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Inhaled Corticosteroid and Secondary Glaucoma: A Meta-analysis of 18 Studies

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Trial Registration
University Hospital Medical Information Network Center Clinical Trial Registry Identifier: UMIN000040351

Disclosure
Takeshi Kaneko received lecture fees from GlaxoSmithKline, Novartis International, Boehringer Ingelheim, and AstraZeneca. The other authors have no conflict of interest to declare.

ABSTRACT

Purpose: Guidelines and systematic reviews frequently warn of inhaled corticosteroid (ICS)-induced glaucoma. However, most of the published studies deny it.
Methods: We performed a systematic review of randomized, cohort, nested-case control, cross-sectional studies by using Meta-analyses of Observational Studies in Epidemiology statement. Four major databases, PubMed, EMBASE, Cochrane Search Manager, and the Web of Science Core Collection as well as meta-analysis were used. Studies comparing incidence, prevalence and intraocular pressure (IOP) between patients who were treated with and without ICSs were included. A random-model meta-analysis was performed using the inverse variance method.
Results: Out of 623 studies screened, 18 with 31,665 subjects were finally included. No significant difference between the 2 groups was observed for crude glaucoma incidence (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.86–1.04; $P = 0.26$; $I^2 = 0\%$; P for heterogeneity = 0.57) as a primary endpoint, adjusted glaucoma incidence (OR, 0.90; 95% CI, 0.65–1.24; $P = 0.64$), crude prevalence (OR, 1.82; 95% CI, 0.23–14.19; $P = 0.57$), adjusted prevalence (OR, 1.22; 95% CI, 0.50–2.96; $P = 0.66$), IOP change during ICS treatment (mean difference [MD] +0.01 mmHg; 95% CI, −0.19–0.20; $P = 0.95$), and single measurement IOP (MD +0.37 mmHg; 95% CI, −0.24–0.97; $P = 0.23$). Time-to-event analysis for glaucoma development as one of the secondary endpoints (adjusted hazard ratio, 0.52; 95% CI, 0.28–0.96) suggested a reverse association between ICS and glaucoma.
Conclusions: The ophthalmological side effects of ICSs, such as glaucoma and intraocular hypertension, should not be exaggerated.

Trial Registration: University Hospital Medical Information Network Center Clinical Trial Registry Identifier: UMIN000040351

Keywords: Asthma; chronic obstructive pulmonary disease; adrenal cortex hormones; glaucoma; meta-analysis; cohort studies; review; intraocular pressure

INTRODUCTION

Asthma is a chronic airway inflammatory disease characterized by recurrent, fluctuating, reversible airflow obstruction.[1] Chronic obstructive pulmonary disease (COPD) is another

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pulmonary disease with chronic airflow obstruction and systemic inflammation.[2] To improve our clinical understanding and treatment of patients with obstructive airway diseases, a disease concept of asthma COPD overlap (ACO) has recently been established.[3] Inhaled corticosteroids (ICSs) are accepted as the first-choice treatment strategy for stable asthma and ACO and as one of the treatment options for COPD.[1-3] Corticosteroid is directly delivered to the airways via an inhaler device and intensely ameliorates inflammation of the respiratory system. Compared to oral corticosteroids, ICSs cause less systemic side effects because a small portion of ICS is absorbed into the whole-body circulation. Nonetheless, ICS causes systemic adverse events including hypothalamic-pituitary-adrenal axis insufficiency, decreased bone mineral density, and dermal thinning.[4-7] Attention should also be paid to ocular effects such as cataracts and glaucoma. A large-scale case-control study with 9,793 cases and 38,325 controls by Garbe *et al.*[8] showed that prolonged administration of high doses of ICS increased the risk of composite ocular hypertension or open-angle glaucoma. Their report in 1997 raised a serious concern for physicians who take care of patients with respiratory diseases because glaucoma is a lifelong eye disease that can lead to permanent vision impairment if not properly controlled.[9-11]

However, the majority of subsequent studies denied the increased glaucoma risk by administering ICS.[12-25] Furthermore, no meta-analysis assessed the impact of ICS on the risk of secondary glaucoma and ocular hypertension, although a few systematic reviews warned of ICS-induced glaucoma based on the report by Garbe *et al.*[4-8] Glaucoma is an age-related disease that occurs mainly in the elderly. Nonetheless, many published studies suggest that glaucoma or elevated intraocular pressure (IOP) of kids caused by ICS is a serious concern for both pulmonologist and ophthalmologist. This systematic review and meta-analysis aimed to clarify whether ICS increases the risk of glaucoma and elevated IOP using data from both randomized controlled trials (RCTs) and observational studies that evaluated child and adult patients with asthma, COPD, and other respiratory conditions.

MATERIALS AND METHODS

Ethics and protocol registration

Institutional Review Board approval for ethical issues was waived because of the review nature of the current study. The protocol of this systematic review complying with Meta-analyses of Observational Studies in Epidemiology statement has been registered in the University Hospital Medical Information Network Center Clinical Trial Registry (Japan) as UMIN000040351 (**Supplementary Table S1**).[26,27]

Study search

We searched for candidate articles using 4 major electronic databases, namely PubMed, Cochrane, EMBASE, and Web of Science Core Collection on May 10th, 2020 by Mai Ishii and Nobuyuki Horita. The search strategies are presented elsewhere (**Supplementary Table S2**). An author of the original research was contacted if needed. Review articles and included original studies were hand searched to identify additional reports. Hand search was done by H.M. and N.H.

Study selection, study design, and publication type

Our systematic review included studies with any design such as RCT, nested case-control study, cohort study, and cross-sectional study as long as studies compared the incidence or

prevalence of glaucoma between patients who were treated with ICS and those who were not. In this study, not only a case-controlled study that compared glaucoma and non-glaucoma individuals, but also a study that compared ICS-treated and ICS-non-treated populations without chronological follow-up were regarded as cross-sectional studies. Traditionally, a case-control study compares the prevalence of risk exposure between groups with and without an outcome. However, we did not use the term "case-control study" in this review so as to avoid confusion because some published cohort studies that compared ICS and non-ICS cohorts that followed subjects over time were referred to as "case-control studies."

Studies that offered information concerning only secondary endpoints such as IOP and a conference abstract were also included. According to the protocol, non-English language articles were accepted, regardless of authors' interpretation skill of the language. Articles Written in non-familiar languages were translated by outside translators.

Subjects and treatment

No limitation was set for the type of ICS, inhalational device, dosage of medication, duration for treatment, or type of glaucoma.[1,9,10] Background respiratory diseases, for which ICS was prescribed, were not restricted to asthma, ACO, or COPD. Subjects without any respiratory disease were included because respiratory condition was not considered a key determinant of glaucoma liability. When patients in the ICS arm were planned to be treated with ICS plus muscarine antagonist, the patients in the non-ICS arm should have also been treated with the same muscarine antagonist because muscarine antagonist is a potential cause of glaucoma.[28,29]

Primary outcome

The protocol-specified primary outcome was glaucoma incidence in the form of a crude odds ratio (OR) between the ICS and non-ICS population. The crude OR of incidence was selected as the primary outcome. Study design-based subgroup analyses were also our key concern.

Secondary outcome

The secondary outcomes included glaucoma incidence (adjusted OR and adjusted hazard ratio [HR]), glaucoma prevalence (crude and adjusted OR), IOP change from baseline (mmHg mean difference [MD]), and single-measurement IOP (mmHg MD). Data from an RCT were used for both crude and adjusted outcomes.

Quality assessment

The risk for the bias of each study was assessed using the Newcastle-Ottawa Scale.[30]

Statistics

Data were independently extracted by M.I. and N.H.. When one or more cells in the 2-by-2 contingency were null, 0.5 was added to all the cells before calculating crude OR. The OR and HR were pooled after logarithmic transformation. The inverse variance method was used for all meta-analyses. MD (mmHg) was pooled for the IOP analyses.

A random-effect model meta-analysis was conducted using Review Manager version 5 for the main analysis, regardless of the degree of heterogeneity (Cochrane, London, UK). Heterogeneity was assessed using I^2 statistics and P values. A forest plot was made by using the same software. A fixed model and leave-one-out method were used as part of the sensitivity analysis. Publication bias was checked using the Begg-Kendall test with a statistical cutoff of $P = 0.1$, unlike the standard $P < 0.05$.

RESULTS

Studies

A total of 623 articles passed our first-step criteria from database search and hand search. Finally, 18 studies including 7 RCTs,[12-18] 4 prospective cohort studies,[19-22] 1 retrospective cohort study,[23] 2 nested case-control studies,[24,25] and 4 cross-sectional studies[31-34] published from 1987 to 2019 were adopted for our analysis (**Table 1**, **Fig. 1**).

The number of subjects in each study varied greatly from 22 to 12,312 with a median of 466, summing up to 31,665 patients (ICS 10,886, non-ICS 20,779; **Table 1**). The patient background of each study was also not consistent. Six studies evaluated only pediatric patients aged 16 years or younger, 9 studies recruited adolescents and adults who were 15 years or older, and 2 assessed patients aged between 6 and 70 years. Another trial recruited only pediatric cases and evaluated them after a long follow-up when the patients' mean age was years. Asthma was the most common reason for ICS prescription (n = 13), followed by COPD (n = 2) and chronic airflow obstruction (n = 1). No study specifically recruited or reviewed the ACO cases. A trial randomly assigned glaucoma patients without any respiratory diseases (**Table 1**). The total Newcastle-Ottawa Scale score to assess the quality of included studies ranged from 3 to 8 points with a median of 6.5 points, with 9 points suggesting the best study quality (**Supplementary Table S3**).

Qualitative description of the conclusion in each study

The conclusion of the 18 studies included are summarized in **Table 2**. While 3 cross-sectional studies mentioned confirmed or possible risk of glaucoma or elevated IOP by ICS,[32-34] a prospective cohort study revealed decreased risk of glaucoma by ICSs. The other 14 studies, including 7 RCTs, made a neutral statement in conclusion (**Table 2**).[20]

Table 1. Background characteristics of the studies included

Author	Country	ICS type	Respiratory disease	Glaucoma	Pt age (yr)	F/U duration	Subjects (ICS, non-ICS)	NOS
Randomized controlled								
Duh *et al.*[18]	USA	Budesonide	Asthma	NA	6–70	12–20 wk	937, 318	7
Kerwin *et al.*[12]	USA	Budesonide	COPD	NA	40–80	52 wk	132, 125	7
Li *et al.*[13]	USA	FP	Asthma	Any	18–50	2 yr	32, 32	8
Moss *et al.*[14]	Canada	FP	None	OAG	18–85	6 wk	11, 11	7
Pelkonen *et al.*[15]	Finland	Budesonide	Asthma	NA	5–10	18 mon	58, 58	8
Reed *et al.*[16]	USA	Any	Asthma	Any	6–65	1 yr	384, 363	7
Silverman *et al.*[17]	UK	Budesonide	Asthma	Any	5–10	3 yr	1,004, 977	6
Prospective cohort								
Alsaadi *et al.*[19]	Saudi Arabia	Fluticasone	Asthma	Any	5–15	12 wk	69, 24	4
Chang *et al.*[20]	China	Any ICS	Asthma	Any	0–6	Up to 15 yr	1,232, 4,148	7
Marcus *et al.*[21]	Netherlands	Any ICS	NS	OAG	≥ 55	Median 9.8 yr	572, 3,367	5
Pedersen *et al.*[22]	Denmark	Budesonide	Asthma	NA	Mean 11	Mean 15.7 yr	148, 53	4
Retrospective cohort								
Nassif *et al.*[23]	USA	Beclomethasone	Asthma	NA	3–16	Mean 2.8 yr	32, 20	7
Nested case-control								
Gonzalez *et al.*[24]	Canada	Any ICS	CAO	Any	≥ 65	Mean 4 yr	4,931, 7,383	7
Miller *et al.*[25]	USA	Any ICS	COPD	Any	≥ 45	At least 1 yr	478, 498	6
Cross sectional								
Emin *et al.*[31]	Turkey	FP	Asthma	Any	7–11	NA	266, 160	6
Mitchell *et al.*[32]	Australia	Any ICS	Asthma	OAG	49–97	NA	370, 3,012	5
Shroff *et al.*[33]	India	Any ICS	NS	Any	15–89	NA	200, 200	6
Novak-Lauš *et al.*[34]	Croatia	Any ICS	Asthma	Any	19–62	NA	30, 30	5

Duh *et al.*[18] pooled the data of 4 randomized controlled trials. Pedersen *et al.*[22] was a conference abstract and the others were full articles.
ICS, inhaled corticosteroid; Pt, patient; FP, fluticasone propionate; COPD, chronic obstructive pulmonary disease; CAO, chronic airway obstruction; NS, not specified; OAG, open-angle glaucoma; NA, not applicable since the study assessed intraocular pressure but not glaucoma risk; F/U, follow-up; NA, not applicable because of cross-sectional study design; NOS, Newcastle-Ottawa Scale score wherein the maximal score of 9 suggests the best quality.

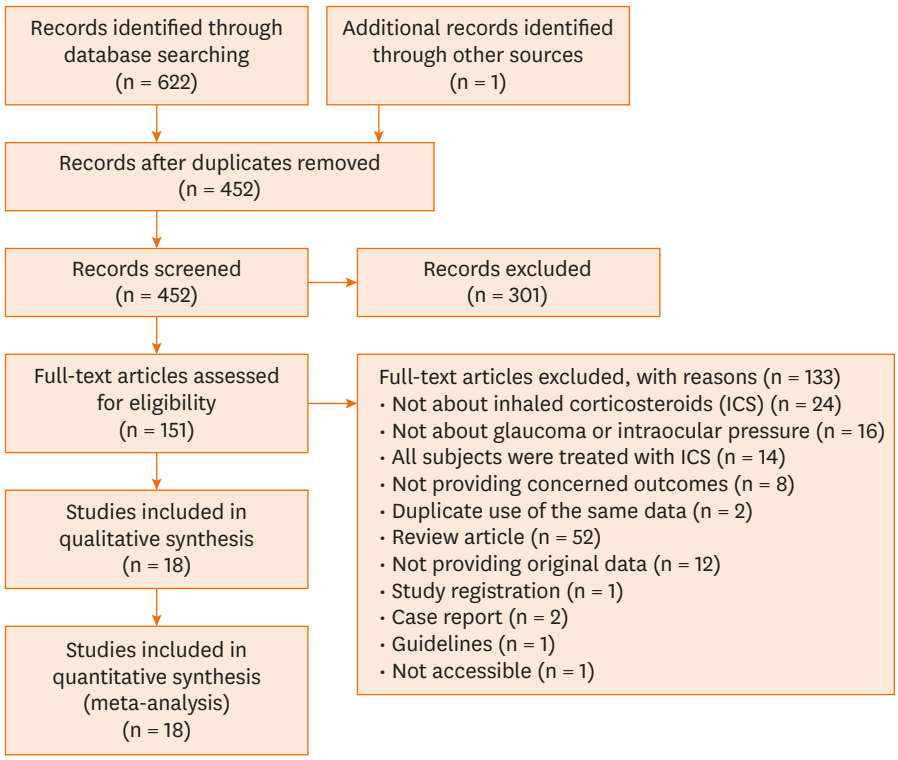


Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow chart.

Table 2. Author conclusion of included original studies

Author	Author conclusion
Randomized controlled trial	
Duh *et al.*[18]	No association with an increased IOP was observed in asthmatic patients treated with budesonide.
Kerwin *et al.*[12]	In patients with COPD, ICS-containing therapies were well tolerated.
Li *et al.*[13]	FP was well tolerated in adults with mild asthma.
Moss *et al.*[14]	No increase in mean IOP in patients with well-controlled OAG and ocular hypertension.
Pelkonen *et al.*[15]	Budesonide did not cause clinically important increases in IOP in children with asthma.
Reed *et al.*[16]	ICS may be the preferred agent for most adult patients and for some children according to the risk/benefit profiles.
Silverman *et al.*[17]	Addition of budesonide to usual care is safe and well tolerated in children with recent-onset mild persistent asthma.
Prospective cohort study	
Alsaadi *et al.*[19]	Inhaled fluticasone over a short period was not associated with a significant effect on IOP in asthmatic children without a family history of glaucoma.
Chang *et al.*[20]	Glaucoma incidence in the ICS group is lower than that in the non-ICS group in children with asthma.
Marcus *et al.*[21]	None of the classes of steroids were associated with the incidence of OAG in elderly population.
Pedersen *et al.*[22]	Inhaled budesonide in children with chronic asthma for a mean of 15.7 years was not associated with any adverse effects in adulthood on IOP.
Retrospective cohort study	
Nassif *et al.*[23]	IOP effects of Inhaled beclomethasone appeared not to be of clinical importance.
Nested case-control study	
Gonzalez *et al.*[24]	Continuous use of high-dose ICS did not result in an increased risk of glaucoma or raised intra-ocular pressure requiring treatment.
Miller *et al.*[25]	ICS exposure was not associated with an increased odd of glaucoma.
Cross sectional study	
Emin *et al.*[31]	Long-term intermittent treatment inhaled FP spray in children with asthma seems to be safe for some eye functions.
Mitchell *et al.*[32]	Ever use of ICS was associated with a finding of elevated IOP or glaucoma in subjects with a glaucoma family history.
Shroff *et al.*[33]	Probable association between ICS and IOP was suggested.
Novak-Lauš *et al.*[34]	Long-term use of high doses of ICS was correlated with the occurrence of intraocular hypertension in patients with a positive family history of glaucoma.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; FP, fluticasone propionate; OAG, open-angle glaucoma; IOP, intraocular pressure.

Crude incidence as the primary endpoint

The incidence of glaucoma using crude OR as the primary endpoint was assessable from 3 RCTs, 2 prospective cohort studies, and 1 nested case-control study consisted of 20,579 patients. However, no new glaucoma cases were identified from the 3 RCTs. A random model meta-analysis of these 7 studies comprising 7,652 ICS-treated subjects, 12,927 non-ICS-treated subjects, 1,929 glaucoma cases, and 18,650 individuals without glaucoma revealed that ICS was associated with a tendency toward decreased glaucoma incidence with no heterogeneity (OR, 0.95; 95% confidence interval [CI], 0.86–1.04; $P = 0.26$; $I^2 = 0\%$; P for heterogeneity = 0.57) (**Fig. 2A**). A funnel plot did not suggest a publication bias (tau = −0.316; $P = 0.449$; **Supplementary Fig. S1**). A sensitivity analysis using a fixed model replicated the same result (OR, 0.95; 95% CI, 0.86–1.04; $P = 0.26$). Although a nested case-controlled trial[24] represented a proportion as large as 97.2% of the total weight in the random model, leave-one-out sensitivity analysis excluding this study resulted in a trend toward the same direction (OR, 0.54; 95% CI, 0.30–0.97; $P = 0.04$; $I^2 = 0\%$; P for heterogeneity = 0.99).

According to study design-based subgroup analyses, the pooled value from the 3 RCTs resulted in no significant change in the incidence (OR, 0.97; 95% CI, 0.10–9.4; $P = 0.98$; $I^2 = 0\%$; P for heterogeneity = 1.00), while 2 prospective cohort studies yielded a lower pooled glaucoma incidence in favor of ICS (OR, 0.52; 95% CI, 0.29–0.95; $P = 0.03$; $I^2 = 0\%$; P for heterogeneity = 0.84) (**Fig. 2A**).

Adjusted incidence of glaucoma during ICS use

Because the crude incidence in observational studies might be affected by bias, assessing the impact of ICS on the incidence of glaucoma using multivariate adjusted OR was designed in the protocol.

One cohort study and 1 nested case-control study described adjusted OR for glaucoma incidence. A random-model pooled value did not suggest any increased risk of glaucoma using ICS (OR, 0.90; 95% CI, 0.65–1.24; $P = 0.51$; $I^2 = 0\%$; P for heterogeneity = 0.64) (**Fig. 2B**).

Chang *et al.*[20] reviewed randomly selected preschool children using the Taiwan National Database. The Cox hazard was a model applied to 1,232 ICS cases and 4,148 non-ICS cases whose clinical data were followed up for 15 years indicated a substantially decreased hazard of developing glaucoma in ICS-treated children (HR, 0.52; 95% CI, 0.28–0.96; $P = 0.04$) (**Fig. 2C**).

Prevalence

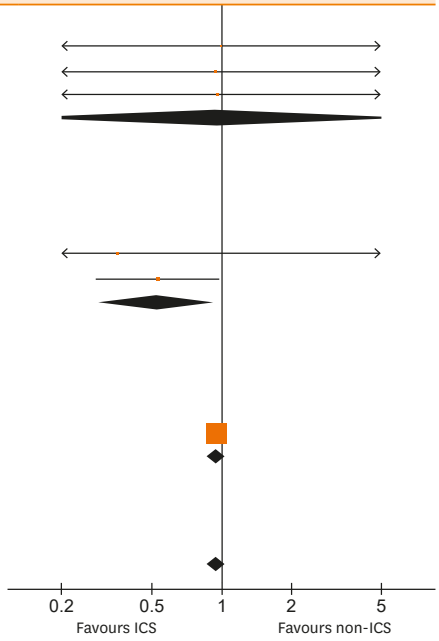
Prevalence analyses based on cross-sectional studies did not show any significant increase in prevalence due to ICS treatment. Three studies yielded imprecise pooled crude OR of 1.82 (95% CI, 0.23–14.19; $P = 0.57$; $I^2 = 0\%$; P for heterogeneity = 0.66). Adjusted OR was estimated by a case-controlled study by Mitchell *et al.*,[32] which separately provided data for cases with and without a glaucoma family history. After combining them, the pooled adjusted OR was 1.22 (95% CI, 0.50–2.96; $P = 0.66$; $I^2 = 37\%$; P for heterogeneity = 0.21) (**Fig. 3**).

Change in IOP during ICS use

A random-model meta-analysis using data from 3 RCTs did not reveal any change in IOP change from baseline during ICS treatment (MD +0.01 mmHg; 95% CI, −0.19–0.20; $P = 0.95$; $I^2 = 0\%$; P for heterogeneity = 0.70) (**Fig. 4A**).

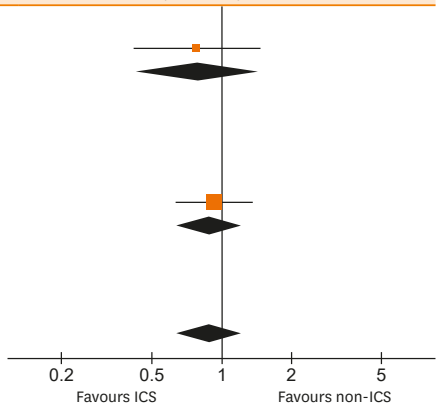
A

Study or subgroup	log[OR]	SE	Weight	OR IV, random, 95% CI
1.1.1 Randomized controlled trial				
Li *et al.* (1999)[13]	0.00	2.02	0.1%	1.00 (0.02, 52.41)
Reed *et al.* (1998)[16]	−0.06	2.00	0.1%	0.94 (0.02, 47.46)
Silverman *et al.* (2006)[17]	−0.03	2.00	0.1%	0.97 (0.02, 48.91)
Subtotal (95% CI)			**0.2%**	**0.97 (0.10, 9.40)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.00$, df = 2 ($P = 1.00$); $I^2 = 0\%$				
Test for overall effect: Z = 0.03 ($P = 0.98$)				
1.1.2 Prospective cohort study				
Alsaadi *et al.* (2012)[19]	−1.04	2.01	0.1%	0.35 (0.01, 18.17)
Chang *et al.* (2017)[20]	−0.64	0.31	2.5%	0.53 (0.29, 0.97)
Subtotal (95% CI)			**2.6%**	**0.52 (0.29, 0.95)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.04$, df = 1 ($P = 0.84$); $I^2 = 0\%$				
Test for overall effect: Z = 2.12 ($P = 0.03$)				
1.1.3 Nested case-control study				
Gonzalez *et al.* (2010)[24]	−0.04	0.05	97.2%	0.96 (0.87, 1.06)
Subtotal (95% CI)			**97.2%**	**0.96 (0.87, 1.06)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.80 ($P = 0.42$)				
Total (95% CI)			**100.0%**	**0.95 (0.86, 1.04)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 3.89$, df = 5 ($P = 0.57$); $I^2 = 0\%$				
Test for overall effect: Z = 1.13 ($P = 0.26$)				
Test for subgroup differences: $\chi^2 = 3.85$, df = 2 ($P = 0.15$); $I^2 = 48.1\%$				



B

Study or subgroup	log[OR]	SE	Weight	OR IV, random, 95% CI
1.2.1 Prospective cohort study				
Marcus *et al.* (2012)[21]	−0.236	0.321	27.2%	0.79 (0.42, 1.48)
Subtotal (95% CI)			**27.2%**	**0.79 (0.42, 1.48)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.74 ($P = 0.46$)				
1.2.2 Nested case-control study				
Miller *et al.* (2011)[25]	−0.062	0.196	72.8%	0.94 (0.64, 1.38)
Subtotal (95% CI)			**72.8%**	**0.94 (0.64, 1.38)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.32 ($P = 0.75$)				
Total (95% CI)			**100.0%**	**0.90 (0.65, 1.24)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.21$, df = 1 ($P = 0.64$); $I^2 = 0\%$				
Test for overall effect: Z = 0.65 ($P = 0.51$)				
Test for subgroup differences: $\chi^2 = 0.21$, df = 1 ($P = 0.64$); $I^2 = 0\%$				



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Study or subgroup	log[HR]	SE	Weight	HR IV, random, 95% CI
1.3.1 Prospective cohort study				
Chang *et al.* (2017)[20]	−0.654	0.314	100.0%	0.52 (0.28, 0.96)
Subtotal (95% CI)			**100.0%**	**0.52 (0.28, 0.96)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.08 ($P = 0.04$)				
Total (95% CI)			**100.0%**	**0.52 (0.28, 0.96)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.08 ($P = 0.04$)				
Test for subgroup differences: Not applicable				

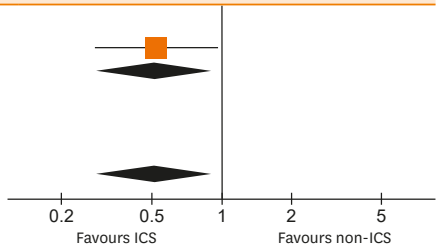


Fig. 2. Forest plots for the incidence of glaucoma by ICSs. (A) Crude OR. (B) Adjusted OR. (C) Adjusted HR.
SE, standard error; IV, inverse variance; ICS, inhaled corticosteroid; CI, confidence interval; OR, odds ratio; HR, hazard ratio.

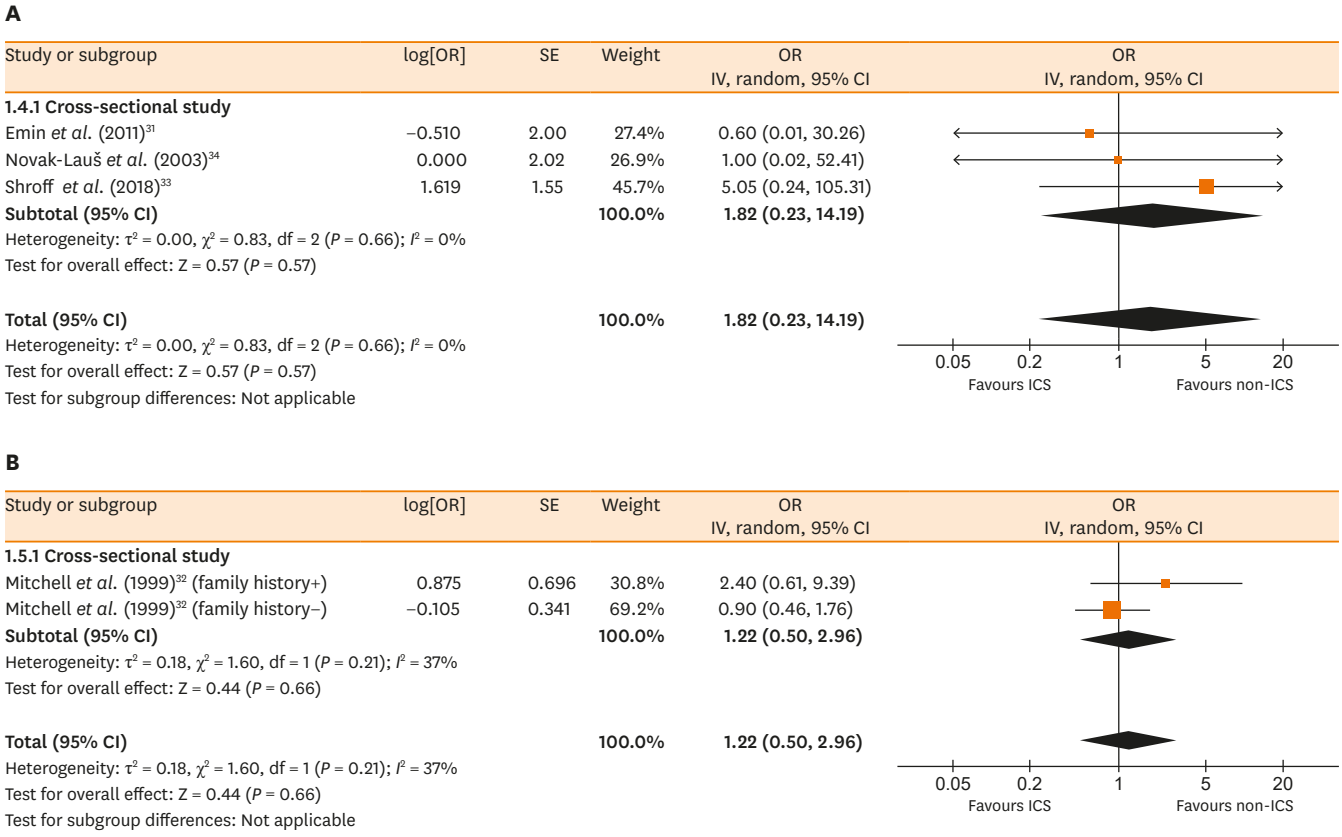


Fig. 3. Forest plots for prevalence of glaucoma by ICSs. (A) Crude OR. (B) Adjusted OR. Mitchell *et al.*[32] provided the data from subjects with and without a family history separately.
SE, standard error; IV, inverse variance; ICS, inhaled corticosteroid; CI, confidence interval; OR, odds ratio.

Single-measurement IOP values pooled from 8 studies were not significantly elevated with an MD of +0.37 mmHg in the ICS arm (95% CI, −0.24–0.97; $P = 0.23$; $I^2 = 99\%$; P for heterogeneity < 0.001). However, this analysis could not confirm elevated IOP among ICS-treated cases due to the small MD, statistical insignificance, and extreme heterogeneity (**Fig. 4B**).

Sensitivity analyses in adult-and child-specific subgroups

Age subpopulation analyses are shown in **Supplementary Figs. S2-4**. For these subgroup analyses, a study with subjects at the age of > 15 years was classified as an adult one, a study with subjects at the age of > 20 or < 20 years was classified as a child one. When a study included subjects of both 21 years old or older and 14 years old or younger, a study was deemed to include both adults and children.

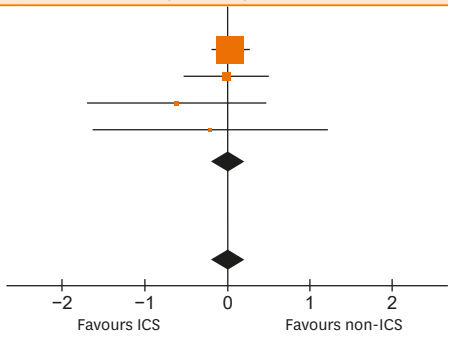
In these subgroup analyses, ICS administration did not lead to increased risk of glaucoma, higher glaucoma prevalence, or elevated IOP. No subgroup heterogeneity among the age subgroups was observed in any outcome.

DISCUSSION

Glaucoma is a leading cause of irreversible vision loss worldwide. Because a patient with early glaucoma often does not have any symptoms, delayed diagnosis of glaucoma may result in

A

Study or subgroup	Mean difference	SE	Weight	Mean difference IV, random, 95% CI
1.7.1 Randomized controlled trial				
Duh *et al.* (2000)[18]	0.04	0.112	79.2%	0.04 (−0.18, 0.26)
Kerwin *et al.* (2019)[12]	−0.01	0.253	15.5%	−0.01 (−0.51, 0.49)
Pelkonen *et al.* (2008)[15] (left eye)	−0.60	0.546	3.3%	−0.60 (−1.67, 0.47)
Pelkonen *et al.* (2008)[15] (right eye)	−0.20	0.722	1.9%	−0.20 (−1.62, 1.22)
Subtotal (95% CI)			**100.0%**	**0.01 (−0.19, 0.20)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.41$, df = 3 ($P = 0.70$); $I^2 = 0\%$				
Test for overall effect: Z = 0.06 ($P = 0.95$)				
Total (95% CI)			**100.0%**	**0.01 (−0.19, 0.20)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 1.41$, df = 3 ($P = 0.70$); $I^2 = 0\%$				
Test for overall effect: Z = 0.06 ($P = 0.95$)				
Test for subgroup differences: Not applicable				



B

Study or subgroup	Mean difference	SE	Weight	Mean difference IV, random, 95% CI
1.8.1 Randomized controlled trial				
Moss *et al.* (2016)[14]	−0.10	1.005	5.8%	−0.10 (−2.07, 1.87)
Pelkonen *et al.* (2008)[15]	−0.60	0.539	10.2%	0.60 (−0.46, 1.66)
Subtotal (95% CI)			**15.9%**	**0.44 (−0.49, 1.37)**
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.38$, df = 1 ($P = 0.54$); $I^2 = 0\%$				
Test for overall effect: Z = 0.93 ($P = 0.35$)				
1.8.2 Prospective cohort study				
Alsaadi *et al.* (2012)[19]	0.00	0.408	11.7%	0.00 (−0.80, 0.80)
Pedersen *et al.* (2011)[22]	−0.60	0.025	14.7%	−0.60 (−0.65, −0.55)
Subtotal (95% CI)			**26.4%**	**−0.44 (−0.96, 0.08)**
Heterogeneity: $\tau^2 = 0.10$, $\chi^2 = 2.15$, df = 1 ($P = 0.14$); $I^2 = 54\%$				
Test for overall effect: Z = 1.65 ($P = 0.10$)				
1.8.3 Retrospective cohort study				
Nassif *et al.* (1987)[23]	0.00	0.128	14.4%	0.00 (−0.25, 0.25)
Subtotal (95% CI)			**14.4%**	**0.00 (−0.25, 0.25)**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.00 ($P = 1.00$)				
1.8.4 Cross-sectional study				
Emin *et al.* (2011)[31] (left eye)	0.70	0.044	14.7%	0.70 (0.61, 0.79)
Emin *et al.* (2011)[31] (right eye)	0.20	0.063	14.6%	0.20 (0.08, 0.32)
Shroff *et al.* (2018)[33]	1.92	0.190	14.0%	1.92 (1.55, 2.29)
Subtotal (95% CI)			**43.3%**	**0.90 (0.33, 1.47)**
Heterogeneity: $\tau^2 = 0.24$, $\chi^2 = 93.55$, df = 2 ($P < 0.00001$); $I^2 = 98\%$				
Test for overall effect: Z = 3.09 ($P = 0.002$)				
Total (95% CI)			**100.0%**	**0.37 (−0.24, 0.97)**
Heterogeneity: $\tau^2 = 0.65$, $\chi^2 = 844.09$, df = 7 ($P < 0.00001$); $I^2 = 99\%$				
Test for overall effect: Z = 1.19 ($P = 0.23$)				
Test for subgroup differences: $\chi^2 = 12.70$, df = 3 ($P = 0.005$); $I^2 = 76.4\%$				

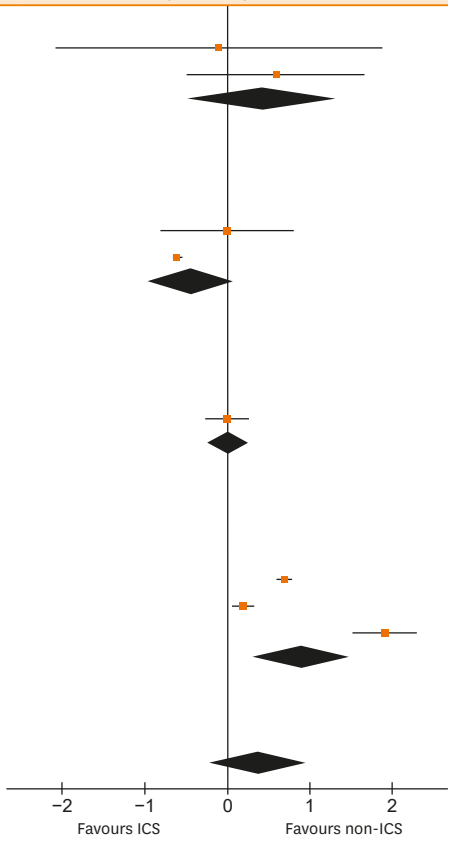


Fig. 4. Forests plots for intraocular pressure mean difference by ICSs. (A) Change from baseline (mmHg). (B) Single-measurement difference (mmHg). Pelkonen *et al.*[15] and Emin *et al.*[31] provided the data for right and left eyes separately.
SE, standard error; IV, inverse variance; ICS, inhaled corticosteroid; CI, confidence interval; MD, mean difference.

permanent visual impairment.[9-11] Glaucoma is an eye disease characterized by optic nerve and visual field deterioration. We selected IOP as a protocol-specified secondary outcome because steroid-induced glaucoma is a secondary one with intraocular hypertension. It is believed that the current systematic review is the first one accompanied by data from

meta-analysis regarding ICS-induced glaucoma because published systematic reviews that were identified from our search did not present data from the meta-analysis.[4-7] Quantitative synthesis using published data did not reveal any evidence to support ICS-induced glaucoma. Surprisingly, patients on ICS treatment had a decreased incidence of glaucoma as the secondary endpoint or in the subgroup analysis (**Fig. 2A and C**).

Corticosteroids are believed to decrease aqueous humor outflow by preventing degradation of extracellular matrix material in the trabecular meshwork, resulting in the accumulation of an excessive volume of the material within the outflow channels and a subsequent increase in outflow resistance.[35] In addition to systematic corticosteroids, topically used steroids, such as inhaled drugs, nasal spray, or ointment, were historically documented as potential risk factors for glaucoma.[35] However, a meta-analysis by Valenzuela *et al.*[36] in 2019 concluded that intranasal corticosteroids were not associated with a significant risk of elevated IOP. In fact, oral corticosteroids absorbed into the systemic circulation have a stronger impact on systemic adverse events compared to topical steroids. Nonetheless, Black *et al.*[37] have recently revealed that systemic corticosteroids for rheumatoid arthritis did not increase the risk of glaucoma according to meta-analyses of RCTs (incidence difference 0.01%; 95% CI −2%–4%; $P = 0.52$) and observational studies (incidence difference 0.00; 95% CI, −0.01–0.02). The results from our systematic review are compatible with those from these meta-analyses regarding corticosteroid-induce ophthalmological adverse events.

Our analysis of 31,665 individuals from 18 studies did not reveal any evidence that ICS increases glaucoma incidence, glaucoma prevalence, or ocular hypertension. In contrast, ICS prescription led to a trend toward decreased glaucoma incidence with a crude OR of 0.95 (95% CI, 0.86–1.04) as the primary endpoint. Surprisingly, the adjusted HR of 0.52 (95% CI, 0.28–0.96) in the time-to-event Cox model analysis implies a reduce risk of glaucoma in ICS-treated patients. These data are trustworthy because of the lack of heterogeneity, sufficient sample size, and consistent trends among crude OR, adjusted OR, adjusted HR, and sensitivity analyses. However, there is no known mechanism directly explaining why ICS decreases the risk of glaucoma.

ICS is the key inhaled medication for stable asthma and ACO. According to epidemiological research, two-thirds of the asthmatic patients have mild intermittent or mild persistent asthma, which is manageable with ICS alone or with long-acting beta stimulants.[1,38] Such patients do not need additional controllers such as long-acting muscarinic antagonists or antihistamines. In addition, when appropriately prescribed for mild asthma, ICS alone decreases the risk of attack that demands short-acting bronchodilators including short-acting muscarinic antagonists. Long-acting and short-acting muscarinic antagonists narrow the corner angle by relaxing the ciliary muscle, increasing the aqueous outflow resistance, and eventually increasing IOP and risk of glaucoma in observational studies.[39] Antihistaminic agents also have a similar anticholinergic effect.[40] ICS prescription may have decreased the incidence of glaucoma in asthmatic patients by precluding exposure to muscarine antagonists and antihistamines.

A report by Garbe *et al.*[8] published in one of the leading medical journals was a milestone concerning the concept of ICS-induced glaucoma and was referred by many successive reviews and guidelines, though the article presented composite ocular hypertension or open-angle glaucoma, which was not allowed in our protocol.[1,47] Garbe *et al.*[8] described that a current user of high dose of ICS was at increased risk of composite ocular hypertension or open-angle

glaucoma with an OR of 1.44 (95% CI, 1.01–2.06). According to the dose-response principle, low- or moderate-dose ICS should have had less impact on increasing the incidence of the composite outcome if ICS truly increases the risk. Nonetheless, Garbe *et al.*[8] reported that low- to medium-dose ICS showed a trend towards a decreased risk of the composite outcome (OR, 0.95; 95% CI, 0.77–1.19). Murray[41] criticized that an important confounders, use of concomitant anticholinergic medications, was not adjusted in the observational study by Garbe *et al.*[8] Mitchell *et al.*[32] detected a phenomenon that was similar to the observation by Garbe *et al.*[8] The risk of open-angle glaucoma increased with higher ICS doses (OR, 6.3; 95% CI, 1.0–38.6) for persons who used ICS more than 4 puffs per day; however, low-dose ICS, ≤ 2 pullfs/day, led to a trend toward lower risk of open-angle glaucoma (OR, 0.6; 95% CI, 0.1–5.3). Indications for and dosage of ICSs are determined on the basis of the severity of asthma or ACO.[1,3] The results from the observational studies and treatment decision-making process led us to speculate some confounding factors in the observational studies. The non-ICS population may mean poorly controlled asthma requiring rescue use of a short-acting muscarinic antagonist. A mild asthmatic patient treated with low-dose ICS might suggest proper control by ICS, making additional controller and rescue treatment dispensable. High-dose ICSs may surround severe asthma, which requires additional treatments besides ICSs such as muscarinic antagonists and antihistamines. This hypothesis also explains why ICS administration for a child led to lower risk of glaucoma in a cohort study in Taiwan.[20] Children with ICSs usually achieved good asthma control and needed less rescue use of anticholinergic. Future research should adjust for such key possible confounders.[41] A beta-agonist is rarely considered a glaucoma-causing medication. However, beta-adrenergic blocking agent is an established medication for glaucoma by reducing aqueous humor production. Given this mechanism, inhaled beta-agonists should also be adjusted as a covariable in future studies. We also noticed that Garbe *et al.*[8] concentrated on a subgroup analysis with a marginal *P* value, even though the subgroup analysis was not of protocol-specified primary outcome. Moreover, incorporating the study by Garbe *et al.*[8] into our analysis did not largely change the result (**Supplementary Fig. S5**).

There are some limitations to our analysis. First, most of the data incorporated in our meta-analysis were derived from observational studies. However, we suppose that an observational study, especially one with a nested case-control design, is a reasonable choice as long as co-variates are appropriately adjusted because the incidence of glaucoma in respiratory patients is not high enough to be suitable for an RCT. Secondly, the numbers of studies that presented data for each of our outcomes were not very large due to the inconsistent study design of original studies. However, a variety of quantitative syntheses (**Figs. 2-4**) and qualitative analysis (**Table 2**) convinced us that ICSs do not induce secondary glaucoma. Thirdly, not all eligible studies were adjusted for anticholinergic medication. Finally, our analysis could not show sufficient data to discuss dose responsiveness.

In conclusion, our systematic review of 18 studies and 31,665 individuals assessed glaucoma risk and IOP outcomes. Available data did not support any positive association between ICS and glaucoma or between ICS and IOP. In contrast, ICS-treated asthmatic patients had substantially lower glaucoma incidence in the time-to-event analysis with pooled adjusted HR of 0.52 in the prospective cohort studies We would not like to infer that ICS directly decreases the glaucoma risk because this conclusion is not biologically persuasive. Since ICSs are an established powerful medication for stable asthma and ACO, patients with low-dose ICSs may less frequently use antihistamine and anti-cholinergic, known glaucoma risk drugs, as rescue medication or add-on treatment. The avoidance of these drugs may explain the decreased incidence of glaucoma in the ICS-treated population. ICSs are an essential

medicine to control asthma and ACO. The ophthalmological side effects of ICSs, such as glaucoma and intraocular hypertension, should not be overly exaggerated.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Meta-analyses of Observational Studies in Epidemiology checklist

Click here to view

Supplementary Table S2

Search formulas

Click here to view

Supplementary Table S3

Newcastle-Ottawa Scale score

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Supplementary Fig. S1

Funnel plot for the primary endpoint. This funnel plot was generated using Review Manager version 5 (Cochrane, London, UK). Begg-Kendall test: tau = −0.316, $P = 0.449$ (> 0.10).

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Supplementary Fig. S2

Forest plots for incidence of glaucoma by inhaled corticosteroids. Age subgroup analyses. (A) Crude odds ratio. (B) Adjusted odds ratio. (C) Adjusted hazard ratio. Adult: 15 years old or elder. Child: 20 years old or younger. Adult and child: include both 14 years old and 21 years old.

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Supplementary Fig. S3

Forest plots for prevalence of glaucoma by inhaled corticosteroids. Age subgroup analyses. (A) Crude odds ratio. (B) Adjusted odds ratio. Mitchell *et al.*[32] provided the data for subjects with and without family history separately. Adult: 15 years old or elder. Child: 20 years old or younger. Adult and child: include both 14 years old and 21 years old.

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Supplementary Fig. S4

Forests plots for intraocular pressure MD by inhaled corticosteroids. Age subgroup analyses. (A) Change from the baseline (mmHg). (B) Single-measurement difference (mmHg). Pelkonen *et al.*[15] and Emin *et al.*31 provided the data for right and left eyes separately. Adult: 15 years old or elder. Child: 20 years old or younger. Adult and child: include both 14 years old and 21 years old.

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Supplementary Fig. S5

Forest plots for prevalence of glaucoma by inhaled corticosteroids. Including a study by Garbe *et al.*[8] in 1997. (A) Crude odds ratio. (B) Adjusted odds ratio. Mitchell *et al.*[32] provided the data for subjects with and without family history separately.

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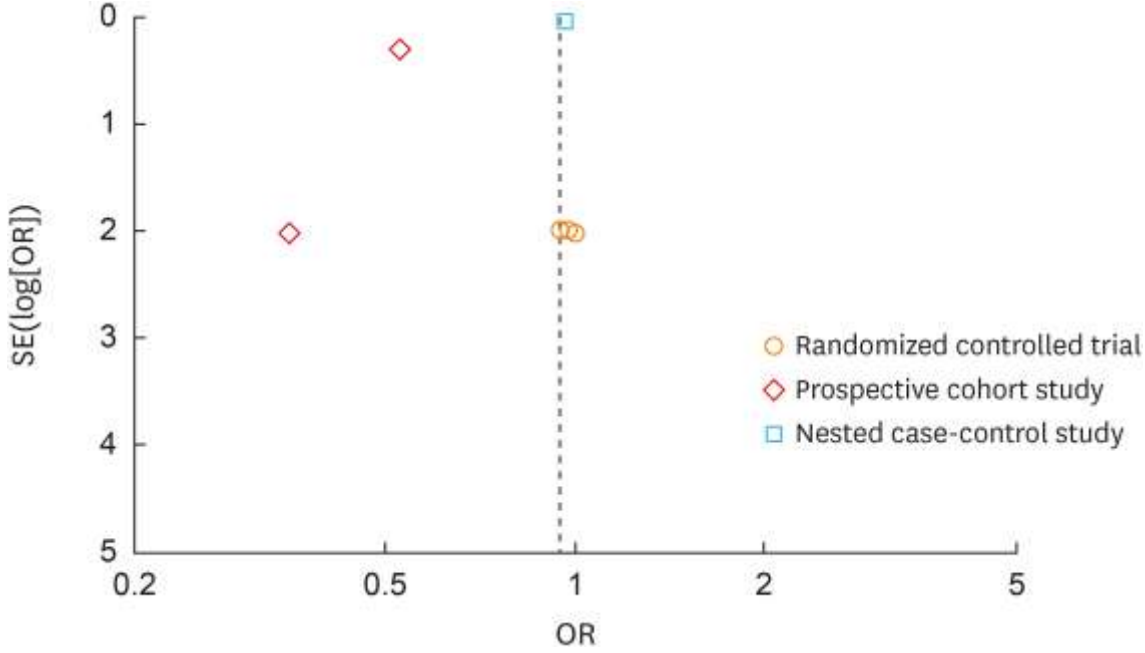

Supplementary Fig. S1. Funnel plot for the primary endpoint. This funnel plot was generated using Review Manager version 5 (Cochrane, London, UK). Begg-Kendall test: tau = −0.316, P = 0.449 (> 0.10).

SE, standard error; OR, odds ratio.

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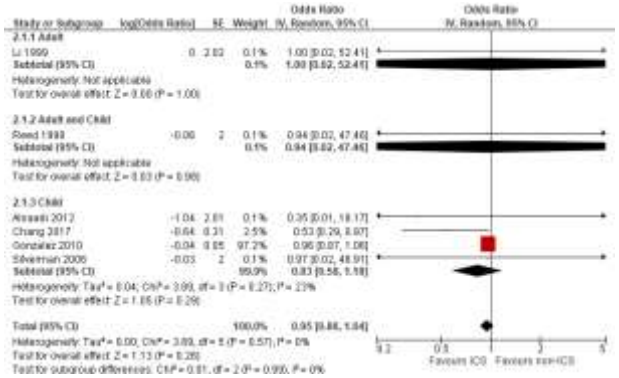

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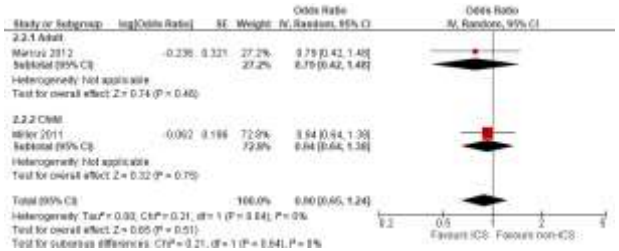

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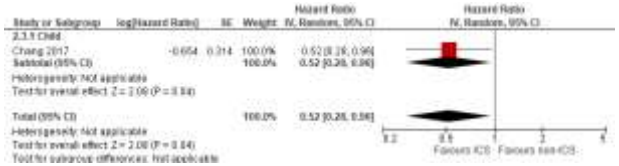

Supplementary Fig. S2. Forest plots for incidence of glaucoma by inhaled corticosteroids. Age subgroup analyses. (A) Crude odds ratio. (B) Adjusted odds ratio. (C) Adjusted hazard ratio. Adult: 15 years old or elder. Child: 20 years old or younger. Adult and child: include both 14 years old and 21 years old. SE, standard error; IV, inverse variance; ICS, inhaled corticosteroid; CI, confidence interval; OR, odds ratio; HR, hazard ratio.

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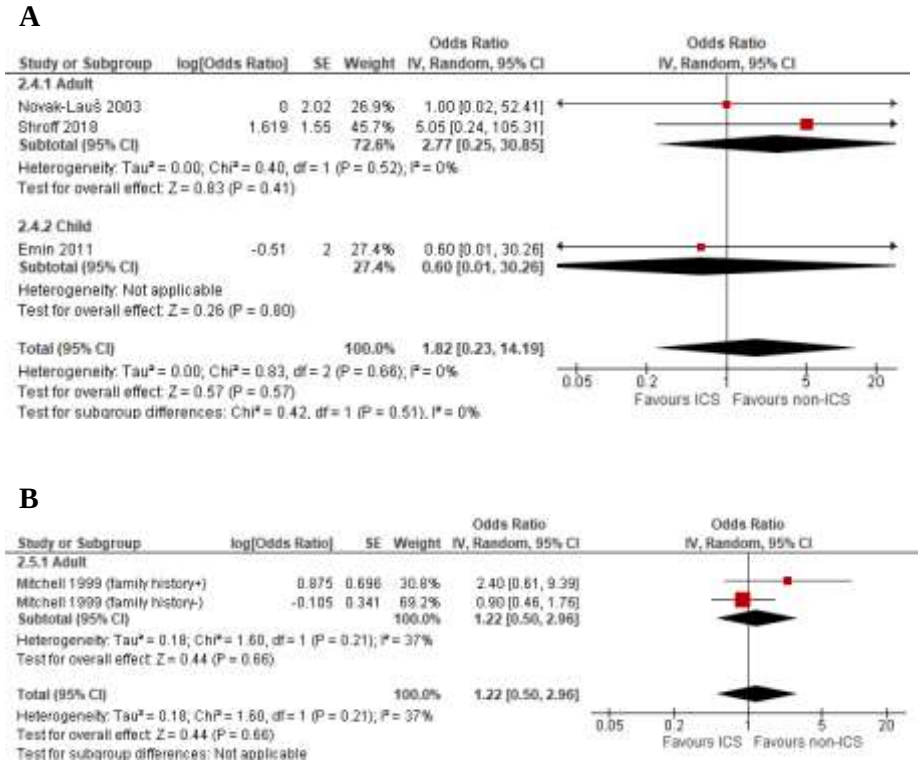

Supplementary Fig. S3. Forest plots for prevalence of glaucoma by inhaled corticosteroids. Age subgroup analyses. (A) Crude odds ratio. (B) Adjusted odds ratio. Mitchell *et al*.[32] provided the data for subjects with and without family history separately. Adult: 15 years old or elder. Child: 20 years old or younger. Adult and child: include both 14 years old and 21 years old. SE, standard error; IV, inverse variance; ICS, inhaled corticosteroid; CI, confidence interval; OR, odds ratio.

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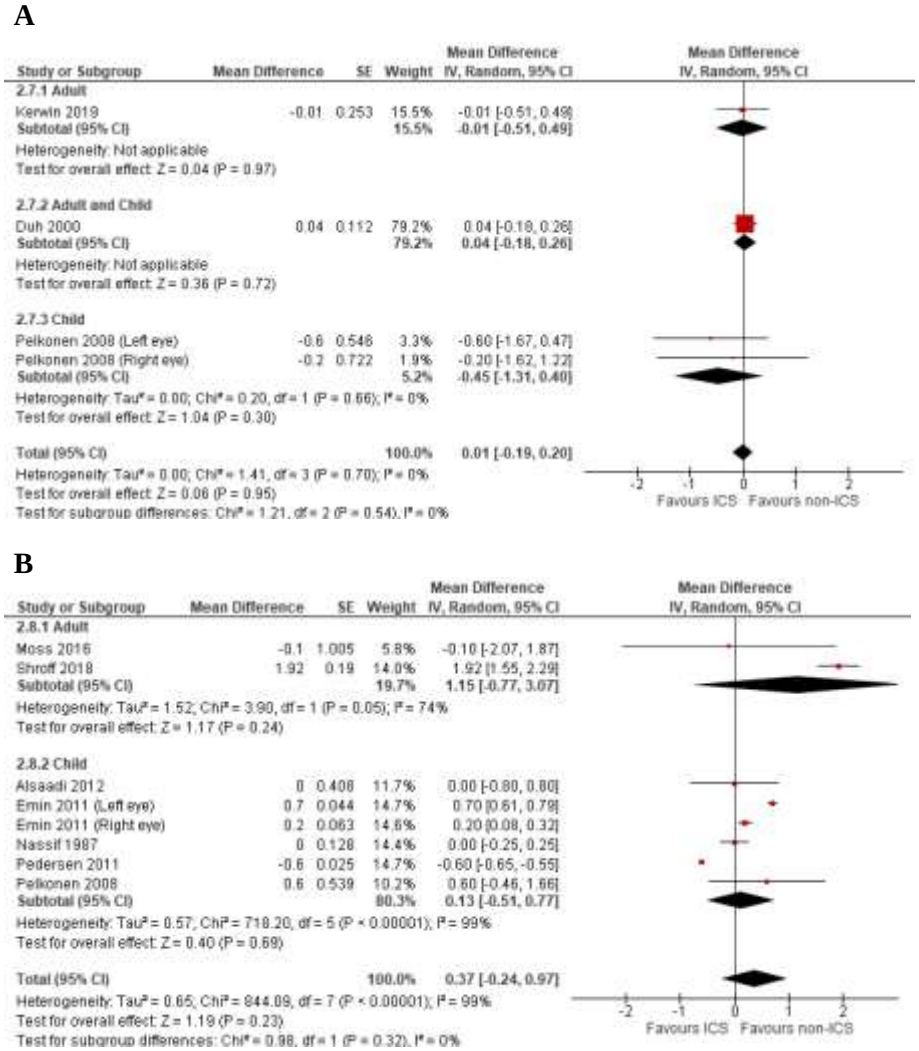

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