Is tobacco consumption a risk factor for central serous chorioretinopathy? A systematic review and meta-analysis

Fakhril-Din, Z.; Arnold-Vangsted, A.; Boberg-Ans, L.C.; Anguita, R.; Desideri, L.F.; Dijk, E.H.C. van; ... ; Subhi, Y.

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REVIEW ARTICLE

Is tobacco consumption a risk factor for central serous chorioretinopathy? A systematic review and meta-analysis

Zainab Fakhril-Din[1] | **Andreas Arnold-Vangsted**[2] | **Lars Christian Boberg-Ans**[3] | **Rodrigo Anguita**[4,5] | **Lorenzo Ferro Desideri**[4,6,7] | **Elon H. C. van Dijk**[8,9,10] | **Jakob Grauslund**[11,12,13] | **Oliver Niels Klefter**[2,14] | **Özge Yanik**[15] | **Yousif Subhi**[1,2,13]

[1]Department of Ophthalmology, Zealand University Hospital, Roskilde, Denmark

[2]Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark

[3]Department of Ophthalmology, Innlandet Hospital Trust, Elverum, Norway

[4]Department of Ophthalmology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland

[5]Moorfields Eye Hospital, NHS Foundation Trust, London, UK

[6]Department for Bio Medical Research, University of Bern, Bern, Switzerland

[7]Bern Photographic Reading Center, Inselspital, University Hospital Bern, Bern, Switzerland

[8]Lions Eye Institute, Perth, Western Australia, Australia

[9]Department of Ophthalmology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

[10]Department of Ophthalmology, Leiden University Medical Centre, Leiden, The Netherlands

[11]Department of Ophthalmology, Odense University Hospital, Odense, Denmark

[12]Department of Ophthalmology, Vestfold Hospital Trust, Tønsberg, Norway

[13]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[14]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[15]Department of Ophthalmology, Ankara University School of Medicine, Ankara, Turkey

Correspondence
Yousif Subhi, Department of Clinical Research, University of Southern Denmark, J.B. Winsløws Vej 19, DK-5000 Odense, Denmark.
Email: ysubhi@gmail.com

Abstract

Central serous chorioretinopathy (CSC) is a prevalent exudative maculopathy. Understanding risk factors for CSC is important for disease prevention and to provide evidence-based advice to patients. In this study, we systematically reviewed the literature and performed meta-analysis on the association between tobacco consumption and CSC. We searched 12 literature databases on May 5, 2024, and identified 11 eligible studies of 27 595 patients with CSC and 105 354 control individuals. Studies were predominantly clinic-based case–control studies. We calculated a summary estimate of tobacco consumption as a risk factor for CSC at an odds ratio of 2.99 (95% CI: 1.82–4.93, p=0.000017), which remained statistically significant in the sensitivity analyses. The exact mechanism by which tobacco consumption contribute to the pathophysiology of CSC remains unclear, although several potential hypotheses exist. However, tobacco consumption is a modifiable behaviour and tobacco cessation is an actionable advice with which patients with CSC themselves can play a large role in disease management. Further studies are warranted to understand the impact of tobacco cessation for risk modification and for the prognosis of patients who already have CSC.

KEYWORDS

central serous chorioretinopathy, meta-analysis, risk factor, systematic review, tobacco consumption

1 | INTRODUCTION

Central serous chorioretinopathy (CSC) is considered the fourth most prevalent exudative maculopathy, after neovascular age-related macular degeneration, diabetic macular oedema and retinal venous occlusion (Feenstra et al., 2024). In CSC, enlarged choroidal vessels can be observed due to venous congestion, outflow problems at vortex veins, and arteriovenous anastomoses (Brinks et al., 2022; Cheung et al., 2019; Spaide et al., 2021, 2022). The increased hydrostatic pressure in the choroid lead to serous detachment of the retinal pigment epithelium (RPE), damage to the RPE, which is then followed by the accumulation of subretinal fluid (SRF). The SRF is typically seen as the clinical hallmark of CSC. Although most cases of acute CSC resolve spontaneously and can be observed without treatment (Feenstra et al., 2024; Mohabati et al., 2020), long-standing cases of SRF in chronic CSC should be treated to avoid irreversible vision loss due to photoreceptor atrophy (Breukink et al., 2016; Feenstra et al., 2024; Peiretti et al., 2015; Sirks et al., 2024; van Dijk et al., 2023; Wang et al., 2002).

CSC predominantly occurs in men aged 30–50 years (Haimovici et al., 2024; Kido et al., 2022; Subhi et al., 2023), and the strongest known risk factor is corticosteroid use or more rarely endogenous causes of excessive corticosteroid levels such as Cushing's disease (Haimovici et al., 2024; Holtz et al., 2022; van Dijk et al., 2016; van Haalen et al., 2018). Certain personality traits and psychological characteristics have also been associated with CSC, e.g., type A personality, higher levels of anxiety, and a higher rate of psychological distress (Bazzazi et al., 2015; Çam et al., 2024; Kim et al., 2018; Sahin et al., 2014), although parts of these associations remain debated (van Haalen et al., 2019). Understanding risk factors for CSC is crucial for both disease prevention, mapping of the disease mechanisms which remain incompletely understood (Borgersen et al., 2021; Jain et al., 2022; Subhi et al., 2019), and to be able to provide evidence-based advice to patients. In our clinical experience, patients often ask if there is anything they can do to prevent or lower the risk of CSC onset or relapse. This requires a better understanding of the risk factors and, in particular, those related to lifestyle factors. It is critical to identify modifiable lifestyle factors in order to provide strategies for prevention and management. One such lifestyle factor is tobacco consumption (Haimovici et al., 2024). Studies suggest that tobacco consumption may influence the anatomy of the choroid (Okawa et al., 2021; Sigler et al. 2014), which at least provides a pathophysiological reason to suspect that tobacco consumption may be a lifestyle-related risk factor for pachychoroid related diseases such as CSC. To better understand this potential relationship, we systematically reviewed the literature and performed meta-analysis on the association between tobacco consumption and CSC.

2 | METHODS

This systematic review and meta-analysis was designed according to the elements of the Cochrane Handbook (Higgins et al., 2023). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for the dissemination of this study (Moher et al., 2009). Our protocol was registered a priori at PROSPERO (protocol no. CRD42024549028).

2.1 | Study eligibility criteria and outcomes of interest

Eligible studies were defined as any prospective and retrospective observational studies of humans to evaluate the association between tobacco consumption and CSC, i.e., both cross-sectional and cohort study designs were considered eligible. For all studies, exposure was defined as tobacco consumptions without further restrictions on this definition. For all studies, outcome of interest was the smoking-associated risk of CSC, which could be odds ratio (OR), risk ratio or raw numbers (i.e., prevalence or incidence of CSC in groups defined according to their tobacco habits). For cross-sectional studies, eligible studies had to include both a group of individuals with CSC and a group of individuals without CSC. For cohort studies, eligible studies had to include a group of individuals without CSC and record incident CSC within a defined time period.

Studies without original data or case studies were not considered eligible. Relevant conference abstracts were included if they fulfilled the eligibility criteria. We did not restrict eligibility based on geography or journal but did restrict to language of dissemination (English) for practical purposes.

2.2 | Information sources and literature search

One trained author (Y.S.) searched the databases *Cochrane Central, Embase, PubMed, BIOSIS Previews, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Preprint Citation Index, ProQuest™ Dissertations & Theses Citation Index, SciELO Citation Index, and Web of Science Core Collection*. All searches were conducted on 5 May 2024. Detailed documentation of the literature search in individual databases is provided in File S1.

2.3 | Study selection, data extraction, and risk of bias within studies

One author (Y.S.) screened title and abstracts of all records to remove duplicates and obviously irrelevant records. Two authors (Z.F-D. and L.C.B-A.) independently assessed the remaining references in full text for eligibility. Reference lists were examined to identify other potentially eligible studies. Disagreements were discussed with a senior author (Y.S.) for final decision making.

Upon consensus, data were extracted from each study on study and population characteristics, tobacco consumption, diagnosis of CSC and results from individual studies. Risk of bias within individual studies was

evaluated using the relevant items from the Agency for Healthcare Research and Quality (AHRQ) checklist (Zeng et al., 2015). Data extraction and risk of bias evaluation were made independently by two authors (Z.F-D. and A.A-V.). Disagreements were discussed with a senior author (Y.S.) for final decision making.

2.4 | Data analysis, data synthesis and risk of bias across studies

All eligible studies underwent qualitative review in text and tables. For meta-analyses, the tobacco consumption-associated risk for each study was either extracted based on reported OR or a study-specific OR was calculated based on the reported data. Where available, we extracted OR estimates from multivariable adjusted analyses. Meta-analyses were made using MetaXL 5.3 (EpiGear International) for Microsoft Excel 2013 (Microsoft) with the random-effects model to account for potential heterogeneity in designs across the eligible studies. Heterogeneity was evaluated using the Cochran's Q and I^2. Funnel plot was used to evaluate potentially skewness of results and publication bias. Sensitivity analyses were conducted by removing each study in turn and by re-calculating the summary measures to evaluate how the results from individual studies impact the calculated overall summary estimates.

3 | RESULTS

3.1 | Study selection

We extracted 174 records based on our literature search, of which 109 were duplicates and 92 obviously irrelevant. The remaining 17 records were all examined in full text. Six studies were excluded as they did not fulfil our predefined study eligibility criteria. In total, 11 studies were eligible for the qualitative and the quantitative review (Figure 1).

3.2 | Study characteristics

The 11 studies summarized data from a total of 132 949 individuals, of which 27 595 were patients with CSC and 105 354 were controls (Chatziralli et al., 2017; Chen et al., 2019; Ersoz et al., 2019; Gundlach & Tsui, 2021; Haimovici et al., 2024; Karimi et al., 2023; Kunikata et al., 2020; Latalska et al., 2020; Sakai & Tsuneoka, 2017; Tahara et al., 2023; van Dijk et al., 2017). Studies were

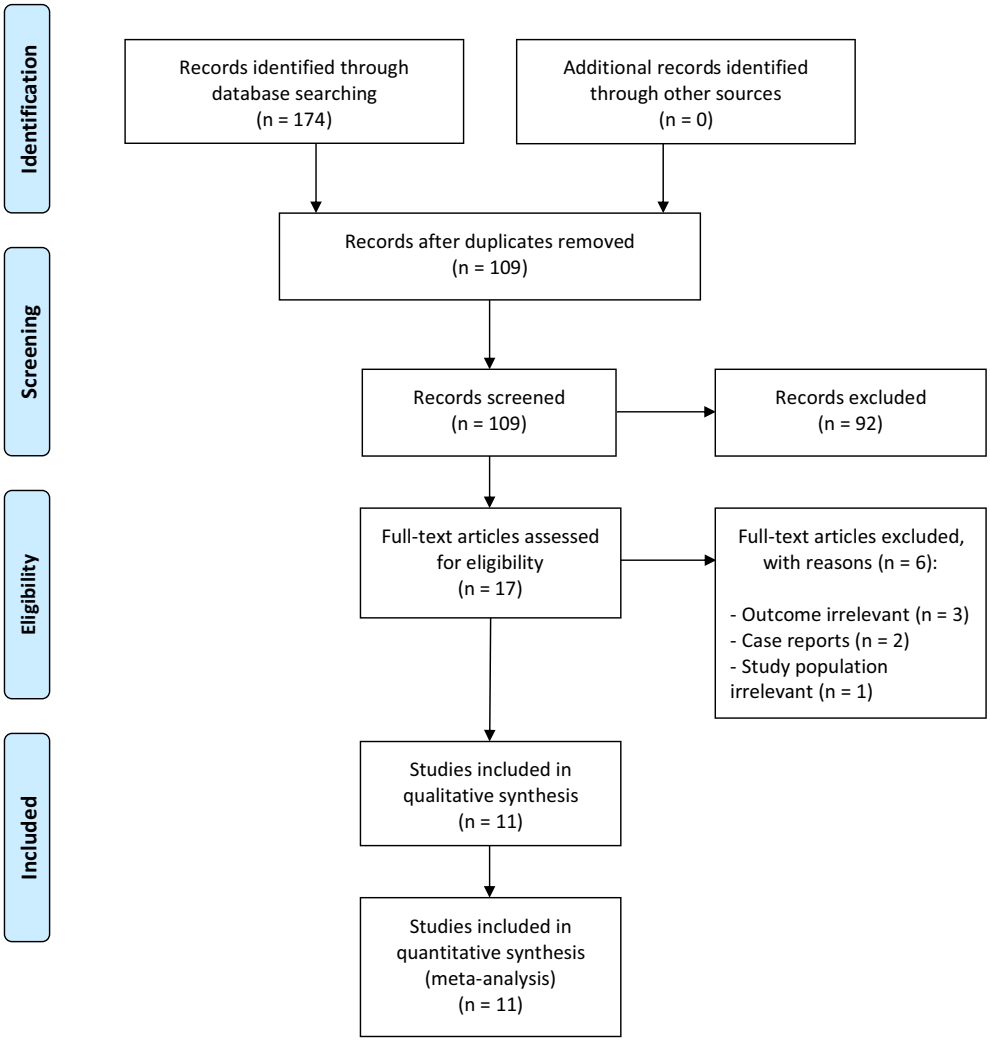

FIGURE 1 PRISMA flow diagram of study selection process.

conducted in Greece ($n=1$), Iran ($n=1$), Japan ($n=3$), the Netherlands ($n=1$), Poland ($n=1$), Taiwan ($n=1$), Turkey ($n=1$) and the United States ($n=2$). Ten studies were clinic-based case–control studies, and one study was a nationwide registry-based cohort study. Nine studies were retrospective in nature and two were prospective. Mean age of the patients ranged between 43 and 63 years. In all studies apart from Karimi et al. (2023), the majority of the patient population were males. Overall, the control group of individual studies were matched in demographical variables to those of the patient group. Where specified, CSC was diagnosed using different definitions (acute CSC, classic CSC, chronic CSC), but a common definition of CSC was based on the presence of SRF together with other disease stigmata present on fundus autofluorescence, fluorescein angiography or indocyanine green angiography. Five studies specifically stated that they excluded cases with macular neovascularization (Ersoz et al., 2019; Latalska et al., 2020; Sakai & Tsuneoka, 2017; Tahara et al., 2023; van Dijk et al., 2017). Where specified, evaluation of tobacco consumption was based on interview ($n=7$) or an approximation approach that is used in epidemiological studies based on the presence of a diagnosis code for chronic obstructive pulmonary disease ($n=1$). Further details of the study characteristics are outlined in Table 1.

4 | RESULTS OF INDIVIDUAL STUDIES

Six studies investigated various risk factors for CSC and reported on tobacco consumption as a risk factor. Chatziralli et al. (2017) used a multivariable analysis approach in which tobacco smoking remained a statistically significant risk factor in the analyses together with male biological sex, high educational status, high income, obstructive sleep apnoea, H. pylori infection, type A personality/stress, steroid use, pregnancy, hyperopia and hyperopia (Chatziralli et al., 2017). Chen et al. (2019) used a nationwide diagnosis registry in Taiwan to follow patients with CSC and control individuals to evaluate if CSC was associated with a higher risk of development of depression. Tobacco consumption was approximated based on the presence of a diagnosis code for chronic obstructive pulmonary disease (Chen et al., 2019). Tobacco consumption was associated with presence of CSC as well as development of depression in patients with CSC (Chen et al., 2019). Ersoz et al. (2019) used a multivariate regression analysis and found that tobacco smoking remained a statistically significant risk factor in their analyses together with pregnancy, steroid use, antidepressant-anxiolytic drug use and hyperopia (Ersoz et al., 2019). Gundlach and Tsui (2021) studied CSC among veterans to understand risk factors. In a multivariable analysis, tobacco smoking was a significant risk factor, together with post-traumatic stress disorder, heart disease, sleep apnoea and steroid use (Gundlach & Tsui, 2021). Haimovici et al. (2024) studied risk factors for CSC using a multicentre clinic-based population sample. Tobacco use, although significant in univariable analyses, lost statistical significance in the multivariate analyses (Haimovici et al., 2024). Multivariable analyses found that diabetes and previous eye surgery were protective factors against CSC; and that allergic respiratory disease, systemic steroid use, antibiotic use and alcohol use were significant risk factors for CSC (Haimovici et al., 2024). Karimi et al. (2023) reported risk factors for CSC in univariate analyses. Here, tobacco smoking was a significant risk factor, as well as alcohol consumption, corticosteroid use and psychological stress (Karimi et al., 2023).

Five studies reported tobacco consumption history as part of their study of systemic biomarkers. Kunikata et al. (2020) studied systemic oxidative stress levels in patients with CSC. More individuals in the CSC group than the control group had a history of tobacco smoking (Kunikata et al., 2020). Latalska et al. (2020) studied nailfold videocapillaroscopy in patients with CSC and reported prevalence of tobacco smokers. The CSC group and the control group had similar rates of tobacco smokers (Latalska et al., 2020). Sakai and Tsuneoka (2017) reported blood serotonin levels in CSC. The prevalence of tobacco smokers was similar between those with CSC and the healthy controls (Sakai & Tsuneoka, 2017). Tahara et al. (2023) reported alpha-klotho as a potential biomarker for CSC. The authors reported that history of tobacco smoking was significantly more prevalent in patients with CSC (Tahara et al., 2023). van Dijk et al. (2017) investigated systemic complement activation in CSC. Any history of tobacco smoking was more prevalent in patients with CSC and compared to the healthy controls (van Dijk et al., 2017).

4.1 | Risk of bias within studies

Overall, the studies included in this review were transparent in reporting the data source and eligibility criteria. Kunikata et al. (2020) was a publication in a brief format (a letter to the editor) with limited information regarding data source and participant eligibility criteria. The time period of participant recruitment was disclosed in seven studies, and consecutive recruitment was present in four studies. No studies described any assessments undertaken for quality assurance of evaluation of smoking (which could have been validation of the employed questions/questionnaire or other methods to ensure that the data obtained was accurate). Our risk of bias evaluation of individual studies is presented in detail in Table 2.

4.2 | Meta-analysis on tobacco consumption as a risk factor for central serous Chorioretinopathy

All 11 studies of 27 595 patients with CSC and 105 354 control individuals were eligible for the meta-analysis. We calculated a summary estimate of tobacco consumption as a risk factor for CSC at an OR of 2.99 (95% CI: 1.82–4.93, $p=0.000017$) (Table 3). Heterogeneity statistics suggested considerable heterogeneity

TABLE 1 Study characteristics.

Reference	Country	Study design	Study population	Diagnosis of CSC	Tobacco consumption evaluation
Chatziralli et al. (2017)	Greece	Clinic-based, retrospective, case–control study	183 patients with acute CSC Age 48±4 years 72% males 183 control individuals Age 49±3.3 years 57% males	Acute CSC with a duration of <3 months defined as a localized neurosensory retinal detachment associated with focal leak(s) at the level of RPE based on FA.	At the time of ophthalmological examination/diagnosis, all patients and control individuals had recorded whether they were current smokers.
Chen et al. (2019)	Taiwan	Population-based, retrospective, cohort study	25939 patients with CSC Age 43±12 years 68% males 103756 control individuals Age 43±12 years 68% males	This nationwide registry study used ICD-9 diagnosis code to identify patients with CSC (362.42), and randomly selected demographically matched controls without the diagnosis of CSC at a ratio of 1:4.	The authors used the presence of chronic obstructive pulmonary disease as an approximation for previous tobacco consumption.
Ersoz et al. (2019)	Turkey	Clinic-based, retrospective, case–control study	811 patients with CSC Age 47±10 years 73% males 816 control individuals Age 46±12 years 73% males	Classic CSC was defined as the presence of serous detachment of the neurosensory retina associated with focal leak(s) at the level of RPE based on FA. Chronic CSC was based on the presence of widespread tracks of RPE atrophy on FAF and focal or diffuse RPE hyperfluorescence on FA with or without serous detachment of the neurosensory retina. OCT was used for evaluation of retinal anatomy. Cases with MNV were excluded.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco use.
Gundlach and Tsui (2021)	USA	Clinic-based, retrospective, case–control study	51 patients with CSC Age 63±13 years 100% males 51 control individuals Age matched, but details not specified 100% males	OCT based diagnosis of CSC by a retinal specialist. Further details were not specified.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco smoking.
Haimovici et al. (2024)	USA	Clinic-based, retrospective, case–control study	312 patients with CSC Age 45±12 years 74% males 312 control individuals Age 45±13 years 74% males	Classic CSC was defined as the presence of a localized neurosensory retinal detachment associated with focal leak(s) at the level of RPE based on FA. Chronic CSC was defined as a sensory retinal detachment associated with more widespread areas of RPE atrophy and pigmentary mottling associated with either focal or diffuse RPE hyperfluorescence by FA.	Not specified.
Karimi et al. (2023)	Iran	Clinic-based, retrospective, case–control study	39 patients with CSC Age 41±8 years 36% males 80 control individuals Age 41±10 years 55% males	CSC was defined as a localized neurosensory retinal detachment associated with a focal leak at the RPE level, and the diagnosis was based on fundus examination, OCT, and FA.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco smoking.

TABLE 1 (Continued)

Reference	Country	Study design	Study population	Diagnosis of CSC	Tobacco consumption evaluation
Kunikata et al. (2020)	Japan	Clinic-based, retrospective, case–control study	20 patients with CSC Age 40 ± 6 years 90% males 16 control individuals Age 41 ± 5 years 69% males	Not specified.	Not specified.
Latalska et al. (2020)	Poland	Clinic-based, prospective, case–control study	59 patients with CSC Age 47 ± 9 years 76% males 53 control individuals Age 46 ± 12 years 75% males	CSC was diagnosed based on clinical examination and OCT by confirming the presence of a serous detachment of the neuroretina. OCT-A was performed to exclude any cases with MNV.	Not specified.
Sakai and Tsuneoka (2017)	Japan	Clinic-based, retrospective, case–control study	49 patients with CSC Age 48 ± 9 years 96% males 31 control individuals Age 50 ± 10 years 87% males	CSC was defined as the presence of serous retinal detachment on OCT. Both cases of acute CSC and chronic CSC were included. Cases with MNV were excluded.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco smoking including both past and current use.
Tahara et al. (2023)	Japan	Clinic-based, retrospective, case–control study	56 patients with CSC Age 52 ± 11 years 82% males 27 control individuals Age 50 ± 10 years 70% males	CSC was diagnosed based on serous retinal detachment and thickening of the choroid on OCT imaging, and idiopathic leaks at the level of the RPE on FA. ICGA was performed to confirm choroidal vascular hyperpermeability. Both acute and chronic CSC were included. OCT-A was performed to exclude any cases with MNV.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco smoking.
van Dijk et al. (2017)	Netherlands	Clinic-based, prospective, case–control study	76 patients with CSC Age 49 ± 11 years 92% males 29 control individuals Age 43 ± 11 years 90% males	All cases were of chronic CSC. Chronic CSC was diagnosed on the basis of fundoscopy, fundus photography, FAF, OCT, FA, and ICGA. For the diagnosis of chronic CSC, all of the following had to be present: serous subretinal fluid on OCT, ≥1 area(s) of multifocal diffuse leakage or irregular RPE window defects on FA, and corresponding hypercyanescence on ICGA. Cases with acute CSC or cases with MNV were excluded.	At the time of ophthalmological examination/diagnosis, patients and control individuals were asked about any tobacco smoking.

Abbreviations: CSC, central serous chorioretinopathy; FA, fluorescein angiography; FAF, fundus autofluorescence; ICD-9, International Classification of Diseases version 9; ICGA, indocyanine green angiography; MNV, macular neovascularization; OCT, optical coherence tomography; OCT-A, optical coherence tomography angiography; RPE, retinal pigment epithelium.

TABLE 2 Risk of bias within individual studies.

Reference	Defines source	Eligibility criteria	Time period	Consecutive recruitment	Quality assurance
Chatziralli et al. (2017)	Yes	Yes	Yes	Yes	No
Chen et al. (2019)	Yes	Yes	Yes	Yes	No
Ersoz et al. (2019)	Yes	Yes	Yes	Unclear	No
Gundlach and Tsui (2021)	Yes	Yes	Yes	Yes	No
Haimovici et al. (2024)	Yes	Yes	Unclear	No	No
Karimi et al. (2023)	Yes	Yes	Yes	Yes	No
Kunikata et al. (2020)	No	No	No	No	No
Latalska et al. (2020)	Yes	Yes	Yes	No	No
Sakai and Tsuneoka (2017)	Yes	Yes	No	No	No
Tahara et al. (2023)	Yes	Yes	Yes	No	No
van Dijk et al. (2017)	Yes	Yes	No	No	No

Note: Studies are assessed on relevant items from the Agency for Healthcare Research and Quality checklist: Defines source: Defines the source of information. Eligibility criteria: Lists inclusion and exclusion criteria or refers to previous publications. Time period: Indicates time period used for identifying participants. Consecutive recruitment: Indicates whether or not subjects were consecutively recruited for the study. Quality assurance: Describes any assessments undertaken for quality assurance purposes.

TABLE 3 Meta-analysis on tobacco consumption as a risk factor for central serous chorioretinopathy.

Reference	OR	95% CI	Study weight
Chatziralli et al. (2017)	1.68	1.07–2.51	11.5%
Chen et al. (2019)	5.22	4.99–5.45	12.6%
Ersoz et al. (2019)	1.72	1.30–2.27	12.1%
Gundlach and Tsui (2021)	5.52	1.81–16.81	7.7%
Haimovici et al. (2024)	1.90	1.20–2.80	11.5%
Karimi et al. (2023)	4.00	1.47–10.85	8.4%
Kunikata et al. (2020)	17.00	3.20–90.26	5.2%
Latalska et al. (2020)	1.01	0.36–2.85	8.2%
Sakai and Tsuneoka (2017)	1.39	0.37–5.27	6.7%
Tahara et al. (2023)	10.35	3.14–34.17	7.3%
van Dijk et al. (2017)	3.08	1.21–7.80	8.8%
Summary estimate	***2.99***	***1.82–4.93***	***100.0%***

Abbreviations: CI, confidence interval; OR, odds ratio; *N*, number.

(Cochran's $Q = 122.49$; $I^2 = 92\%$). The Funnel plot showed more spread than expected with skewness towards not finding a significant difference (File S2). Sensitivity analysis showed that omitting studies in turn would only lead to minor changes in the summary estimate (OR range: 2.50–3.29) without loss of statistical significance and thus indicated robustness of the results (File S3).

5 | DISCUSSION

In this systematic review and meta-analysis, we summarize evidence from 11 studies and 132 949 individuals and report that tobacco consumption is a statistically significant risk factor for CSC at an OR of 2.99 (95% CI: 1.82–4.93, $p = 0.000017$). For comparison, male biological sex is a risk factor at reported with an OR of 1.9–2.2 (Chatziralli et al., 2017; Karimi et al., 2023), post-traumatic stress disease is a risk factor with an OR of 9.4 (Gundlach & Tsui, 2021), self-evaluated presence of psychological stress is a risk factor with an OR of 2.7–13.3 (Chatziralli et al., 2017; Karimi et al., 2023), and corticosteroid use is a risk factor with an OR of 2.2–7.0 (Chatziralli et al., 2017; Ersoz et al., 2019; Gundlach & Tsui, 2021; Karimi et al., 2023). Other known risk factors include OR of 4.8–9.3 for current pregnancy (Chatziralli et al., 2017; Ersoz et al., 2019; Haimovici et al., 2024) and 5.0–5.8 obstructive sleep apnoea (Chatziralli et al., 2017; Gundlach & Tsui, 2021). Thus, tobacco consumption seems to be a risk factor of a lower magnitude compared to other well-described risk factors of CSC, although the risk size is particularly difficult in the case of smoking as we do not have sufficient data to evaluate a dose–response relationship and discuss a potentially higher risk among heavy smokers. However, tobacco consumption is a modifiable risk factor in which patients themselves can play a large role.

The exact mechanism by which tobacco consumption may promote the pathophysiology of CSC remains unclear. Wei et al. (2019) studied choroidal differences between active tobacco smokers and non-smokers among otherwise healthy volunteers using OCT and by calculating the choroidal vascularity index (CVI). The CVI is an image-based analysis of the central choroidal area using image-binarization to determine the luminal choroidal area which is then used to calculate the CVI defined as the ratio between the choroidal lumen and the total choroidal area (Agrawal et al., 2016). Wei et al. (2019) reported that tobacco consumption was associated with decreased CVI in a dose dependent manner (using pack years). Okawa et al. (2021) found that tobacco consumption was associated with a thicker choroid in patients with CSC in a dose dependent manner (using pack years). In regression model for the CVI, a history of tobacco smoking was associated with a lower CVI, although not in a dose dependent manner (Okawa

et al., 2021). Choroidal vascular hyperpermeability on indocyanine green angiography was more prevalent in tobacco smokers, although this difference did not reach statistical significance (Okawa et al., 2021). Taken together, these studies indicate that tobacco consumption impacts the choroid and in the case of CSC, we interpret these findings to represent an increased venous congestion in the choroid attributable to tobacco consumption. Although the exact mechanism remains unclear, a number of potential explanations have been proposed. Tobacco consumption has been linked to impaired cardiac structure and function in a dose dependent manner (using pack years) (Leigh et al., 2017) as well as peripheral vascular changes (Lu et al., 2014). Prevalent and regular coughing in tobacco smokers due to lung irritation may also potentially worsen a peripheral venous congestion phenomenon. Tobacco consumption is also extensively examined in immunological studies for its contribution to systemic immunity (Elisia et al., 2020; Strzelak et al., 2018). Tobacco smokers have higher systemic levels of pro-inflammatory cytokines and chemokines, and a disturbed lymphocyte balance towards more T-helper 2-cells (Elisia et al., 2020; Strzelak et al., 2018). Interestingly, pachychoroid neovasculopathy/polypoidal choroidal vasculopathy, i.e., other members of the pachychoroid disease spectrum, have been associated with a pro-inflammatory systemic blood profile and a T-helper 2-cell like disturbed lymphocyte balance (Borgersen et al., 2021; Jain et al., 2022; Subhi et al., 2019). Moreover, an imbalance in the hypothalamic–pituitary–adrenal (HPA) axis is one of the metabolic factors suspected in the pathophysiology of CSC. Hyperactivity of the HPA axis, reflected by higher 24 h urinary free cortisol, and accompanying higher waist circumference and diastolic blood pressure was previously reported in chronic CSC (van Haalen et al., 2018). Schellevis et al. (2019) showed elevated levels of androsterone, estrone, etiocholanolone, and androstenedione indicating that the balance in the steroid hormone system is altered in chronic CSC cases (Schellevis et al., 2019). Other studies also involve different aspects of the HPA pathway but suggest HPA involvement in CSC (Agarwal et al., 2016; Ciloglu et al., 2018). Nicotine, one of the most key constituents of tobacco products, is reported to be strong activator of the HPA axis (Rohleder & Kirschbaum, 2006). Therefore, one explanation may be that the risk from tobacco consumption is a question of exaggeration of ongoing pathophysiological processes in CSC. Further studies are warranted to understand the detailed pathophysiological mechanism through which tobacco consumption increases the risk of CSC.

Limitations of this study should be acknowledged when interpreting its results. First, some studies adjusted for other potential risk factors in multivariable analyses whereas others simply presented estimates from univariable analyses. It can be reasonably assumed that individuals who consume tobacco may differ from those who do not in terms of demographics, co-morbidities, stress/anxiety parameters, and other lifestyle factors (Kondo et al., 2019). Although we extracted results from the multivariable analyses where possible, some studies in this review did not adjust for these factors, which introduces a bias to our summary estimates. Second, the description of the diagnosis of CSC varied slightly across the studies, and some studies did not specify the diagnosis in detail. The diagnosis of CSC can be challenging as the SRF can be a clinical feature of many diseases that can mimic CSC (van Dijk & Boon, 2021). Cases with a misdiagnosis of CSC are likely to influence the accuracy of the estimates. Third, the evaluation of tobacco consumption differed across studies. When putting all who consume tobacco into one single category regardless of their total exposure, or even those who were previous smokers, an accurate estimation of the risk contribution becomes difficult. One study used the presence of chronic obstructive pulmonary disease (COPD) as an approximation for tobacco consumption (Chen et al., 2019), but the average age of the study population was 43 ± 12 years which is a relatively young population in terms of COPD and the study may therefore underestimate the number of smokers especially in the younger age group. Finally, for observational studies, cohort studies represent a higher level of evidence, whereas cross-sectional and case–control studies are more prone to a variety of biases (Burns et al., 2011). In this review, apart from Chen et al. (2019) which was a registry-based cohort study of an entire population, all studies were clinic-based case–control studies. However, it should also be emphasized that when considering risk factors based on observational studies, it remains unclear to which extent modifying that particular risk factor can influence the outcome of interest. In other words, without well-designed randomized controlled trials studying the effect of smoking cessation on the onset and prognosis of CSC, the effect of suggesting reduced tobacco consumption to reduce the risk of CSC remains unclear. However, smoking cessation should still be recommended for its other health benefits (Critchley & Capewell, 2003; Taylor et al., 2014).

In conclusion, we find that tobacco consumption is a statistically significant risk factor for CSC. Tobacco consumption is a modifiable behaviour and tobacco cessation is an actionable advice with which the patients themselves can play a large role in their disease management. Further studies are warranted to understand the impact of tobacco cessation for risk modification and for the prognosis of patients with CSC.

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ORCID

Lorenzo Ferro Desideri https://orcid.org/0000-0003-0715-6369
Jakob Grauslund https://orcid.org/0000-0001-5019-0736
Özge Yanik https://orcid.org/0000-0002-1822-8703
Yousif Subhi https://orcid.org/0000-0001-6620-5365

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SUPPORTING INFORMATION

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