• Meta-Analysis •

Prevalence of amblyopia in congenital blepharoptosis: a systematic review and Meta-analysis

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Abstract

• AIM: To conduct a systematic review and Meta-analysis of the published literature to evaluate the pooled prevalence rate of amblyopia in patients with congenital ptosis.

• METHODS: We searched the PubMed, Embase, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Wanfang Data, and Chongqing VIP databases for studies reporting the prevalence of amblyopia in patients with congenital ptosis. The reference lists of relevant studies were scanned. Heterogeneity of effect sizes across studies was tested. We calculated prevalence ratios to compare prevalence estimates for different causes of amblyopia in patients with congenital ptosis, as well as for different geographical regions, year of publication and sample size in subgroup analyses. A systematic review and Meta-analysis were performed.

• RESULTS: We identified 29 eligible surveys with a total population of 2436. Prevalence rates of amblyopia ranged from 13.8% to 69%. We noted substantial heterogeneity in prevalence estimates for amblyopia in congenital ptosis (Cochran's χ^2 significant at P<0.0001; I^2=90%). The pooled prevalence using random-effects models of 29 studies was 32.8% (95%CI: 27.3%-38.4%) in the overall population. Compared to the overall pooled prevalence, amblyopia prevalence was higher in studies in which only subjects with blepharophimosis syndrome were included.

• CONCLUSION: We confirm that nearly one-third of congenital ptosis patients are suffering from or at risk for amblyopia. Patients with blepharophimosis syndrome are more likely to develop amblyopia. The identification and management of amblyopia should be integral to the treatment of congenital ptosis.

• **KEYWORDS:** amblyopia; congenital ptosis; blepharophimosis; systematic review

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INTRODUCTION

Congenital blepharoptosis is an eyelid disorder that is characterized by an involuntary drooping of the upper eyelid since birth. Etiologically, myogenic factors are most common, referring to dysgenesis or weakness of the levator muscle and sometimes the superior rectus muscle. The etiological subtypes of congenital ptosis include simple congenital ptosis, blepharophimosis-ptosis-epicanthus inversus syndrome (BPES), Marcus Gunn jaw-winking syndrome (MGJWS), congenital fibrosis of the extraocular muscles, congenital cranial nerve (CN) III palsy and myotonic dystrophy[1]. Congenital ptosis in patients is frequently associated with amblyopia, refractive error and strabismus. The incidence of amblyopia in patients with congenital ptosis has been reported to be higher than that in the general population. Population-based studies focused on the prevalence of amblyopia in the general population have reported a prevalence varying from 0.74% to 5.6% depending on ethnic group[2-5]. However, the frequency of amblyopia among patients with congenital ptosis has varied widely in reported studies[6-34]. Whitehouse *et al*[7] found amblyopia in 13.8% of patients with congenital ptosis. Gusek-Schneider and Martus[8] identified amblyopia in 69.5% of ptotic eyes in Germany. There is a general paucity of scientific systematic reviews that seek to identify the prevalence of amblyopia in patients with congenital ptosis.

Given the importance of the potential for the treatment of amblyopia in pediatric ptosis and visual quality improvement after corrective surgery[35], it is crucial to provide robust evidence for clinicians regarding the prevalence of amblyopia and the significance of early inventions. This study therefore set out to systemically review and perform a Meta-analysis on the prevalence of amblyopia in congenital blepharoptosis.

MATERIALS AND METHODS

Search Strategy and Selection Criteria This systematic review and Meta-analysis were performed in accordance with the guidance for Meta-analysis of observational studies in epidemiology (MOOSE)[36]. The search was initially applied to the Medline, Embase, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Wanfang Data and Chongqing VIP databases. The last search was run on September 9th, 2018. The search strategy included "amblyopia" and "ptosis" as MeSH terms and their synonyms in both English and Chinese languages. Similar strategies were used for the other databases. In addition, the reference lists of articles meeting the inclusion criteria were also screened.

Reports potentially eligible for inclusion in this systematic review and Meta-analysis had to meet the following criteria: 1) Investigated patients were all congenital cases; 2) There was no additional inclusive criteria regarding sex, severity of ptosis and dominant eye; 3) The study included an outcome measure of amblyopia; 4) The report provided sufficient information to estimate the pooled prevalence of amblyopia in patients with congenital ptosis. If more than one study was based on the same population sample, the study with better quality was included.

We excluded reports if the incidence of amblyopia was calculated by eye instead of by person, and the original data could not be obtained from the authors; patients with acquired ptosis were included in the study; the study population was selected, for example, with criteria of unilateral ptosis; or the definition of amblyopia was unclear. Studies of low quality based on the adjusted scale recommended by the Agency for Healthcare Research and Quality (AHRQ)[37] were excluded after quality assessment as well.

Data Extraction and Quality Assessment Independently, two reviewers (Zhang JY and Zhu XW) assessed titles, abstracts and full text articles and extracted the data. Extraction sheets for each study were cross-checked for consistency by three authors (Zhang JY, Ding X, and Lin M). Any disagreements were resolved by consensus and, when necessary, through consultation with the corresponding author (Li J). The following data were extracted from each paper: 1) first author, geographical location, and year of publication; 2) characteristics of participants in each study including number, age, sex, number of unilateral or bilateral ptosis; 3) definition of amblyopia; 4) sample size and numbers of patients diagnosed with amblyopia; and 5) additional information about types or causes of amblyopia and its correlation with ptosis severity.

For cross-sectional studies, quality assessments were conducted using an 11-item instrument recommended by the AHRQ[37]. An item would be scored "1" if it was answered "Yes". An item would be scored "0" if it was answered "No" or "Unclear". Studies assessed with quality scores of 0-3 indicated "low quality" reports; scores of 4-7 indicated "moderate quality" studies, and scores of 8-11 indicated "high quality" reports. The quality scores for each study are shown in Table 1.

Statistical Analysis Data management, transformation of effect sizes, and calculations of pooled prevalence were performed using STATA software package (version 14.1, STATA Corporation) and Revman 5.3 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and were cross-checked on consensus. Forest plots were provided, which illustrated the effect estimate, 95%CI for each study and the weight given to each study in the Meta-analysis along with the overall pooled result. Heterogeneity of effect sizes across studies was tested by Cochran's Q (reported as χ^2 and P values) and the I^2 statistic[38]. I^2 represents the percentage of the variability in effect estimates, independent of the number of studies included. Values of 25%, 50%, and 75% were considered low-, moderate-, and high-level heterogeneity, respectively. Because heterogeneity was high, we used random-effects models to pool the data[38]. Sensitivity analyses were conducted to investigate the influence of each study on the overall pooled results. Subgroup analyses were also performed on sample size (by comparing investigations of more than 100 individuals with smaller studies), subtypes of congenital ptosis, geographical region (Western countries and Australia versus Eastern countries), and year of publication to assess the potential effect modification of these variables on outcomes. Potential publication bias was assessed by visual inspection of the funnel plot and tested using Begg's and Egger's tests[39]. A P value <0.05 was considered statistically significant.

RESULTS

We initially identified 440 potentially eligible studies. The flow chart showing the study selection process is presented in Figure 1. After removal of duplicates and ineligible reports based on titles or abstracts, we reviewed 51 papers in full. In total, 29 studies met the inclusion criteria. The other 22 articles were eliminated for the following reasons: 4 studies included patients with acquired ptosis; 14 reports did not report detailed information about the definition of amblyopia or exact number of patients whose visual acuity was assessed; and the other 4 papers were graded as low quality using the AHRQ quality assessment.

Table 1 displays the characteristics of the included studies. The studies varied in size between 28 and 216 subjects, with an overall sample size across the studies of 2436. All 29 studies enrolled consecutive patients from the ophthalmology center or pediatric ophthalmology department. Estimates of the prevalence of amblyopia in congenital ptosis ranged from 14% to 69% (Figure 2); heterogeneity was substantial (I^2=90%,

Table 1 Characteristics of the included studies

Studies No.	First author (year)	Location	Age	Type of CP	Bilateral-unilateral	Sample size (*n*)	Case (*n*)	Quality score
1	Beaconsfield M (1991)[9]	UK	NA	BPES	101-0	101	57	9
2	Beckingsale PS (2003)[10]	Australia	0-6y, 58y, 76y	BPES	28-0	28	11	9
3	Cai J (2008)[12]	China	NA	BPES	34-0	64	34	8
4	Chen L (1989)[13]	China	5-33y	All	12-88	100	32	9
5	Dawson EL (2003)[14]	UK	NA	BPES	204-0	204	83	5
6	Doucet TW (1981)[11]	Canada	1-32y	MGJWS	2-53	55	19	9
7	Griepentrog GJ (2013)[15]	USA	1mo-10.2y (4y)	All	NA	96	14	9
8	Guo Q (1992)[16]	China	NA	All	22-87	109	33	7
9	Gusek-Schneider GC (2000)[8]	Germany	1-68y (11y 10mo)	All	28-72	100	69	7
10	Harrad A (1988)[23]	UK	NA	Simple	44-172	216	37	8
11	Jiao Y (2004)[17]	China	4-14 y (6.28y)	BPES	34-0	34	14	7
12	Kasaee A (2010)[18]	Iran	NA	All	14-86	100	34	7
13	Li C (2012)[19]	China	2-4 y (3.5±1.22y)	All	0-52	52	16	8
14	Li L (2008)[20]	China	4-28y	All	7-34	41	14	4
15	Li S (2009)[21]	China	3-24y (3.98y)	BPES	51-0	51	27	8
16	Lin LK (2008)[24]	USA	2mo-17y	All	28-102	130	28	8
17	Merriam WW (1980)[22]	USA	NA	All	16-49	65	19	7
18	Mokhtarzadeh A (2016)[26]	USA	1.5-17.8y (5.6y)	All	4-43	47	7	10
19	Oral Y (2010)[25]	Turkey	10mo-70y (15.78±14.88y)	all	11-61	72	35	8
20	Paik JS (2016)[27]	Korea	5-19y (15.1±4.2y)	All	13-41	54	11	10
21	Pratt SG (1984)[28]	USA	9mo-42y	MGJWS	2-69	71	42	6
22	Skaat A (2013)[29]	Israel	10.37±0.9mo	All	42-120	162	26	7
23	Srinagesh V (2011)[6]	USA	1mo-13y (30±37mo)	All	5-87	92	22	8
24	Stein A (2014)[34]	USA	60±11.8mo	All	31-53	84	15	9
25	Su N (2005)[30]	China	2.8-24y	All	18-36	54	18	6
26	Wang DH (1995)[31]	China	5-27y	All	8-32	40	11	4
27	Whitehouse GM (1995)[7]	Australia	4mo-14y (4.5y)	All	15-50	65	9	8
28	Wu SY (2008)[32]	Taiwan, China	16mo-20y (5.1y)	BPES	18-0	18	5	8
29	Yuan TG (1989)[33]	China	4-35y (16.81y)	All	41-90	131	37	5

NA: Not available; CP: Congenital ptosis; BPES: Blepharophimosis-ptosis-epicanthus inversus syndrome; MGJWS: Marcus Gunn jaw-winking syndrome; BCVA: Best corrected visual acuity. Age is recorded as range or mean±standard deviation. The CP category "all" indicates that the corresponding article did not specify between and might include all types of congenital ptosis.

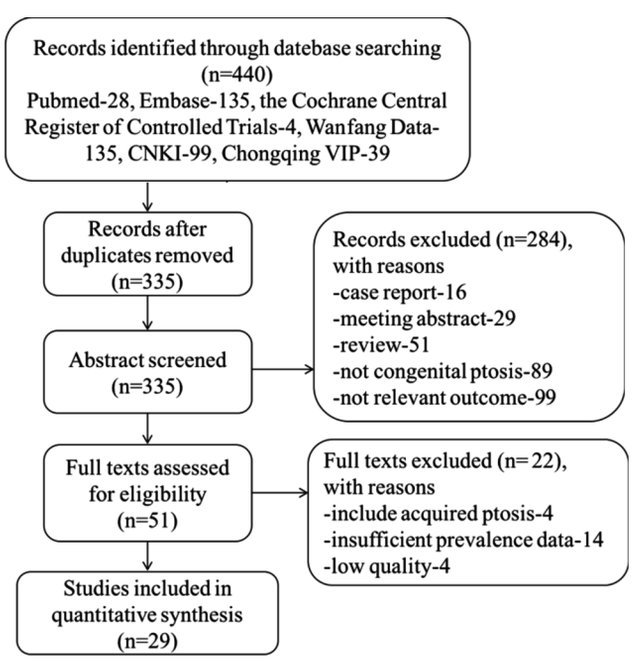

Figure 1 The flowchart of study selection process.

χ^2=224, P<0.0001). The pooled prevalence using random-effects models of the 29 studies was 32.8% (95%CI: 27.3%-38.4%) in the overall population (Figure 2).

Twelve studies were from East Asia (China, Korea), 7 from the USA, 3 from Australia, 2 from the UK, and 1 from Canada, Turkey, Iran, Israel and Germany. The pooled prevalence in Eastern countries was 31% (95%CI: 23%-40%). Compared with the rest of the studies investigating Western patients with a prevalence rate of 34% (95%CI: 29%-40%), there was no significant difference between the two geographic regions (I^2=0, χ^2=0.85, P=0.36).

The subtypes of congenital forms of ptosis based on etiology were simple congenital ptosis, BPES, MGJWS, congenital fibrosis of the extraocular muscles, and congenital CN III palsy. Seven of the 29 studies focused on patients with BPES, two on MGJWS, and the others on general congenital ptosis without specifying the underlying causes. We performed a subgroup analysis by subtype of congenital ptosis, comparing

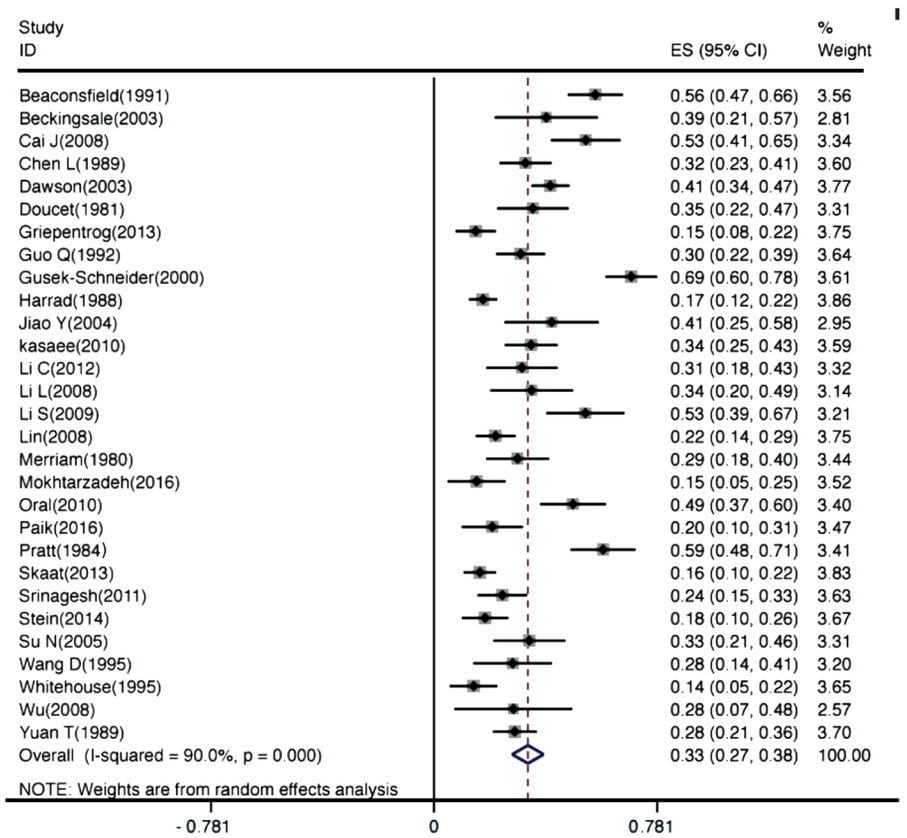

Figure 2 Forest plot of 29 studies using random-effects models ES: Effect size.

Table 2 Subgroup analysis

Subgroup	No. of studies (*n*)	Estimated prevalence (%; 95%CI)	I^2 value (%)	Subgroup difference
General congenital ptosis	20	27 (21-33)	86	
MGJWS	2	46 (24-70)	94	P^a=0.11
BPES	7	47 (40-53)	50	P^a<0.0001
Sample size: <100	19	32 (25-39)	83	*P*=0.80
Sample size: ≥100	10	33 (24-44)	93	
Country of study: Western and Australia	12	34 (29-40)	59	*P*=0.50
Country of study: Eastern	17	31 (23-40)	92	
Publication year: within 10y	13	28 (21-34)	89	*P*=0.18
Publication year: over 10y	16	35 (28-44)	85	

BPES: Blepharophimosis-ptosis-epicanthus inversus syndrome; MGJWS: Marcus Gunn jaw-winking syndrome. [a]Compared with the subgroup of general congenital ptosis, referring to the studies that did not specify the type of congenital ptosis.

the prevalence of amblyopia in BPES and MGJWS with general congenital ptosis, which showed greater odds in BPES (prevalence rate of 47%, 95%CI: 40%-53%). The difference between the two subgroups was remarkably significant (*P*<0.0001), indicating a higher prevalence of amblyopia in BPES. There were no significant differences for subgroups based on sample size or publication year (Table 2).

To conduct a sensitivity analysis of these studies, each study was sequentially omitted to rerun the Meta-analysis. The results remained similar to one another, demonstrating that the overall prevalence was stable and robust. Regarding publication bias, the funnel plot indicated slight asymmetry through visual inspection (Figure 3). However, Begg's test (*Z*=0.73, *P*=0.464) and Egger's test (*P*=0.376) did not reveal a risk of publication bias.

The causes of amblyopia in congenital ptosis (*e.g.* stimulus deprivation, refractive error and strabismus) were initially calculated in several enrolled studies (Table 3). Estimates of stimulus deprivation amblyopia as the cause ranged from 5% to 60%, while strabismic amblyopia accounted for 4.3% to 84% and refractive amblyopia accounted for approximately 9% to 79% of the cases. The pooled odds ratio was unable to be calculated as a result of insufficient information provided.

Table 3 Causes of amblyopia in congenital ptosis extracted from enrolled studies

First authors (year)	Amblyopia rate	Strabismus (%)	Refractive error (%)	Stimulus deprivation (%)	Strabismus & refractive error (%)
Merriam WW (1980)[22]	19/65	26	36	32	5
Doucet TW (1981)[11]	19/55	84			
Pratt SG (1984)[28]	42/71	58	25		
Harrad A (1988)[23]	37/216	51	21	14	
Chen L (1989)[13]	32/100	11	14	7	
Guo Q (1992)[16]	33/109			21	
Gusek-Schneider GC (2000)[8]	69/100	6	67	5	22
Beckingsale PS (2003)[10]	11/28	46	9	27	18
Su N (2005)[30]	18/54	22	78		
Lin LK (2008)[24]	28/130			57	
Li L (2008)[20]	14/41	42.9	35.7	21.4	
Oral Y (2010)[25]	35/72	20	54	26	
Kasaee A (2010)[18]	34/100	4.3	29.8	10.5	
Srinagesh V (2011)[6]	22/92	18.2	54.5		18.2
Griepentrog GJ (2013)[15]	14/96	17	25	58	
Skaat A (2013)[29]	26/162	42			
Stein A (2014)[34]	15/84	26.7	13.3	60	
Paik JS (2016)[27]	11/54		79	21	

Data presented in % of amblyopia.

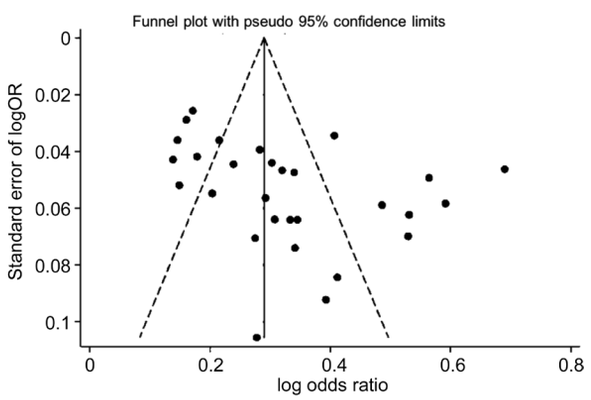

Figure 3 Funnel plot of 29 studies.

DISCUSSION

This is a systematic review and Meta-analysis to define the aggregate prevalence of amblyopia in congenital ptosis with a total of 2436 subjects from 29 eligible studies. Our study showed a pooled prevalence rate of 32.8%, which was much higher than that of the general population[2-5,40-41]. The enrolled studies differed in the diagnostic criteria for amblyopia, selection of the study population, and number of subjects. Heterogeneity between the studies was hence substantial. The main implication of our results is that the identification and management of amblyopia should be integral to the treatment of congenital ptosis. Our study highlights the need for ophthalmologists and orthoptists to carefully examine the visual development of these patients.

Further subgroup analyses revealed that there was a significant difference between the incidence of amblyopia in patients with BPES and that in the general group of patients with congenital ptosis. Patients with BPES had a much higher incidence of amblyopia. The prevalence rates ranged from 28% to 56% across the included studies with a pooled rate of 47% (95%CI: 40%-53%). This outcome is rather surprising. It has been presumed in the past that these patients were not at high risk of amblyopia since the ptosis occurred bilaterally and equally. As reported by Beaconsfield *et al*[9], amblyopic cases were associated with strabismus or anisometropia and more frequently occurred in severe degrees of bilateral ptosis. Although the leading causes of amblyopia in congenital ptosis have not yet been discovered, several retrospective studies have shown that surgical correction of congenital ptosis could aid in the treatment of amblyopia[9,24,27,32]. Lin *et al*[24] reported that preoperative amblyopia rates of 37.5% dropped to 5% postoperatively, which was comparable to a report by Woo *et al*[42]. Traditional management of blepharophimosis syndrome has included medial canthoplasty at the age of 3-5y, followed by ptosis correction approximately 6mo later[43-44]. Wu *et al*[32] recommended correcting ptosis first for the prevention of amblyopia in BPES, which could be followed by correcting the telecanthus and small horizontal palpebral fissure length (HPFL) at an older age. We take the view, similar to many researchers[10,32,42], that surgical intervention should be carried out at a younger age (less than 3y) rather than risking normal visual development in the blepharophimosis cohort.

In previous studies of amblyopia in the general population, approximately one-third of cases are the result of anisometropia,

one-third are due to strabismus, and the remaining third are a combination of both disorders or a form of visual deprivation[15]. The predominant cause of the increased prevalence of amblyopia among patients with congenital ptosis has been a much-debated topic. Some authors[15,34] of the papers included in this report have reported that occlusion of the visual axis was the leading cause of amblyopia in patients with congenital ptosis. Other studies, however, have found that the leading causes of amblyopia were strabismus[23,25,29] or significant refractive errors[18,25,27]. In Srinagesh *et al*'s[6] article, amblyopia associated with ptosis mostly occurred in the context of coexisting anisometropia or strabismus. To date, which causal factors contribute the most to the development of amblyopia in patients with congenital ptosis remains controversial.

Another major theoretical issue characterized by inconsistent findings is whether the incidence of amblyopia in congenital ptosis is related to ptosis severity. Srinagesh *et al*[6] found that amblyopia affected the eye with more severe ptosis, suggesting that amblyopia was more likely to be encountered in children with a greater degree of ptosis. Similar observations were made by Merriam *et al*[22] in 1980, although they did not provide a detailed statistical analysis. Additionally, these studies demonstrated characteristic refractive changes in a group of patients with unilateral or asymmetric bilateral ptosis who developed amblyopia in the more severely affected eye. This interpretation contrasts with that of Stein *et al*[34] who found no consistent relationship between interocular margin reflex distance (MRD) differences and amblyopia. They considered the lack of a relationship to be a result of compensatory behaviors, such as the recruitment of the frontalis muscle or a chin-up posture. Paik *et al*[27] compared the clinical and refractive findings between ptotic eyes associated with amblyopia and nonamblyopic ptotic eyes and found no association between the degree of ptosis and amblyopia. They stressed that refractive errors have a major effect on the development of amblyopia in congenital ptosis; thus, the best indicator of amblyopia in children is visual acuity rather than MRD measurements.

With regard to the research methods, some limitations need to be acknowledged. First, the pooled prevalence data were estimated using a Meta-analysis of studies with different sample sizes rather than prevalence in a global multicenter population-based study. Second, due to differences in the average age of the study subjects and diagnostic criteria of amblyopia, the heterogeneity of this Meta-analysis was substantial and could not be fully corrected after the sensitivity analysis. The characteristics of each survey might have been associated with heterogeneity, such as the severity of ptosis, previous treatment, laterality and comorbidity. Thus, the results of this Meta-analysis should be prudently considered. Moreover, our systematic review is mainly composed of cross-sectional or retrospective studies and thus has not been able to confirm certain risk factors or causality.

In conclusion, compared with amblyopia in the general population, the pooled prevalence of amblyopia among patients with congenital ptosis is strikingly high. While this study did not confirm the dominant cause of amblyopia, it did substantiate that patients with BPES are more likely to develop amblyopia. The present study serves as a basis for future studies and provides important insights into the role of visual development among ptotic patients. The issue of the ideal surgical timing for congenital ptosis is an intriguing one that could be usefully explored in future research.

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