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ASSOCIATION ORAL CORTICOSTEROIDS AND LONG-TERM RISK OF CATARACT: A SYSTEMATIC REVIEW AND META-ANALYSIS STUDY

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ABSTRACT

Background: *Cataracts are a significant health concern, particularly in aging populations, impacting vision, mental well-being, and overall quality of life. Corticosteroid use has been linked to cataract development. This study aims to explore the relationship between oral corticosteroid (OCS) exposure and the long-term risk of cataract.*

Method*: Following PRISMA guidelines, a systematic review and meta-analysis were conducted to investigate this association. Relevant studies were identified through comprehensive searches across multiple databases. Data included cataract incidence/prevalence and OCS therapy.*

Results*: A total of 1,270 articles were retrieved from online databases (PubMed, SagePub, SpringerLink and Google Scholar). After three rounds of screening, five articles directly relevant to the systematic review were selected for full-text reading and analysis. These five studies collectively involved 27,250 cases of cataract following oral corticosteroid (OCS) exposure, while 47,267 controls did not develop cataracts. No statistically significant association is found between OCS and cataract formation (OR= 0.117, CI 95% 0.0085 to 1.6021, p=0.11).*

Conclusion: *Cataracts in oral corticosteroid (OCS) users result from abnormal lens cell movement and protein composition changes due to protein adduct formation. Increased OCS dosage and frequency correlate with higher cataract risk. However, evidence quality was deemed low to moderate, highlighting the need for well-designed RCTs to minimize bias and heterogeneity.*

Keywords: *Cataract, oral corticosteroids*

INTRODUCTION

Cataract poses significant health challenges in aging populations, impacting vision, mental well-being, and quality of life while also increasing mortality rates and economic burdens. Cataracts are characterized by the clouding of the eye's lens, resulting in vision impairment. WHO estimates suggest that approximately 95 million individuals were visually impaired due to cataracts in 2014.[1]

Studies show that the prevalence of cataracts increases significantly with age, ranging from 3.9% in individuals aged 55-64 to 92.6% in those aged 80 and above. Over the past two decades, the prevalence of cataracts has decreased due to advancements in surgical techniques and increased access to surgery. Nonetheless, cataracts remain a leading cause of blindness in middle and low-income countries, accounting for 50% of blindness, compared to only 5% in developed nations.[1,2]

Various types of cataracts cause different visual symptoms. Patients commonly report blurred vision, glare, and haloes around lights. Nuclear cataracts primarily affect distance vision more than near vision, while posterior subcapsular cataracts often impair near visual acuity more than distance vision. Progressive changes in nuclear sclerotic cataracts lead to an increase in the lens refractive index, resulting in increased light refraction and potential myopia. Glare is common in patients with posterior subcapsular cataracts, and some may experience monocular diplopia due to localized variations in lens opacity. Certain patients may only experience visual difficulty during daily activities such as reading or driving, indicating visual disability.[3]

Cataract formation can be triggered by various factors, including certain medications such as corticosteroids, phenothiazines, busulfan, miotics, and occasionally amiodarone. The association between statin use and cataract formation remains debated. Additionally, cataracts can result from mechanical trauma, chemical or electrical injury, as well as exposure to ionizing, infrared, or ultraviolet radiation. Chronic uveitis, Fuchs' heterochromic uveitis, and pseudoexfoliation syndrome can also contribute to lens changes leading to cataracts.[2]

The increased use of corticosteroids for various medical conditions raises concerns about ocular complications, especially steroid-related cataracts and glaucoma, which add to the global burden of visual impairment. Steroid usage ranks as the fourth most significant risk factor for secondary cataracts, contributing to about 4.7% of all cataract removals. The connection between steroid use and the development of posterior subcapsular cataract (PSC) was first identified by Black et al. in 1960.[4] The aim of this study is to systematically review and conduct a meta-analysis the dose-response relationship between oral corticosteroids (OCS) exposure and long-term risk of cataract formation.

METHODS

This systematic review meta-analysis was conducted in adherence to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines. Our health care question was defined a priori using the PICOS (Population, Intervention, Comparator, Outcomes, and Study Design) format. Population: Individuals at risk for cataract development. Intervention: Oral corticosteroid therapy. Comparison: Risk of cataract without OCS. Outcome: cataract incidence/prevalence.

ELIGIBILITY CRITERIA

For inclusion in this systematic review and meta-analysis on the association of oral corticosteroids use in long-term risk of cataract. This encompasses randomized controlled trials (RCTs), observational studies, quasi-experimental designs, and case-control studies. Studies must specifically investigate the effect if long term oral corticosteroid use and the risk of cataract.

The eligible population includes patients of varying ages, genders, and medical backgrounds who have received OCS treatment for various indications, such as autoimmune diseases, respiratory conditions, or inflammatory disorders. The study excluded individuals with pre-existing diagnoses of cataracts prior to OCS intake.

Intervention being investigated is the administration of oral corticosteroids. This involves the use of medications that are taken orally and contain corticosteroid compounds, such as prednisone, prednisolone, or dexamethasone.

Comparison group in the study would consist of individuals who have not been prescribed oral corticosteroids. These individuals may have similar demographic characteristics and medical conditions to the OCS group but have not received OCS treatment during the study period.

The primary outcome of interest is the long-term risk of developing cataracts among individuals who have been exposed to oral corticosteroids. Cataracts are characterized by the clouding of the lens in the eye, leading to visual impairment, and the study aims to assess whether OCS use is associated with an increased risk of developing this condition over time.

The study design used to investigate the association between oral corticosteroid use and the long-term risk of cataracts would likely be observational in nature. This could include cohort studies, where individuals are followed over time to assess the development of cataracts in relation to OCS exposure, or case-control studies, where individuals with cataracts are compared

to those without cataracts in terms of their OCS use history. These observational designs allow researchers to examine associations between exposures (OCS use) and outcomes (cataract development) without directly intervening or manipulating variables.

DATA SOURCES AND SEARCH STRATEGY

To develop a comprehensive understanding of the association between oral corticosteroids (OCS) and the long-term risk of cataracts, authors may utilize various data sources and search strategies, including the Medical Subject Headings (MeSH) database. A comprehensive search was conducted across PubMed, SagePub, SpringerLink, and Google Scholar to identify relevant studies. MeSH terms related to OCS and cataract were combined, and articles with relevant terms within the title or abstract were identified ((Oral Corticosteroids OR Glucocorticoids) OR "Corticosteroid-induced Cataract" OR ("Oral Prednisone" OR "Oral Prednisolone")) AND ((Cataract OR Lens Opacities) OR ("Cataract Risk" OR "Lens Opacities Risk")) AND ((Risk OR Epidemiology OR "Long-term Effects" OR "Chronic Effects" OR "Epidemiology" OR "Observational Study") OR ("Cohort Studies" OR "Case-Control Studies")) AND (2014:2024[pdat]))

STUDY SELECTION

Two authors independently reviewed the search results to eliminate duplicates. Subsequently, screening based on titles and abstracts was carried out. Full texts of pertinent studies were acquired and assessed against the predefined eligibility criteria. The JBI critical appraisal tools were also used as selection criteria in Table 1. The JBI critical appraisal tool for case series studies includes 10 questions addressing the internal validity and risk of bias of case series designs, particularly confounding, selection, and information bias, in addition to the importance of clear reporting. Studies meeting the eligibility criteria were selected, and the full-text articles were obtained and reviewed.

Table 1. JBI Critical Appraisal checklist for included studies

No.	JBI Appraisal Criteria	Bloechliger 2018	Gaur 2014	Minkus 2021	Nath 2017	Shabbir 2023
1.	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	✓	✓	✓	✓	✓
2.	Were cases and controls matched appropriately?	✓	✓	✓	✓	✓
3.	Were the same criteria used for identification of cases and controls?	✓	✓	✓	✓	✓
4.	Was exposure measured in a standard, valid and reliable way?	✓	✓	✓	✓	✓
5.	Was exposure measured in the same way for cases and controls?	-✓	✓	✓	✓	✓
6.	Were confounding factors identified?	✓	✓	✓	✓	✓
7.	Were strategies to deal with confounding factors stated?	✓	✓	✓	✓	✓
8.	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	✓	✓	✓	✓	✓
9.	Was the exposure period of interest long enough to be meaningful?	✓	✓	✓	✓	✓
10.	Was appropriate statistical analysis used?	✓	✓	✓	✓	✓

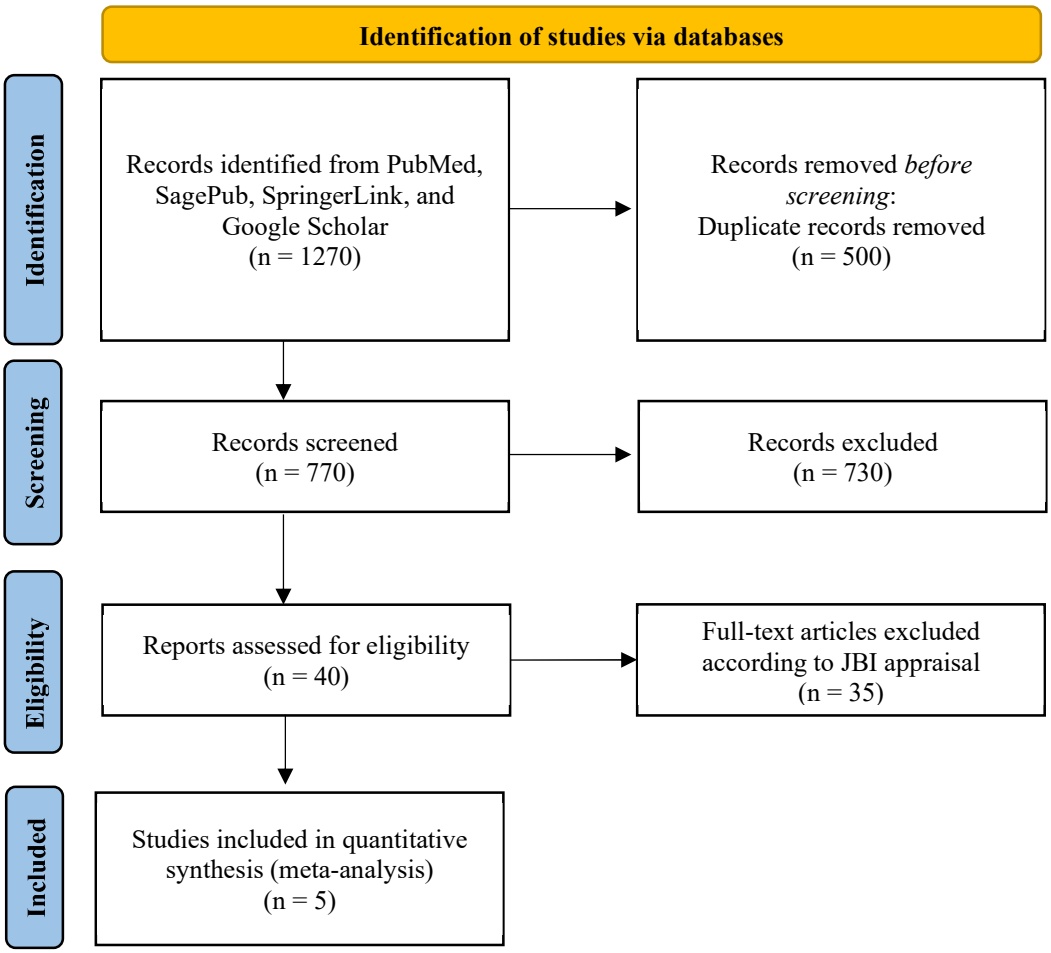


Figure 1. Search strategy and selection of studies for the meta-analysis.

DATA EXTRACTION

Data extraction was performed in duplicate from full-text versions of eligible studies by authors. Information regarding exposure to oral corticosteroids (OCS) and the risk of cataracts was extracted at various time intervals. Data presented in tabular format were the primary source for extraction.

RISK OF BIAS

The risk of bias in each trial was assessed across six domains using the RevMan 5.4 tool (Cochrane, UK). These domains included sequence generation, allocation concealment, blinding, attrition bias, selective outcome reporting, and other potential sources of bias. Trials were categorized as having high, low, or unclear bias in each domain, with detailed justifications provided for each determination.

DATA SYNTHESIS AND ANALYSIS

The study reported dichotomous outcomes along with their Odds Ratios (OR) and 95% Confidence Intervals (CI) by calculating the number of participants experiencing a particular outcome and the total number of participants. A random-effects model was employed, which was deemed superior to a fixed-effect model, to generate pooled OR estimates.

Forest plots were generated to present the findings related to the meta-analysis. Forest plots are commonly employed to display individual study results alongside summary statistics, such as effect sizes and confidence intervals, facilitating comparisons across studies. Heterogeneity in the data was assessed by examining the similarity of point estimates, overlap of confidence intervals, and statistical measures. Subgroup comparisons were conducted to investigate potential sources of heterogeneity among the included studies.

EVALUATING THE QUALITY OF EVIDENCE

The GRADE approach was employed to upgrade the quality of evidence, considering factors such as large pooled effects, dose-response relations, and confounders.

RESULT

The total number of articles retrieved from online databases (PubMed, SagePub, SpringerLink, and Google Scholar) is 1270 articles. After conducting three levels of screening, five articles that directly relate to the current systematic review have been chosen for further scrutiny through full-text reading and analysis. In all five studies included in the analysis, a total of 27,250 cases experienced cataract after OCS exposure, while 47,267 controls did not experience cataract. The baseline characteristics of participants mainly comprised patients with chronic diseases who were dependent on steroids. Some studies also reported multiple adverse effects from OCS aside from cataract like glaucoma, hypertension, peptic ulcer, etc but for this study we only included participants with cataract. The largest study included in this analysis was conducted by Bloechliger, et al.[5] (2018), which involved 269,368 participants.

The risk of bias analysis was conducted utilizing the RevMan 5.4 tool, developed by Cochrane, UK and presented in Figure 2 and Figure 3. In this assessment, four of the included studies were deemed to possess a high risk of performance bias. This classification primarily stemmed from the retrospective nature of these studies, which inherently limits the possibility of blinding participants and personnel, thereby introducing a potential source of bias. Additionally, the evaluation revealed that selection bias was largely unreported across the studies, resulting in an unclear risk assessment in this domain. Furthermore, incomplete outcome data were observed in some of the studies, with the master data sheet notably absent from the supplementary appendix, which may impact the comprehensiveness of the analysis. Despite these limitations, no other forms of bias were detected in the included studies.

On the aspect of reporting bias, the assessment indicated a low risk for most studies. This determination was based on the comprehensive reporting and analysis of all relevant outcomes within the studies, suggesting transparency and completeness in the presentation of findings. Overall, while certain studies exhibited notable limitations in terms of performance bias and incomplete outcome data, the risk of reporting bias was generally low, underscoring the thoroughness and reliability of the reported outcomes in the majority of the included studies.

Table 2. Characteristics of studies included in the meta-analysis

Author	Origin	Method	Sample Size	Outcome	Result
Bloechliger, et al.[5] (2018)	Switzerland	The study utilized data from the UK-based Clinical Practice Research Datalink to conduct multiple cohort studies and nested case-control analyses. These analyses aimed to quantify the incidence rates, incidence rate ratios, and odds ratios for 11 potential adverse events associated with corticosteroid use. These adverse events included bone-related conditions, hypertension, peptic ulcer, severe infections, herpes zoster, diabetes mellitus type 2, cataract, glaucoma, chronic kidney disease, affective disorders, and cardiovascular events.	269,368 asthma patients	The association between timing, frequency, cumulative and average daily doses of OCS use, and the occurrence of corticosteroid-related adverse events including cataract.	Cataract was associated with an increase in risk at cumulative doses > 2000 mg, average daily doses > 5 mg/day, or ≥4 prescriptions/year (ORs = 1.43, 3.29, and 1.80, respectively), but not at lower doses.
Gaur, et al.[6] (2014)	India	In this cross-sectional study, children aged 4-18 years diagnosed with nephrotic syndrome and who had received steroid treatment for at least six months were included. The study gathered demographic, clinical, and treatment information from case records. Additionally, a comprehensive ocular evaluation was conducted to identify posterior subcapsular cataracts (PSCC) and measure intraocular pressure (IOP).	82 children with nephrotic syndrome	The prevalence of ocular complications, specifically posterior subcapsular cataract (PSCC) and raised intraocular pressure (IOP), in children undergoing long-term steroid therapy for nephrotic syndrome.	A total of 118 children were initially screened, with 82 included in the final analysis, having a median follow-up duration of 4.2 years (interquartile range, 2.4 to 6.3 years). At recruitment, the median age of the children was 9.3 years (interquartile range, 6 to 12.5 years). Among the participants, 22 out of 82 (26.8%) were found to have posterior subcapsular

				Additionally, it sought to evaluate the relationship between the cumulative dosage and duration of steroid consumption with the occurrence of these ocular complications.	cataract (PSCC), while 9 out of 82 (10.97%) had raised intraocular pressure (IOP). Older age was significantly associated with PSCC (p=0.009). However, there was no significant difference in the median cumulative dose of steroids between those with and without cataract (p=0.58), nor in the median duration of steroid therapy (p=0.73). Among children with PSCC, 9 out of 22 (42.8%) experienced mild diminution of vision.
Minkus, et al.[7] (2021)	USA	Patients were selected from the Systemic Immunosuppressive Therapy for Eye Diseases Cohort Study, where medical records were thoroughly examined to collect demographic and clinical information from each visit at five major uveitis centers in the United States. The main focus was on identifying the development of vision-compromising cataracts, defined by a decrease in visual acuity to 20/40 or worse, or necessitating cataract surgery. Survival analysis was employed to assess visually defined cataracts, ensuring avoidance of bias related to the timing of surgery concerning the inflammatory status.	1302 patients with uveitis	The incidence of and predictive factors for cataract in intermediate uveitis	In a study involving 2,190 eyes of 1,302 patients with intermediate uveitis, the cumulative incidence of cataract formation was found to be 7.6% by 1 year, increasing to 36.6% by 10 years. Factors associated with increased cataract risk included concurrent anterior uveitis causing posterior synechiae and epiretinal membrane formation. Higher dose corticosteroid therapy, particularly topical corticosteroids used at least twice daily or four periocular corticosteroid injections, was also linked to a significantly higher incidence of cataract. However, low-dose corticosteroid medications (oral prednisone 7.5 mg daily or less, or topical corticosteroid drops less than twice daily) did not increase cataract risk.
Nath, et al.[4] (2017)	India	The study focused on COPD patients aged 50 years or older, who had been exposed to steroids for at least 4 months and were using corticosteroids between March 2014 and March 2015. Daily doses of corticosteroids were categorized as low, medium, and high.	357 patients with COPD	The prevalence of steroid-induced cataract and glaucoma among patients diagnosed with chronic obstructive pulmonary disease (COPD) and dose-	Out of 405 initially screened COPD patients, 48 were excluded, leaving 357 for analysis. Among these, 58 patients were diagnosed with cataract (prevalence of 16.24%) and 14 with glaucoma (prevalence of 3.92%). The study found a dose-response

				response relationship between these conditions and steroid usage.	relationship, with the highest prevalence of cataract (39.6%) and glaucoma (42.8%) observed at daily doses of 501–1000 µg fluticasone propionate equivalents. The findings suggest that higher doses and longer duration of corticosteroid use in COPD patients are associated with a greater prevalence of cataract and glaucoma.
Shabbir, et al.[8] (2023)		The study enrolled children aged 2 to 15 years with nephrotic syndrome (NS), specifically those with frequent relapses or steroid dependency, who had been on steroid treatment for at least 6 months. Baseline demographic data, including age, gender, duration of NS, duration of steroid treatment, present steroid doses, and total cumulative steroid dose, were collected. Ophthalmological examinations were conducted using slit lamp examination to assess the frequency of posterior cataracts.	154 patients with NS	The frequency of posterior cataract occurrence in children with steroid-dependent or frequently relapsing nephrotic syndrome (NS).	Among 154 children, 84 (54.5%) were girls, with a mean age of 3.41 years. Periorbital edema, fever, and pedal edema were the most common presenting complaints. Posterior cataracts were found in 23 (14.9%) children. Age, frequent relapse, longer duration of NS, duration of steroid treatment, number of relapses, and cumulative steroid dose were significantly associated with posterior cataracts.

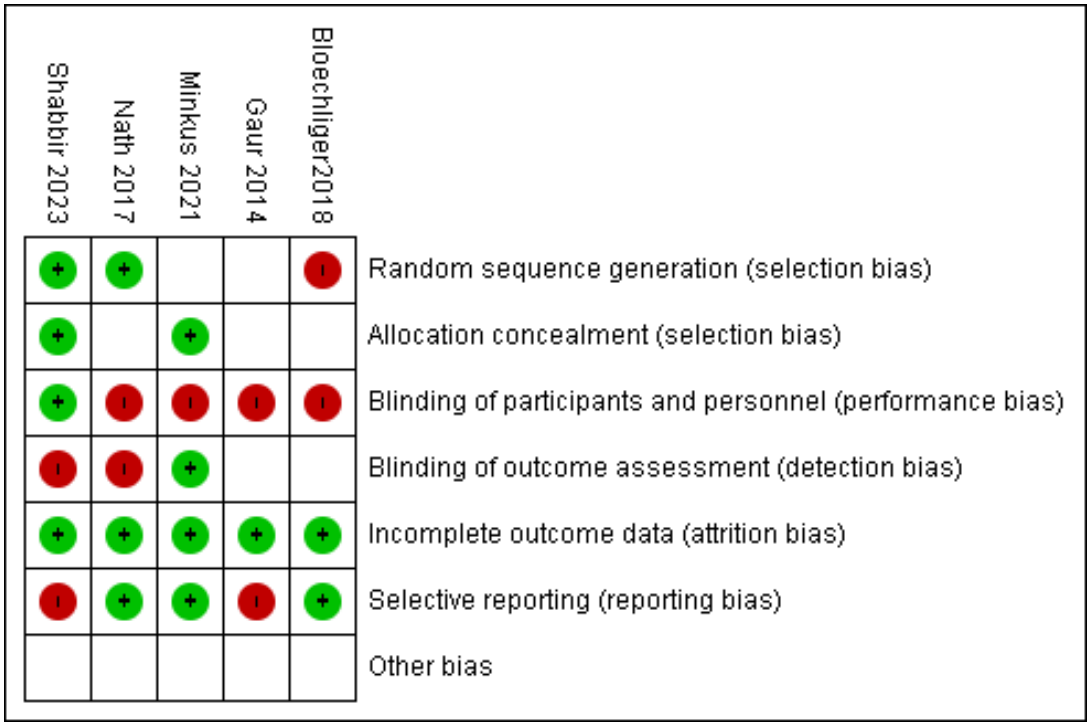


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

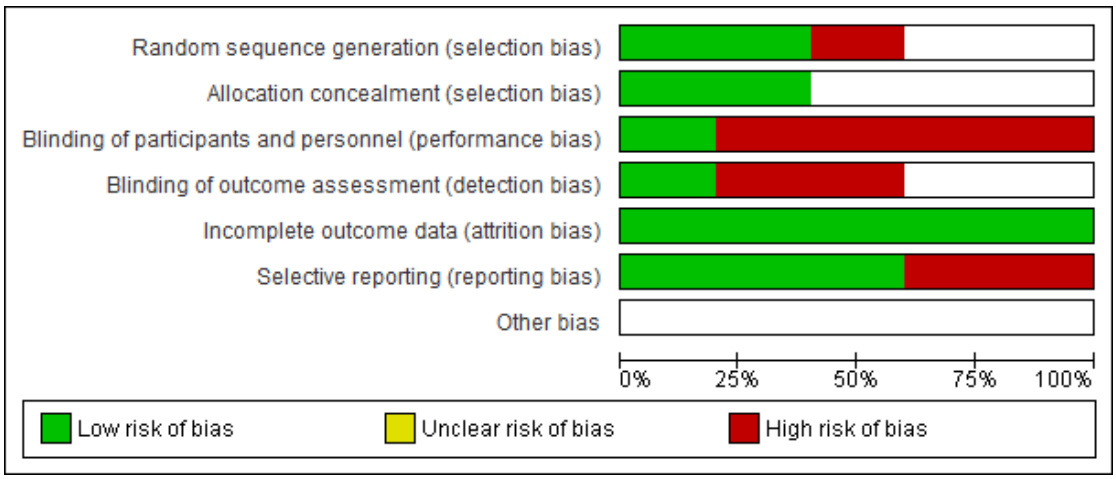
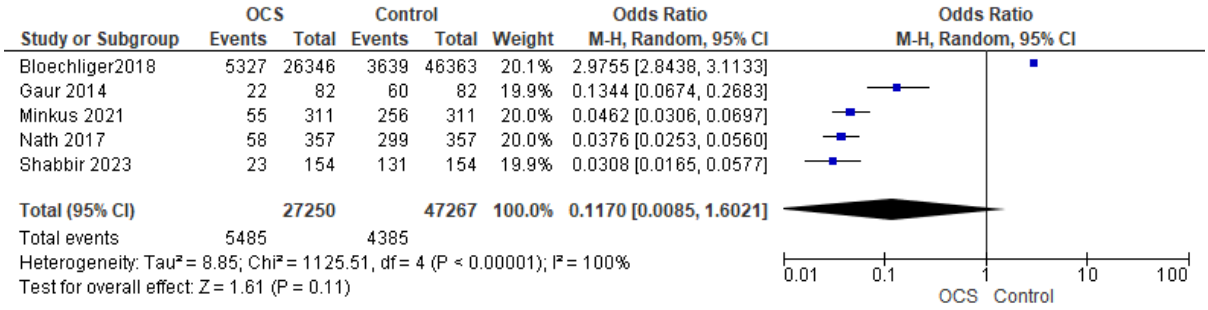


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

The primary goal of this analysis is to assess the risk of cataract and OCS use. Forest plots are presented in Figure 4 for the odds ratio of cataract risk associated with OCS use, with a simple plot of log odds ratio and associated 95% CI versus control. In this study, out of 27,250 patients who used oral corticosteroids (OCS), a proportion experienced cataract. Additionally, there were 47,267 controls who did not develop cataract. The odds ratio (OR) comparing the likelihood of developing cataract between the group exposed to OCS and the control group was calculated to be 0.117. The 95% confidence interval (CI) for this OR ranged from 0.0085 to 1.6021. The p-value associated with this comparison was 0.11. This suggests that there was no statistically significant difference in the likelihood of developing cataract between the group exposed to OCS and the control group.

Additionally, a heterogeneity test utilizing I^2 showed a value of 100%, suggesting that all observed variability in effect sizes across studies is due to heterogeneity rather than sampling error. This extreme heterogeneity, where there is no overlap in the confidence intervals of individual studies, indicates significant inconsistency among the study results.



DISCUSSION

The meta-analysis conducted quantified the risk of cataracts associated with oral corticosteroid (OCS) therapy. Initially noted by Black et al. in 1960, the connection between corticosteroid therapy and cataract development was observed in patients with conditions like posterior subcapsular cataracts (PSCC) and steroid therapy for rheumatoid arthritis. This correlation was further evident in patients with intermediate uveitis, chronic obstructive pulmonary disease, and nephrotic syndrome who received higher doses of corticosteroid medications.[4,8]

Steroid-induced cataract, a well-documented phenomenon in ophthalmology, is characterized by the development of cataracts resulting from corticosteroid medication usage. This condition is attributed to several underlying mechanisms, notably involving abnormal movement of lens epithelial cells and changes in the protein composition of the lens due to the formation of protein adducts. The irregular migration of lens epithelial cells plays a crucial role in the process of steroid-induced cataract formation. Typically, these cells maintain the lens's transparency and integrity by effectively eliminating damaged or denatured proteins. However, corticosteroids disrupt this process, leading to the accumulation of abnormal proteins within the lens structure. This accumulation disturbs the orderly arrangement of lens fibers and contributes to the development of lens opacities characteristic of cataracts. Furthermore, corticosteroids can alter the protein composition of the lens through the formation of protein adducts. These adducts result from the attachment of corticosteroid molecules to lens proteins, causing structural changes and functional impairment. Consequently, the lens loses its transparency and becomes increasingly opaque over time, ultimately leading to the formation of cataracts.[5]

Cataract development was found to be correlated with dose exposure to oral corticosteroids (OCS). Notably, the highest level of exposure across various categories of OCS use—such as highest cumulative and daily doses, as well as the most frequent regimens—showed an association with cataract formation. This suggests that higher OCS exposure corresponds to an increased risk of developing cataracts. This significant finding highlighted the potential ocular side effects of corticosteroid medications and emphasized the importance of careful monitoring of patients undergoing long-term steroid therapy.[6,7]

However, this meta-analysis found no significant link between oral corticosteroid (OCS) use and long-term cataract risk. The limitations in this study may include inherent bias risk and heterogeneity among studies, affecting evidence quality graded as low to moderate. Heterogeneity may arise from varied study designs, participant characteristics, or outcome measures. To improve evidence reliability, future studies should address these limitations through well-designed, larger-scale, and independently funded research with standardized protocols and reporting practices.

CONCLUSION

In summary, the occurrence of cataracts in oral corticosteroid (OCS) users is attributed to abnormal movement of lens epithelial cells and changes in lens protein composition caused by protein adduct formation. Increased dosage and frequency of OCS intake are associated with a heightened risk of cataract development. However, the evidence used in this meta-analysis showed low to moderate quality, further studies need well-designed RCTs to lessen risk of bias and heterogeneity.

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