• Meta-Analysis •

Association between central serous chorioretinopathy and *Helicobacter pylori* infection: a systematic review and Meta-analysis

Da-Wen Wu[1,2], *Fei-Peng Jiang*[1,2], *Ge Ge*[1,2], *Mei-Xia Zhang*[1,2]

[1]Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
[2]Research Laboratory of Macular Disease, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
Co-first authors: Da-Wen Wu and Fei-Peng Jiang
Correspondence to: Mei-Xia Zhang. Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. zhangmeixia@scu.edu.cn
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Abstract

● **AIM:** To investigate the association between central serous chorioretinopathy (CSC) and *Helicobacter pylori* (Hp) by summarizing all available evidence.

● **METHODS:** The Scopus, Embase, EBSCO, PubMed, Web of Science, and Cochrane Library databases for all relevant studies published from inception to October 2022 were searched, and manually searched for relevant reference lists as a supplement. Studies investigating the association between CSC and Hp infection were included. Finally, 8 case-control studies were included in the Meta-analysis after study selection.

● **RESULTS:** The results showed no significant correlation between Hp infection and CSC [odds ratio (OR) 1.89, 95% confidential interval (CI) 0.58–6.15, I^2=96%, P=0.29]. After subgroup analysis based on the degree of development of the study (developing/developed countries), it was found that the results of the two subgroups were the same as the whole, and no significant difference between the two subgroups existed. Meta-regression showed that the effect of sample size on heterogeneity among studies was more prominent (P<0.01, adjusted R^2=89.72%), which can explain 89.72% of the sources of heterogeneity.

● **CONCLUSION:** This Meta-analysis reveals no significant correlation between Hp infection and CSC, which still warrants further well-designed extensive sample studies to reach a more reliable conclusion and promote a better understanding of the treatment of CSC.

● **KEYWORDS:** central serous chorioretinopathy; *Helicobacter pylori* infection; retinal diseases; Meta-analysis
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INTRODUCTION

As an idiopathic disease, central serous chorioretinopathy (CSC) is characterized by malfunction of the retinal pigment epithelium (RPE), resulting in neurosensory retinal detachment, serous pigment epithelium detachment (PED), and RPE atrophy[1]. CSC usually occurs in healthy, working-age men, but the incidence has begun to increase in women as well[2]. Patients typically present with loss of central vision, central scotoma, micropsia, or metamorphopsia[3]. Although CSC is self-limiting with few sequelae in most cases, 30%–45% of patients experience disease recurrence with poor visual prognosis, and some patients present with chronic CSC or diffuse RPE lesions.

The pathophysiology of CSC remains ambiguous and further basic research is needed, but several risk factors have been identified to be associated with CSC. Genetics[4-6], corticosteroids, endocrinological abnormalities, androgens, pregnancy, drugs[7], cardiovascular risk, refractive error, stress & psychological profile, hypoxia & obstructive sleep apnoea[8], *etc*. *Helicobacter pylori* (Hp) has also drawn the attention of investigators[9]. In ocular diseases, associated studies have shown that Hp infection may be related to blepharitis[10], glaucoma[11-12], anterior uveitis[13-14], and CSC. Hp is a gram-negative bacterium of corkscrew appearance that has been proven to be the direct pathogenic factor of digestive system diseases such as gastritis, gastric ulcer, and gastric mucosa-associated lymphoid tissue lymphoma[15]. The possible relationship between Hp and CSC was initially proposed by Giusti[16], who found that the recurrence of CSC was accompanied by negative to positive Hp tests after a close follow-up of a 43-year-old male CSC patient. After

Hp eradication therapy, the retinal anatomical structure and best-corrected visual acuity (BCVA) of the patient were significantly improved. After that, several case reports and observational studies exploring the relationship between Hp and CSC were published, but they have drawn controversial conclusions. We conducted this Meta-analysis by integrating all available studies measuring the association between CSC and Hp to address the discrepancy between these studies. A Meta-analysis on risk factors for CSC was published in 2016, which only included three articles on the association between CSC and Hp and the results showed a significant correlation between Hp infection and CSC[9].

To the best of our knowledge, this is the most comprehensive Meta-analysis exploring the association between CSC and Hp, and it may help ophthalmologists decide on treatments and provide preventive measures for patients at high risk and prone to recurrence.

MATERIALS AND METHODS

Ethical Approval This study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines[17]. This Meta-analysis was registered (PROSPERO Registered ID: CRD42022353329).

Search Strategy A comprehensive search of related studies was conducted in Scopus, Embase, EBSCO, PubMed, Web of Science, and the Cochrane Library from inception to October 2022. The following keywords were used as search terms ("Central Serous Chorioretinopathy" OR "Central Serous Retinopathy" OR "CSC" OR "CSCR") AND ("Helicobacter pylori" OR "Helicobacter nemestrinae" OR "Campylobacter pylori" OR "Campylobacter pylori subsp. Pylori" OR "Campylobacter pyloridis"). The search strategy for other databases was adapted from the initial PubMed strategy. Additional strategies included a manual search of the reference lists of all retrieved review papers and critical articles. This study adhered to the PRISMA guidelines[18]. In total, 8 studies were included in the Meta-analysis (Figure 1).

Inclusion and Exclusion Criteria According to the preestablished literature screening criteria, two reviewers independently screened all the retrieved literature. Discrepancies were resolved by checking the primary article and consulting a third reviewer. Original studies were included if they met the following inclusion criteria: 1) study designs were original observational studies (cohort or case-control studies); 2) studies evaluated the association between Hp infection and the occurrence of CSC; 3) studies evaluated the outcome with odds ratios (ORs) and their confidence intervals (CIs) or with raw data provided for calculation. No language limitation was applied. Studies were excluded according to the following criteria: 1) animal studies, reviews, editorials, commentaries, case reports, abstracts, or letters; 2) studies with insufficient data or outcomes for analysis; 3) studies from the same author that reported repeated outcomes of the same cohort (study with more comprehensive data was included in this case).

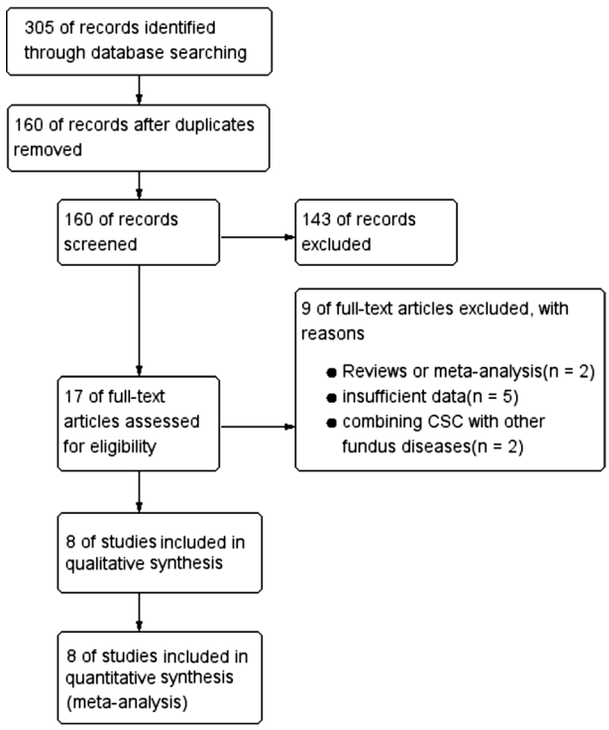

Figure 1 Prisma flow diagram of the study selection process CSC: Central serous chorioretinopathy.

Quality Assessment Two reviewers independently evaluated the methodological quality of each included study using the Newcastle-Ottawa Scale (NOS)[19]. This scale consists of 3 aspects: selection (0–4 points), comparability (0–2 points), and ascertainment of outcome (0–3 points). Studies were considered of satisfactory quality if they scored 5 and above out of 9. A study with a score of 7–9 points was defined as high quality. Any discrepancies were resolved through discussion or referred to a third reviewer. The NOS scores are displayed in Table 1[8,20-26].

Data Extraction Data were extracted from the retrieved studies independently by two reviewers with customized datasheets. Discrepancies were resolved by checking the primary article and consulting a third reviewer. Data were collected as follows: research characteristics (first author, year of publication, country of study, study design, language, sample size), studied population characteristics (the number of patients in the CSC case group and control group, the race of the study population, the ratio of males in each group, the average age of each group, and the method used to diagnose Hp infection), and result index (the number and ratio of Hp positive cases in case group and control group, adjusted and unadjusted OR, 95%CI, *P* value, adjusted factors).

Statistical Analysis REVMAN 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) was used for the Meta-

Table 1 Basic characteristics and quality evaluation of the included studies

Study	Country	Hp test	Size		Masculinity ratio (%)		Age (y)		Hp+, *n* (%)		Unadjusted OR (95%CI)	Adjusted OR (95%CI)	NOS Score
			CSC cases	Controls	CSC cases	Controls	CSC cases	Controls	CSC cases	Controls			
Asensio-Sánchez, 2008[20]	Spain	C13 UBT	16	20	68.8	65.0	46.3±13.2	50.2±12.4	11 (68.8)	6 (30.0)	NA	NA	6
Chatzirallim, 2017[8]	Greece	NA	183	183	71.6	57.4	48.3±4.2	48.5±3.3	36 (19.7)	21 (11.5)	NA	1.89 (1.06–3.39)	8
Cotticelli, 2006[21]	Italy	Blood antibody and stool antigen test	23	23	95.7	95.7	47	50	18 (78.2)	10 (43.5)	4.6 (1.28–16.9)	NA	7
Feghhi, 2008[22]	Iran	C13 UBT and blood antibody test	54	59	88.9	42.4	35.7±10.1	42.6±11	37 (68.5)	38 (65.0)	NA	NA	8
Galdós Iztueta, 2008[23]	Spain	C13 UBT	27	36	81	69	40	36	21 (77.8)	23 (63.9)	NA	NA	6
Misiuk-Hojło, 2009[24]	Poland	Blood antibody test and stool antigen test	55	55	NA	NA	NA	NA	37 (67)	26 (47)	NA	NA	7
Roshani, 2014[25]	Iran	C13 UBT	35	138	91.4	92.8	34.1±5.7	34.0±11.0	30 (85.7)	76 (55.1)	4.895 (NA)	NA	8
Zhou, 2019[26]	America	NA	35492	177460	69.2	69.2	49.1±12.2	45.0±14.1	71 (0.20)	1871 (1.05)	NA	0.32 (0.25–0.40)	8

UBT: Urea breath test; CSC: Central serous chorioretinopathy; Hp: *Helicobacter pylori*; OR: Odds ratio; CI: Confidence interval; NOS: Newcastle-Ottawa Scale; NA: Missing data.

analysis. Through comprehensive analysis we assume that the true effect size varies from study to study, and the summary effect is our estimate of the mean of the distribution of the effect size, so we pooled the data using the random-effects model to determine the risk of infection with CSC[27]. We calculated the pooled OR of case-control studies with 95%CI, and $P<0.05$ was defined as a statistically significant difference. The heterogeneity of the included studies was measured according to the Cochrane Q test and I^2 test[28-29]. The cut-off for defining heterogeneity was $I^2>50\%$[30]. To explore the sources of heterogeneity and the potentially significant associations, subgroup analyses were stratified by country economic levels. Furthermore, a random effect Meta-regression analysis model in STATA 12.0 (StataCorp, College Station, TX, USA) was used to explore the influence of some predefined covariables on the combined effect and the source of heterogeneity in the meta-analysis, including publication year, sample size, publication language, the ratio of males in the experimental group, the ratio of males in the control group, the average age of the experimental group, and the average age of the control group. If $P<0.05$ (0.10 for Q test), it was considered that this factor was one of the sources of heterogeneity among studies. Considering that the data used in this study are binary, all the estimated values are transformed by Meta-regression using the natural logarithm to meet the parameter hypothesis of normal distribution. To test the robustness of the results, we used sensitivity analysis by sequentially excluding one study at a time and combining the pooled ORs of the remaining studies to determine whether the results were changed[31]. Publication bias was assessed through visual funnel plot inspection and quantified by Begg's test and Egger's test using STATA 12.0 statistical software (Stata Corp, College Station, TX, USA), in which $P<0.1$ indicated a statistically significant difference[32-33].

RESULTS

Search Results A total of 305 potentially relevant studies were yielded after 160 duplicate articles were removed. A total of 143 articles were removed after the title and abstract review because they were not observational studies or their topics, and the results did not meet our requirements, leaving 17 studies included for full-length article review. After that, 2 reviews or Meta-analyses were excluded, another 5 studies were excluded because of insufficient data for analysis, and 2 studies were excluded because they studied combining CSC with other fundus diseases. Finally, 8 case-control studies[8,20-26] were identified (Figure 1).

Study Characteristics and Data A summary of the basic characteristics of the included studies is shown in Table 1. All studies attained a score of 6 or above on the assessment of methodological quality using the NOS.

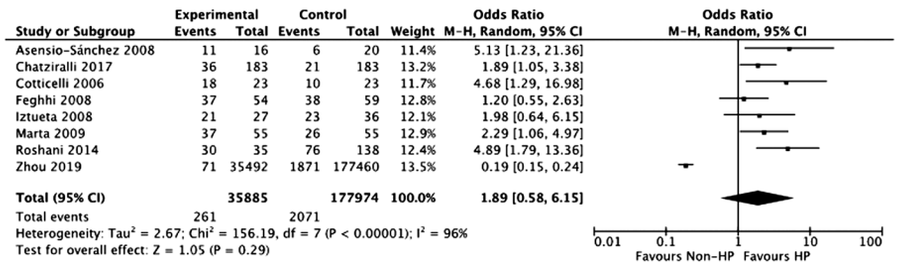

Figure 2 Overall ORs and 95%CIs of the correlation between Hp infection and CSC OR: Odds ratio; CSC: Central serous chorioretinopathy; Hp: *Helicobacter pylori*.

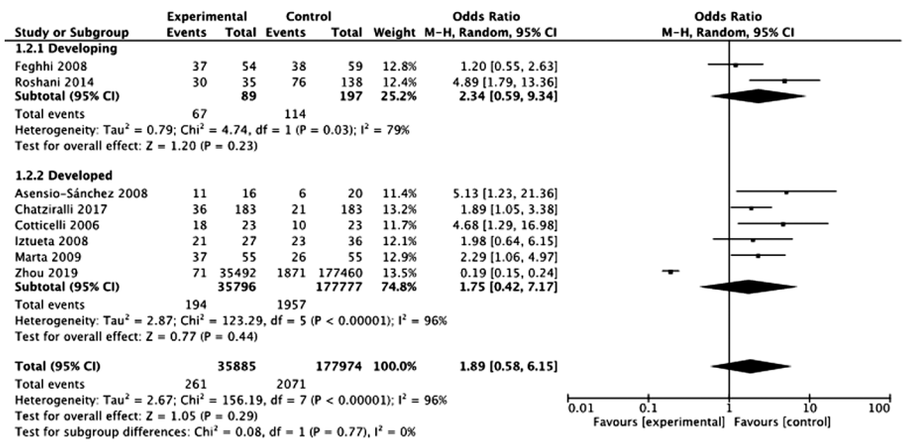

Figure 3 Subgroup analysis for the degree of development of the country.

Correlation Between Hp Infection and CSC A total of 8 articles[8,20-26] met the inclusion criteria, including 35 885 CSC cases and 177 974 healthy controls. After the heterogeneity test, I^2 was more than 50%, so the random effect model was used for analysis. The results showed no significant correlation between Hp infection and CSC (OR 1.89, 95%CI 0.58–6.15, I^2=96%, P=0.29; Figure 2).

Subgroup Analyses The population infection rate of Hp is closely related to the degree of development of the region[34], so we further grouped the study according to the degree of development of the country (developed/developing countries) and carried out a subgroup analysis. The heterogeneity of each subgroup was significant (I^2>50%), so the random effect model was used. No significant correlation between Hp infection and CSC in the two subgroups was detected in either developing countries or developed countries (developing countries group: OR 2.34, 95%CI 0.59–9.34, I^2=79%, P=0.23; developed countries group: OR 1.75, 95%CI 0.42–7.17, I^2=96%, P=0.44). There was no significant difference between the subgroups (P=0.77; Figure 3).

Meta-Regression Analyses To address the potential sources of heterogeneity, a random-effect Meta-regression was conducted for analyses. Due to the lack of Misiuk-Hojło *et al*[24] data, 7 articles[8,20-23,25-26] met the Meta-regression criteria. Restricted maximum likelihood (REML) single-factor Meta-regression analysis was used for each factor since the conditions of multifactor Meta-regression analysis were not satisfied, and the variance of the estimation coefficient was modified. The P value and confidence interval were calculated by the t-distribution principle. From the factors (publication year, sample size, publication language, ratio of males in the experimental group, ratio of males in the control group, average age of the experimental group, average age of the control group) that may affect heterogeneity, "sample size" was selected as heterogeneity (P<0.01, adjusted R^2=89.72%), which can explain 89.72% of the sources of heterogeneity. The study of Zhou *et al*[26], with a relatively large sample size (n=212 952), played a dominant role in this effect. Thus, additional analysis without the study was conducted, and the result was nonsignificant (P=0.59), indicating that the study is likely to be an outlier (Table 2).

Publication Bias and Heterogeneity Analysis Publication bias of experimental events was identified by Begg's and Egger's tests. The funnel plot showed that the distribution of the included studies was asymmetric, and Zhou *et al*[26] significantly deviated from the midline, as shown in Figure 4A, 4C, indicating that there may be publication bias (Begg's test P=1.00, Egger's test P<0.10). When we excluded Zhou *et al*[26], the rest of the included studies were roughly symmetrical above and below the midline as shown in Figure 4B, 4D, showing that the publication bias of experimental events was not identified at this time (Begg's test P=0.26, Egger's test P=0.12). We also conducted a sensitivity analysis, and significant heterogeneity was observed in one analysis. When

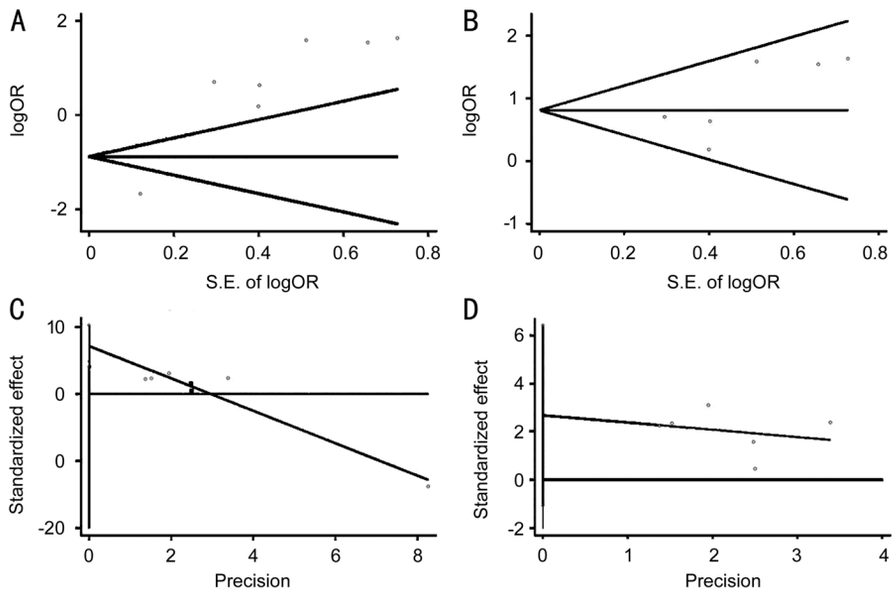

Figure 4 Funnel plot of Begg's and Egger's tests A, B: Begg's funnel plot with pseudo 95% confidence limits; C, D: Egger's publication bias plot.

Table 2 Meta-regression analysis of factors affecting heterogeneity

Variable	Coefficient (95%CI)	Statistical significance (*P*)	adj R^2
Publication year	0. 87 (0.70, 1.08)	0.16	26.68%
Sample size	1.00 (1.00, 1.00)	<0.01	89.72%
Publication language[a]	0.47 (0.03, 8.47)	0.53	-7.78%
Ratio of males in the experimental group	1.05 (0.94, 1.18)	0.28	12.93%
Ratio of males in the control group	1.03 (0.95, 1.10)	0.41	-3.87%
Average age of the experimental group	0.94 (0.76, 1.16)	0.48	-4.25%
Average age of the control group	0.99 (0.80, 1.24)	0.95	-18.97%

Confidence interval; [a]Reference: Spanish 1; English 2.

Zhou *et al*[26] was excluded, the heterogeneity was reduced, and Hp infection was a risk factor for CSC (I^2 decreased from 96% to 22%, OR 2.34, 95%CI 1.59–3.46, P<0.0001), but all the other results remained consistent. Therefore, the potential sources of heterogeneity in this study will be discussed in the discussion section shown in Table 3[8,20-26].

Table 3 Sensitivity analysis results

Included study	I^2	OR (95%CI)	*P*
Asensio-Sánchez, 2008[20]	96%	1.66 (0.48, 5.72)	0.42
Chatziralli, 2017[8]	95%	1.89 (0.50, 7.22)	0.35
Cotticelli, 2006[21]	96%	1.67 (0.48, 5.78)	0.42
Feghhi, 2008[22]	96%	2.03 (0.53, 7.75)	0.30
Galdós Iztueta, 2008[23]	96%	1.88 (0.52, 6.75)	0.34
Misiuk-Hojło, 2009[24]	96%	1.84 (0.51, 6.66)	0.36
Roshani, 2014[25]	95%	1.64 (0.48, 5.62)	0.43
Zhou, 2019[26]	22%	2.34 (1.59, 3.46)	<0.0001

OR: Odds ratio; CI: Confidential interval.

DISCUSSION

CSC is a common cause of visual impairment, estimated to affect up to 10 per 100 000 individuals annually[35]. Nevertheless, consensus regarding the association between Hp infection and the risk of developing CSC remains elusive. To address this gap, we conducted a comprehensive Meta-analysis to integrate all available studies and investigate the potential association between CSC and Hp infection. Given the limited sample size of existing case-control studies, we endeavored to enhance our understanding by synthesizing relevant literature through Meta-analysis. In the Meta-analysis, we included a total of 8 articles, all of which were case-control studies, including 35 885 CSC cases and 177 974 healthy controls. The results of the Meta-analysis showed that there was no significant correlation between Hp infection and CSC. After subgroup analysis based on the degree of development of the study (developing/developed countries), it was found that the results of the two subgroups were basically the same as the whole, and there was no significant difference between the two subgroups. Previously, some research show that Hp infection may correlate with the development of many ocular diseases such as diabetic retinopathy (DR), CSC[21,36]. For those who hold that Hp may be a risk factor for CSC, the mechanism of pathogenesis of Hp in the occurrence and development of CSC has not been clarified. Some scholars[37] believe that the possible mechanism of Hp in the process of atherosclerosis can be analogous; that

is, Hp carries cytotoxin-associated gene-A (CagA), and the infected body produces the corresponding anti-CagA antibody, which has an immune cross-reaction with vascular endothelial cells, thus causing damage to the vascular endothelium[3]. In addition, the deposition of immunoglobulin-G (IgG) produced in the process of anti-infection can aggravate vascular endothelial dysfunction[38]. Some scholars believe that the high expression of anti-heat shock protein antibodies in Hp-infected people will cross-react with homologous host proteins located in the vascular endothelium in the form of "molecular simulation", resulting in vascular endothelial dysfunction and increased platelet activation and aggregation through a series of molecular mechanisms, resulting in choroidal microcirculation disturbance[39-41]. However, a portion of patients infected with Hp could not be detected with existing laboratory examinations, causing bias in the original studies and our Meta-analysis. However, our Meta-analysis findings contradict previous research suggesting a potential association between Hp infection and CSC. By using the random effect Meta-regression analysis model, we found that the year of publication, the language of publication, the ratio of men in the experimental group, the ratio of men in the control group, the average age of the experimental group and the average age of the control group had no significant effect on the heterogeneity between the studies. The conclusion of our study may be influenced by various factors. Notably, limitations in current laboratory methods hindered the detection of Hp infection in some patients, introducing bias into both the original studies and our Meta-analysis. Additionally, heterogeneity analysis identified the study by Zhou *et al*[26] with the largest sample size (n=212 952) as significantly affecting overall heterogeneity, so we removed the study and carried out Meta-regression again, and the results showed that the difference was not statistically significant (P=0.59), indicating that the study is likely to be an outlier.

We also conducted a sensitivity analysis to explore the source of heterogeneity. We found that after the removal of Zhou *et al*[26], the overall heterogeneity decreased significantly, and the conclusion of the Meta-analysis changed considerably; that is, from the original Hp infection, which had no significant correlation with CSC, to Hp infection being the risk factor for CSC, so it was considered that this study was the primary source of heterogeneity and had a significant impact on the total effect. After careful analysis, we think that the origins of heterogeneity in this study may have the following two points.

1) Publication bias. Studies found that statistically significant results were more than twice as likely to be published as those that were not: adjusted OR 2.3 (95%CI 1.3–4.3). Studies with positive results were also more likely to be published in higher impact journals[42]. Many investigators of small studies may lose interest with inconclusive preliminary results and, in turn, refrain from publishing. It is also widely believed that positive results are more favored by editors and reviewers and therefore more likely to be published[43]. Finally, many small studies are appropriately rejected due to lack of credibility. In contrast, most large studies are published, regardless of whether the results are positive or negative. This ultimately leads to publication bias disproportionately affecting those small studies that form the basis of many Meta-analyses[44]. Therefore, the conclusion that Zhou *et al*[26] is the primary source of heterogeneity needs to be viewed with caution, especially when the studies included in the Meta-analysis have a high risk for bias and when the seven small sample studies are included. The number of samples included by Zhou *et al*[26] is significantly larger than that of the other seven case-control studies, so more convincing and accurate results may be obtained compared to the other seven case-control studies, and the calculated 95%CI is also obviously narrow.

2) Recall bias. The sample of Zhou *et al*[26] comes from the database, and the original literature does not specify what kind of Hp detection method is used, so there is the possibility of data loss and inaccuracy.

In summary, considering the good overall quality and large sample size of Zhou *et al*[26], we still believe that it should be included in the overall Meta-analysis and hope that there will be more clinical studies with large sample sizes in the future to continue to explore the relationship between Hp infection and CSC.

Our research also has some limitations. First, all the included studies were observational case-control studies, which are more likely to produce recall bias or selection bias than cohort studies and randomized controlled trials, and the evidence is relatively insufficient[40]. Second, in the works of the literature we included, most of the studies failed to report the effect after multifactor adjustment, so in the process of our Meta-analysis, we could only use the number of cases to calculate the effect and failed to adjust for confounding factors. The resulting potential confounding factors are not fully controlled, leading to the actual results being overestimated or underestimated. In addition, the existing related studies are limited, and most of the sample sizes included in these studies are small. The above conclusions need to be supported by more well-designed large-sample studies.

In summary, this Meta-analysis was an exploratory study of the association between Hp infection and CSC that showed no significant correlation. As our analysis did not reveal a consistent result, the conclusion remains inconclusive, which still warrants further well-designed large sample studies to reach a more reliable conclusion and promote a better understanding of the treatment of CSC.

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REFERENCES

1 Feenstra HMA, van Dijk EHC, Cheung CMG, *et al*. Central serous chorioretinopathy: an evidence-based treatment guideline. *Prog Retin Eye Res* 2024:101236. Epub ahead of print.

2 Fung AT, Yang Y, Kam AW. Central serous chorioretinopathy: a review. *Clin Exp Ophthalmol* 2023;51(3):243-270.

3 Kaye R, Chandra S, Sheth J, Boon CJF, Sivaprasad S, Lotery A. Central serous chorioretinopathy: an update on risk factors, pathophysiology and imaging modalities. *Prog Retin Eye Res* 2020;79:100865.

4 van Dijk EHC, Schellevis RL, Breukink MB, *et al*. Familial central serous chorioretinopathy. *Retina* 2019;39(2):398-407.

5 Miki A, Kondo N, Yanagisawa S, Bessho H, Honda S, Negi A. Common variants in the complement factor H gene confer genetic susceptibility to central serous chorioretinopathy. *Ophthalmology* 2014;121(5): 1067-1072.

6 Sim RB, Ferluga J, Al-Rashidi H, Abbow H, Schwaeble W, Kishore U. Complement factor H in its alternative identity as adrenomedullin-binding protein 1. *Mol Immunol* 2015;68(1):45-48.

7 Smal C, Lepièce G, Bonnet S. Central serous chorioretinopathy following the use of phosphodiesterase 5 inhibitors. *Rev Med Liege* 2017;72(11):475-477.

8 Chatziralli I, Kabanarou SA, Parikakis E, Chatzirallis A, Xirou TN, Mitropoulos P. Risk factors for central serous chorioretinopathy: multivariate approach in a case-control study. *Curr Eye Res* 2017;42(7):1069-1073.

9 Liu B, Deng T, Zhang JJ. Risk factors for central serous chorioretinopathy: a systematic review and meta-analysis. *Retina* 2016;36(1):9-19.

10 Michel JL, Cabibel F. Frequency, severity and treatment of ocular rosacea during cutaneous rosacea. *Ann Dermatol Venereol* 2003;130(1 Pt 1):20-24.

11 Kountouras J, Mylopoulos N, Boura P, Bessas C, Chatzopoulos D, Venizelos J, Zavos C. Relationship between Helicobacter pylori infection and glaucoma. *Ophthalmology* 2001;108(3):599-604.

12 Doulberis M, Papaefthymiou A, Polyzos SA, *et al*. Association between active *Helicobacter pylori* infection and glaucoma: a systematic review and meta-analysis. *Microorganisms* 2020;8(6):894.

13 Otasevic L, Zlatanovic G, Stanojevic-Paovic A, Miljkovic-Selimovic B, Dinic M, Djordjevic-Jocic J, Stankovic A. *Helicobacter pylori*: an underestimated factor in acute anterior uveitis and spondyloarthropathies? *Ophthalmologica* 2007;221(1):6-13.

14 Kim JM, Park KH, Choi MJ, Ha MM, Sohn YH, Kim HK, Caprioli J. The effects of *Helicobacter pylori* infection on intraocular pressure in anterior uveitis. *Eye(Lond)* 2012;26(12):1503-1510.

15 Chey WD, Wong BCY, Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection. *Am J Gastroenterol* 2007;102(8):1808-1825.

16 Giusti C. Central serous chorioretinopathy: a new extragastric manifestation of *Helicobacter pylori*? Analysis of a clinical case. *Clin Ter* 2001;152(6):393-397.

17 Moher D, Liberati A, Tetzlaff J, Altman DG, Group PRISAA. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.

18 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

19 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603-605.

20 Asensio-Sánchez VM, Rodríguez-Delgado B, García-Herrero E, Cabo-Vaquera V, García-Loygorri C. Central serous chorioretinopathy as an extradigestive manifestation of *Helicobacter pylori* gastric infection. *Arch Soc Esp Oftalmol* 2008;83(3):177-182.

21 Cotticelli L, Borrelli M, D'Alessio AC, *et al*. Central serous chorioretinopathy and *Helicobacter pylori*. *Eur J Ophthalmol* 2006;16(2):274-278.

22 Feghhi M, Hajiani E, Khataminia G, Jundishapur A. Incidence of *Helicobacter pylori* in central serous chorioretinopathy: a case control study. *Jundishapur J Microbiol* 2008;2008:15-19.

23 Galdós Iztueta M, Pinar Sueiro S, Martínez Alday N. Risk factors for central serous chorioretinopathy: case reports and controls. *Arch Soc Canar Oftal* 2008;19:16-20.

24 Misiuk-Hojło M, Michałowska M, Turno-Krecicka A. *Helicobacter pylori*—a risk factor for the developement of the central serous chorioretinopathy. *Klin Oczna* 2009;111(1-3):30-32.

25 Roshani M, Davoodi NA, Seyyedmajidi MR, Zojaji H, Sherafat SJ, Hashemi M, Zali MR. Association of *Helicobacter pylori* with central serous chorioretinopathy in Iranian patients. *Gastroenterol Hepatol Bed Bench* 2014;7(1):63-67.

26 Zhou M, Bakri SJ, Pershing S. Risk factors for incident central serous retinopathy: case-control analysis of a US national managed care population. *Br J Ophthalmol* 2019;103(12):1784-1788.

27 Nakagawa S, Noble DW, Senior AM, Lagisz M. Meta-evaluation of meta-analysis: ten appraisal questions for biologists. *BMC Biol* 2017;15(1):18.

28 Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. *Epidemiol Rev* 1992;14:154-176.

29 Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990;6(1):5-30.

30 Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I^2 is not an absolute measure of heterogeneity. *Res Synth Methods* 2017;8(1):5-18.

31 Copas J, Shi JQ. Meta-analysis, funnel plots and sensitivity analysis. *Biostatistics* 2000;1(3):247-262.

32 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-1101.

33 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-634.

34 Burucoa C, Axon A. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2017;22 Suppl 1.

35 Singh RP, Sears JE, Bedi R, Schachat AP, Ehlers JP, Kaiser PK. Oral eplerenone for the management of chronic central serous chorioretinopathy. *Int J Ophthalmol* 2015;8(2):310-314.

36 Liu ZR, Bao T, Xue GJ, Xu QY, Gao YX, Zhang M. Correlation between diabetic retinopathy and *Helicobacter pylori* infection: a cross-sectional retrospective study. *Int J Ophthalmol* 2023;16(8):1260-1267.

37 Giusti C. Association of *Helicobacter pylori* with central serous chorioretinopathy: hypotheses regarding pathogenesis. *Med Hypotheses* 2004;63(3):524-527.

38 Prasad A, Zhu J, Halcox JP, Waclawiw MA, Epstein SE, Quyyumi AA. Predisposition to atherosclerosis by infections: role of endothelial dysfunction. *Circulation* 2002;106(2):184-190.

39 Lamb DJ, El-Sankary W, Ferns GAA. Molecular mimicry in atherosclerosis: a role for heat shock proteins in immunisation. *Atherosclerosis* 2003;167(2):177-185.

40 Byrne MF, Kerrigan SW, Corcoran PA, Atherton JC, Murray FE, Fitzgerald DJ, Cox DM. *Helicobacter pylori* binds von Willebrand factor and interacts with GPIb to induce platelet aggregation. *Gastroenterology* 2003;124(7):1846-1854.

41 Byrne MF, Corcoran PA, Atherton JC, Sheehan KM, Murray FE, Fitzgerald DJ, Murphy JF. Stimulation of adhesion molecule expression by *Helicobacter pylori* and increased neutrophil adhesion to human umbilical vein endothelial cells. *FEBS Lett* 2002;532(3):411-414.

42 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;337(8746):867-872.

43 Sessler DI, Imrey PB. Clinical research methodology 3: randomized controlled trials. *Anesth Analg* 2015;121(4):1052-1064.

44 Bartels K, Sessler DI. Meta-analyses of clinical trials: are we getting lemonade from lemons? *Br J Anaesth* 2022;128(2):233-235.