after INS use was lower by 0.2 mmHg (95% CI: −0.55, 0.95; \( p = 0.60 \)). There was significant heterogeneity between the studies (\( I^2 = 79\% \)), and sensitivity analysis (Supplementary Material, Figure 2) identified significant influence of large study by Chylack; however, overall conclusions remained the same with the study excluded. Similarly, separate analyses of adult and pediatric populations displayed similar trends (Supplementary Material, Figure 3).

Discussion
The new GINA treatment guidelines recommend increased exposure to ICS, notably daily use starting in patients as young as 12 years of age. Given the known effect of corticosteroids on IOP elevation and risk of glaucoma, widespread use of ICS and INS may raise concerns regarding OHT and glaucoma risks as even low absolute risks when applied to hundreds of millions of patients can be of significant impact. Even a 0.1 mmHg increase in IOP over a population can increase the risk of glaucoma or its progression. Our search identified 65 primary studies discussing ocular outcomes in patients using ICS and INS, compared to control. Qualitative assessment revealed that most studies report ICS and INS as well tolerated, and do not raise ocular safety concerns. Quantitative assessment of 41 primary studies including 54,080 patients assessed difference in glaucoma incidence, OHT incidence, IOP between users and non-users, as well IOP changes following ICS or INS use. Overall, there was no statistically significant difference in glaucoma incidence in ICS and INS users compared to controls in overall and subgroup analyses over 45,457 person-years of follow-up. With respect to OHT incidence, there was a lack of consistency in IOP threshold between studies, ranging between 20 and 22 mmHg. Regardless of these differences, tests for overall effect and most subgroup analyses did not identify significant trends in risks for OHT incidence in corticosteroid users compared to control over 4431 person-years of follow-up. While single subgroup analysis of OHT incidence using a 22 mmHg IOP threshold demonstrated significant risk differences between ICS users and non-users, this subgroup includes only a single study with 30 person-years of follow-up, thus this finding is potentially of limited clinical significance.
Interestingly, overall analysis identified a statistically significant increase of 0.69 mmHg IOP in ICS or INS users compared to non-users. Subgroup analysis supported this finding only in NRSI INS studies, with a mean difference between groups of 1.21 mmHg.

There was no significant increase in IOP following ICS or INS use compared to patients’ baseline. However, subgroup analysis identified a significant increase in IOP of 1.09 mmHg following ICS use in RCTs. Potentially, these differences are related to longer duration of use and follow-up (between 6 months and up to 4 years) compared to other groups (between 6 weeks and 1 year). Within this subgroup, the study by Chylack 2009 possessed the greatest weight, resulting in a significant mean increase in IOP for the overall subgroup. Although this study was double-blinded, it lacked a placebo control group. Furthermore, there is well-documented evidence demonstrating that IOP measurements can fluctuate due to patient factors, timing, and evaluator variability. Therefore, caution is warranted when determining whether these results are truly clinically significant.

Overall lack of significant increases in glaucoma or OHT incidence suggests that the use of INS and ICS at the doses prescribed and over the periods studied are alone not a major risk factor. This conclusion, of course is reliant upon the definitions for glaucoma and OHT used in the various reported studies. On a per patient level, a 1 mmHg rise in IOP is unlikely clinically significant. However, at a population level, this number would be significant for a risk of development and progression of glaucoma, especially when patients already have a number of other risk factors for the disease.

Steroid-induced glaucoma is a well-known secondary cause of open-angle glaucoma. A third of the population is designated as steroid responders, as they are more likely to develop IOP elevation, OHT and glaucoma in response to topical ocular steroid administration. Up to 95% of these patients have a family history of glaucoma. Interestingly, many authors excluded patients with family history of glaucoma from enrollment in their studies, which may have resulted in an underestimation of risk by excluding potential steroid responders. As such, the current literature may be underestimating the risk of IOP increase, OHT and glaucoma incidence, which may limit applicability of the findings and risk assessment to general population.

Glaucoma diagnosis and management depend upon an accurate development of a risk factor profile for each patient. The results of this study do support the need for awareness among both practitioners and patients of the potential risk of long-term use of ICS and INS. Upon prescription, it may be prudent to recommend that patients actively seek regular examinations with an eye care professional and report the use of these medications.

Limitations of the current study are consistent with those previously identified by other authors working on the subject. Lack of inclusion of patients with family history of glaucoma is a potential confounder, leading to possible exclusion of potential steroid responders. Large variability in diagnostic methods, such as tonometry measurements, and reporting criteria for ocular outcomes, such as OHT threshold and glaucoma diagnosis, is also widespread. Similarly, there remains a relative lack of IOP data reporting in the field, making meta-analysis challenging and precluding dose-response analysis. Multiple studies were found to have industry sponsorship – on one hand, this may raise concerns of a risk of bias; however, these partnerships fuel research that leads to discovery of vision-saving treatments and is thus an important source of research support. Results suggest future studies may be warranted that are more representative of the at-risk population, capture more detailed risk factors, include tighter definitions of endpoints, and incorporate comparisons of corticosteroid potencies, dosing regimens, and lengths of exposure.

**Conclusion**

In conclusion, a small but significant IOP elevation of 0.69 mmHg was identified in patients using ICS and INS. Increases of this magnitude are known to increase the risk of glaucoma at a population level. The relatively recent GINA recommendations would cause a significant increase in the number of patients exposed to chronic daily corticosteroid use. Awareness of the potential risk of glaucoma may be an important consideration for patient-informed consent and recommendations for patient management.

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