Nonocular Influencing Factors for Primary Glaucoma: An Umbrella Review of Meta-Analysis

Wenman Li^a Jiaxing Pan^a Maoling Wei^b Zhiqing Lv^a Sijie Chen^a Yang Qin^a
Ni Li^a

^aDepartment of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China; ^bThe Center for Evidence-Based Medicine and Clinical Epidemiology, West China Hospital, Sichuan University, Chengdu, China

Keywords

Glaucoma · Risk factors · Environment · Umbrella review

Abstract

Introduction: Glaucoma is the main cause of irreversible blindness worldwide. Still, little is known about nonocular risk factors. We use an umbrella review to examine the meta-analytic evidence of the correlation between nonocular factors and glaucoma. **Method:** We searched PubMed and Embase databases up to July 24, 2020. Eligible meta-analyses (MAs) included cohort, case-control, and randomized controlled study designs. Two authors independently extracted the data and evaluated the methodological quality of the MAs. AMSTAR 2 was used to assess the methodological quality of each included MA. **Results:** This umbrella review contains 22 MAs with 22 unique nonocular factors in total. We identified 11 factors that increase the risk of glaucoma: hyperlipidemia, nocturnal dip in blood pressure, infection with *Helicobacter pylori*, myopia, obstructive sleep apnea syndrome, corneal properties, diabetes, hypertension, hypothyroidism, migraine, and plasma homocysteine. We identified 3 factors that reduce the risk of glaucoma: dietary intake of vitamin A, dietary intake of vitamin C, and short-term statin use. We identified 8 factors that had no association with

glaucoma: dietary intake of vitamin B, dietary intake of vitamin E, cigarette smoking, Alzheimer's disease, serum folic acid, serum vitamin B6, serum vitamin B12, and serum vitamin D. **Conclusions:** In this umbrella review of MAs, evidence was found for associations of various nonocular factors with glaucoma to different degrees. However, risk factors were only mildly associated, suggesting low impact of systemic risk factors. Additional higher quality studies are needed to provide robust evidence.

© 2021 The Author(s)

Published by S. Karger AG, Basel

Introduction

Glaucoma is one of the major causes of blindness worldwide. It is characterized by neurodegenerative optic neuropathy, leading to irreversible visual field defects. It is estimated that by 2020, globally, 65.5 million people will be affected by primary open-angle glaucoma (POAG) [1]. It is estimated that the number of glaucoma patients will augment to 111.8 million by 2040 all over the world, affecting Asia and Africa disproportionately [2, 3].

Evidence has suggested that POAG is associated with genetic risk factors [4]. Studies have proven that a family history of glaucoma is strongly associated with the onset

of POAG [5, 6]. The pathogenesis of glaucoma is intricate and has yet to be fully elucidated. The most prevalent doctrine is intraocular pressure (IOP), and an abnormal pressure gradient across the lamina causes mechanical stress, and tension acting on the posterior structures of the eye leads to mechanical axonal damage and axon transport disruption [7, 8]. However, patients diagnosed with normal-tension glaucoma still develop progressive vision field loss even with a normal IOP. Other factors influence pathogenesis, such as impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress [9–13]. In the clinic, IOP is the solo modifiable risk factor in anti-glaucoma treatment, and all present treatment strategies aim to reduce IOP [14]. It is known that older age, higher IOP, and family history contribute to increased glaucoma risk [15]. Furthermore, thinner central corneal thickness (CCT), lower systolic blood pressure, lower ocular perfusion pressures, male sex, longer axial length, and low body mass index are also risk factors [15–17]. However, there are no overall recommendations to prevent and treat glaucoma.

To the best of our knowledge, no one has summarized the evidence from these meta-analyses (MAs) to date. Umbrella reviews make it possible to summarize the evidence from diverse MAs on the same topic [18]. Based on available systematic reviews and MAs of studies, we conducted the first umbrella review of the evidence to offer a summarization of the scope and effectiveness of the associations of multiple nonocular factors with glaucoma and assess the quality of these MAs. Finally, we graded this evidence by determining the association between glaucoma and multiple nonocular factors.

Methods

Search Strategy and Selection Criteria

We performed an umbrella review (a comprehensive assessment of diverse systematic reviews and MAs focused on a specific topic) [19] and searched PubMed and Embase databases from inception to July 2020 for systematic reviews with MAs of studies that surveyed an association between nonocular factors and primary glaucoma. This review was carried out according to the PRISMA guidelines (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000519247). The search strategy included the keywords “glaucoma” AND (“systematic review” OR “meta-analysis”). Two investigators examined the full text of potential eligible articles.

The inclusion criteria were as follows: (a) the study was an MA or a systematic review and MA; (b) the study assessed the relationship between any nonocular factors and human glaucoma; and (c) the summary risk ratio (RR), odds ratio (OR), and mean differences for MAs were reported. We excluded (a) systematic reviews

without MAs; (b) systematic reviews based on animals; (c) MAs that researched the association between genetic markers of glaucoma; and (d) studies in which the full text was not in English or Chinese. When genetic and nonocular factors existed simultaneously, we extracted results about nonocular factors only. When multiple MAs in the same research subject met the inclusion criteria, the MA containing the largest number of original studies was reserved for the assessment, and if no >3 original studies were enrolled repeatedly in 2 MAs, the 2 studies could be included. All disagreements were discussed by 2 researchers, and a third researcher was consulted for final decisions.

Data Extraction

Two authors extracted data independently, and when disagreements occurred, a third researcher was consulted for final decisions. In each eligible article, we extracted the following data: first author, year of publication, associated factors, number of studies, number of participants, metrics, reported effect sizes (ESs) (i.e., RR, OR, weighted mean differences [WMDs], and related 95% confidence intervals [CIs], *p* values), heterogeneity, and publication bias. When an MA researched >1 associated factor, we recorded each result separately.

Data Synthesis

We extracted only the ESs of the association factors reported in the MA instead of reanalyzing the aggregate estimates and 95% CIs, and we did not search for the original studies that were included in the MA. For each review, if the MA was implemented with both a random-effects model and a fixed-effects model, we preferentially chose the random-effects model as the final result.

Assessment of Methodological Quality and Quality of Evidence of the Included Meta-Analyses

The Multiple Systematic Reviews (AMSTAR) 2 tool was used to assess the methodological quality of each included MA, which is a measurement tool created to assess methodological quality [20]. The AMSTAR 2 also assesses the quality of studies included in the MA, rather than just the technical methodology assessment of the included MA [21].

Assessment of the Credibility of the Evidence

We evaluated the credibility of the evidential associations presented in MAs by referring to several criteria conforming to previously published umbrella reviews [22–24]. The criteria included the sample size, strength of the association, and assessment of the presence of biases. Associations that presented significant random-effects or fixed-effects summary ESs were ranked as convincing, highly relevant, moderately relevant, weakly relevant, or no relevant evidence.

Results

In total, 22 MAs assessed the full-text review stage. We identified 558 articles from PubMed and 630 articles from Embase. A total of 843 articles remained after deleting duplicates, and 797 articles were excluded after reviewing titles and abstracts, which process is shown in Figure 1.

Fig. 1. Flow chart outlining the literature search and evaluation process of published meta-analyses and systematic reviews. MA, meta-analysis.

Finally, 44 full-text articles were reviewed for further assessment. Seventeen articles were excluded for various reasons, including not being the largest MA investigating a risk factor ($n = 10$) [25–34], full text could not be retrieved ($n = 2$) [35, 36], full text was not in English ($n = 1$) [37], full text was about IOP not glaucoma ($n = 5$) [38–

42], and not being an MA ($n = 4$) [43–46]. Finally, 22 full-text articles [40, 47–67] were reviewed for further assessment summarized in Table 1. As shown in Table 1, we divided the nonocular factors into 5 categories: dietary intake, exposure to toxic environmental factors and drugs, disease, biomarkers, and others.

Table 1. Associations between nonocular factors and glaucoma

Risk factor	Author	Subgroup	Type of studies in MA	Studies in MA, n	Case/control, N	Metric of MA	Effects model	ES (95% CI)	Effect p value	I ² %	Publication bias
Dietary intake											
Vitamin A	Ramdas et al. [65]		Cross-sectional case-control, prospective cohort	5	940/123,697	Pooled OR	REM	0.45 (0.30–0.68)	0.02	0	NR
Vitamin B1	Ramdas et al. [65]		Cross-sectional case-control, prospective cohort	3	263/5,241	OR	REM	0.84 (0.47–1.51)	0.56	55	NR
Vitamin C	Ramdas et al. [65]		Cross-sectional case-control, prospective cohort	4	849/121,135	Pooled OR	REM	0.39 (0.23–0.67)	0.2	0	NR
Vitamin E	Ramdas et al. [65]		Cross-sectional case-control, prospective cohort	5	940/123,697	OR	FEM	0.95 (0.75–1.19)	0.66	39	NR
Exposure to toxic environmental and drugs											
Cigarette smoking	Bonovas et al. [47]	Current smoking	Cross-sectional, case-control	4	519/10,255	Pooled OR	FEM	1.37 (1.00–1.87)	0.05	NA	Begg and Mazumdar's test ($p = 0.76$)
		Past smoking		7				1.03 (0.77–1.38)	0.85	NA	Begg and Mazumdar's test ($p = 0.99$)
Diseases											
Statin	McCann et al. [58]	Current smoking	Cohort, case-control	6	NR	Pooled RR	FEM	0.97 (0.81–1.16)	0.74	38	Funnel plot symmetry
		Past smoking		6				0.97 (0.83–1.13)	0.66	46	
		<2 years	Cross-sectional, case-control, cohort	4	583,615	Pooled OR	REM	0.96 (0.94–0.99)	0.005	0	Funnel plots symmetry
		>2 years		3				0.70 (0.46–1.06)	0.09	73	
Diabetes	Zhao et al. [55]		Cross-sectional, case-control, longitudinal cohort	47	2,981,342	Pooled RR	REM	1.48 (1.29–1.71)	NR	82.30	Egger test ($p < 0.001$)
Hyperlipidemia	Pertl et al. [62]		Prospective cohort	7	2,445,203	Pooled RR	FEM	1.36 (1.24–1.50)	NR	0	Funnel plot symmetry
			Case-control	17	1,391/25,575	Pooled mean absolute difference	REM	14.2 (5.8, 22.5)	<0.0001	66.20	NR
Hypertension	Zhao et al. [52]		Cross-sectional, case-control, cohort	18	2,721,615	Pooled OR	REM	1.37 (1.16–1.61)	NR	97.00	Egger test ($p 0.751$)
			Cross-sectional, case-control, longitudinal cohort	27	2,333,996	Pooled RR	REM	1.16 (1.05–1.28)	NR	34.50	Funnel plots symmetry
Nocturnal dip in blood pressure	Bae et al. [49]		Cross-sectional, cohort	16	60,084	Pooled OR	REM	1.22 (1.08–1.37)	NR	7.50	Egger test ($p 0.90$)
		Systolic blood pressure	Retrospective cohort	4	259	OR	FEM	3.32 (1.84–6.00)	<0.0001	0	NR
Hypothyroidism	Wang et al. [63]	Diastolic blood pressure					FEM	2.09 (1.20–3.64)	0.009	0	NR
			Cross-sectional, case-control, cohort	11	381,695	Pooled OR	REM	1.64 (1.27–2.13)	NR	83.20	Egger test ($p 0.612$)
OSAS	Shi et al. [54]		Cross-sectional	9	161,738/2,101,939	Pooled OR	REM	1.41 (1.11–1.79)	0.006	73.00	NR
			Case-control	6	1,032/7,039	Pooled OR	FEM	1.96 (1.37–2.80)	0.0002	0.00	NR
	Liu et al. [57]		Case-control	3	711/6,709	OR	FEM	2.46 (1.32–4.59)	0.005	0.00	Begg's test $Pr > z = 0.348$
			Cohort	3	2,281,281		REM	1.43 (1.21–1.69)	0.000	85.50	

Table 1 (continued)

Risk factor	Author	Subgroup	Type of studies in MA	Studies in MA, <i>n</i>	Case/control, <i>N</i>	Metric of MA	Effects model	ES (95% CI)	Effect <i>p</i> value	<i>I</i> ² %	Publication bias
<i>H. pylori</i> infection	Doulberis et al. [82]		Case-control, cohort	15	872/1,792	OR	REM	2.08 (1.48–2.93)	<0.001	61.54	Egger test (<i>p</i> 0.347)
Myopia	Xiong et al. [51]	> –3.00D ≤ –3.00D	Cross-sectional	11	45,996	Pooled OR	FEM	1.52 (1.23–1.88)	NR	7.30	Egger test (<i>p</i> 0.74)
Migraine	Xu et al. [66]		Case-control, cohort	11	467,008	Pooled RR	REM	2.41 (1.91–3.03)	0		
Alzheimer's disease	Tsilis et al. [50]	Nondemented participants With dementia	Case-control, cohort record-linkage	8	161,978	RR	FEM	1.24 (1.12–1.37)	NR	41.70	Egger test (<i>p</i> 0.272)
								0.92 (0.89–0.94)	NR	89.00	Egger test (<i>p</i> 0.01)
				9	162,790			0.94 (0.92–0.96)		89.40	Egger test (<i>p</i> < 0.001)
Biomarkers											
Plasma tHcy	Li et al. [56]	NTG	Case-control	4	149/148	Pooled WMD	REM	1.16 (–0.13, 2.45)	0.08	72	NR
	Xu et al. [48]	POAG	Case-control	12	546/535	WMD	REM	2.05 (0.63–3.47)	0.005	94.40	NR
Serum folic acid	Li et al. [56]	NTG	Case-control	2	90/82	Pooled WMD	REM	–0.62 (–1.98, 0.74)	0.37	52	NR
	Xu et al. [48]	POAG	Case-control	6	222/252	WMD	FEM	0.34 (–0.37, 1.05)	0.344	0	NR
Serum vitamin B12	Li et al. [57]	POAG	Case-control	6	222/249	WMD	FEM	0.933 (–31.116, 29.249)	0.952	0	Funnel plots symmetry
		NTG	Case-control	4	123/176	WMD	FEM	6.652 (–35.473, 48.777)	0.757	0	
Serum vitamin B6	Li et al. [56]	NTG	Case-control	2	90/82	Pooled WMD	FEM	–16.79 (–86.09, 52.51)	0.63	0	NR
	Li et al. [57]	POAG	Case-control	3	109/115	WMD	REM	2.792 (–3.793, 9.377)	0.406	89.58	Funnel plots symmetry
Serum vitamin D	Li et al. [57]	POAG	Case-control	3	513/5,629	WMD	REM	2.488 (–5.120, 0.145)	0.064	87.23	Funnel plots symmetry
Others											
Corneal properties	Gaspar et al. [60]	CH	NR	19	1,213/1,055	MD	NR	–1.54 (–1.58, –1.41)	<0.00001	78	NR
		CCT						–8.49 (–11.36, –5.62)	<i>P</i>	60	
		Normally active group		7	124			–2.340 (–3.305, –1.375)	<0.00001	91.80	

MA, meta-analysis; OR, odds ratio; RR, relative risk; MD, mean difference; WMD, weighted mean difference; 95% CI, 95% confidence interval; FEM, fixed-effects model; REM, random-effects model; IOP, intraocular pressure; NR, not reported; ΔIOP, the difference between intraocular pressures; POAG, primary open-angle glaucoma; NTG, normal-tension glaucoma; CH, corneal hysteresis; CCT, central corneal thickness; ES, effect size; OSA, obstructive sleep apnea syndrome; *H. pylori*, *Helicobacter pylori*; tHcy, homocysteine.

Table 2. Methodological quality of the included systematic reviews based on AMSTAR 2 criteria and scores

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Total
Ramdas et al. [65]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y	Critically low
Bonovas et al. [47]	Y	N	Y	N	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	N	Critically low
Zhou et al. [59]	Y	PY	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Moderate
McCann et al. [58]	Y	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	N	Low
Zhao et al. [55]	Y	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Zhao and Chen [64]	Y	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Pertl et al. [62]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y	Critically low
Wang and Bao [67]	Y	N	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Zhao et al. [52]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Bowe et al. [53]	Y	N	N	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y	Critically low
Bae et al. [49]	Y	N	N	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Wang et al. [63]	Y	N	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Shi et al. [54]	Y	N	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Liu et al. [57]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Doulberis et al. [82]	Y	PY	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Xiong et al. [51]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	N	Critically low
Xu et al. [66]	Y	N	Y	PY	Y	Y	Y	PY	PY	N	Y	Y	Y	Y	Y	Y	Low
Tsilis, et al. [50]	Y	N	N	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Li et al. [56]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y	Critically low
Xu et al. [48]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	N	Y	Critically low
Li et al. [57]	Y	N	Y	PY	Y	Y	N	PY	PY	N	Y	Y	Y	Y	Y	Y	Critically low
Gaspar et al. [60]	Y	N	N	PY	N	N	N	N	N	N	Y	N	N	N	N	N	Critically low

Q1: Did research questions and inclusion criteria for the review include the components of PICO? Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review? and did the report justify any significant deviations from the protocol? Q3: Did the review authors explain their selection of study designs for inclusion in the review? Q4: Did the review authors use a comprehensive literature search strategy? Q5: Did the review authors perform study selection in duplicate? Q6: Did the review authors perform data extraction in duplicate? Q7: Did the review authors provide a list of excluded studies and justify the exclusions? Q8: Did the review authors describe the included studies in adequate detail? Q9: Did the review authors use a satisfactory technique for assessing the RoB in individual studies that were included in the review? Q10: Did the review authors report on the sources of funding for the studies included in the review? Q11: If MA was performed, did the review authors use appropriate methods for statistical combination of results? Q12: If MA was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the MA or other evidence synthesis? Q13: Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Q15: If they performed quantitative synthesis, did the review authors carryout an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the results of the review? Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review? Y, Yes; PY, Partly yes; N, No; RoB, risk of bias; MA, meta-analysis.

Quality Assessment of MAs

Table 2 summarizes the quality assessment of the included MAs. One MA (4.6%) had a moderate-quality level according to the AMSTAR 2 evaluation; 7 (31.8%) were of low quality, 14 (63.6%) were critically low quality, and no MAs were high quality. The most common crucial defects were lack of a registered protocol (17 MAs, 77.3%) and the absence of a list of excluded studies (16 MAs, 72.7%).

Dietary Intake

Vitamins

Vitamins are indispensable to the human body, even among patients with glaucoma. Dietary intake of vitamins A and C could lower the risk of OAG (the pooled OR was 0.45 [0.30–0.68] and 0.39 [0.23–0.67], respectively). However, for dietary intake of vitamin B1 and E, there was no significant association with OAG (OR [95% CI]: 0.84 [0.47–1.51]; 0.95 [0.75–1.19], respectively) [65]. The eyes and their adnexa are specifically sensitive to vitamin A deficiency and excess [68]. Dark-green leafy vegetables

are rich in vitamins A and C, which are probably beneficial to glaucoma. Therefore, a healthy diet is salutary for eyes.

Exposure to Toxic Environmental and Drugs

Cigarette Smoking

Smoking is a recognized risk factor for eye disorders [69, 70]. Two MAs examined the relation between smoking and glaucoma. However, their results were contradictory. Bonovas et al. [47] found that current smokers could greatly increase the risk of developing POAG (pooled OR [95% CI]: 1.37 [1.00–1.87]), and past smoking had no connection with POAG (pooled OR [95% CI]: 1.03 [0.77–1.38]). Four cross-sectional and 3 case-control studies published before December 2002 were included in the analysis. Zhou et al. [59] found that both current smokers (pooled RR [95% CI]: 0.97 [0.81–1.16]) and former smokers (pooled RR [95% CI]: 0.97 [0.83–1.13]) had no statistically significant association with POAG compared with never smokers. The analysis included 6 observational studies (3 cohort and 3 case-control studies) from 1 January 1966 to 1 December 2015. These contradictory results may be due to the different exclusion and inclusion criteria used for the analysis. The mechanisms by which smoking influences glaucoma can be complex. Smoking can contract episcleral veins [71], increase blood viscosity, and induce vasospasms [72]. Additionally, nicotine could increase cerebral blood flow in humans, potentially by increasing optic nerve oxygen consumption [73].

Statin

Short-term statin use (<2 years) was shown to have a statistically significant association with a reduced incidence of glaucoma (pooled OR [95% CI]: 0.96 [0.94–0.99]). However, long-term statin use (>2 years) did not provide evidence of a significant reduction in the incidence of glaucoma (pooled OR [95% CI]: 0.70 [0.46–1.06]) [58]. Statins may induce IOP reduction by increasing aqueous outflow [74]. However, the use of nonstatin cholesterol-lowering drugs and systemic β -blockers may be possible confounding factors [75, 76]. In addition, hyperlipidemia can increase the risk of OAG [67].

Disease

Diabetes

Two MAs examined the relationship between diabetes and glaucoma, and both reported that diabetes increased the risk of glaucoma. The first study [55] included 47 articles including 2,981,342 individuals, and the pooled relative risk for glaucoma comparing diabetes patients and nondia-

betic patients was 1.48 (95% [CI], 1.29–1.71). Another study [64] examined 7 articles including 2,445,203 individuals, and the pooled RR (95% CI) was 1.36 (1.24–1.50). A significantly increased risk of glaucoma is related to diabetes, diabetes duration, and fasting glucose levels [55].

Hyperlipidemia

Two MAs found that hyperlipidemia is a risk factor for glaucoma. Pertl et al. [62] summarized 17 case-control studies including 26,966 patients and found that glaucoma patients had higher mean triglyceride levels than patients without glaucoma (pooled mean absolute difference [95% CI]: 14.2 mg/dL [5.8–22.5]). Wang et al. [67] examined 18 studies including 2,721,615 patients and found a significant association between hyperlipidemia and glaucoma (OR [95% CI]: 1.37 [1.16–1.61]), which included cross-sectional, case-control, and cohort studies. A possible mechanistic explanation might be that hyperlipidemia increases the external episcleral venous pressure and blood viscosity, resulting in a lower outflow [67].

Hypertension

Hypertension increases IOP and likely work in the development of glaucoma. The pooled RR (95% CI) for POAG when comparing participants with hypertension and without hypertension was 1.16 (1.05–1.28) in one MA of 27 studies involving 2,333,996 individuals [52]. The pooled OR (95% CI) for OAG was 1.22 (1.08–1.37) in another MA of 16 studies involving 60,084 individuals [49]. Hypertension can increase the aqueous humor by elevated capillary pressure in the ciliary body [77] and reduce the drainage of aqueous humor outflow by elevated episcleral venous pressure [78].

Nocturnal Dip in Blood Pressure

Progressive visual field defect in glaucoma is related to a drop of >10% in nocturnal systolic or diastolic blood pressure (systolic blood pressure and diastolic blood pressure OR [95% CI]: 3.32 [1.84–6.00], 2.09 [1.20–3.64], respectively), but mean systolic or diastolic diurnal and nocturnal blood pressure was no different in patients with or without progressive visual field loss [53]. Blood pressure instability might be a result of blood vessel lesion, such as atherosclerosis, insufficient autoregulation, rigidity, and increased resistance, which disturb oxygen and nutrition supply.

Hypothyroidism

Hypothyroidism significantly increased the risk of POAG prevalence (pooled OR [95% CI]: 1.64 [1.27–

2.13)) [63]. Thvilum et al. [27] found an association between hypothyroidism and glaucoma, and the possible mechanisms are that increased deposition of mucopolysaccharides in trabecular structures causes decreased aqueous outflow [79] and autoimmune diseases have common pathogenic mechanisms [79].

Obstructive Sleep Apnea Syndrome

Shi et al. [54] reported 6 case-control studies (pooled OR [95% CI]: 1.96 [1.37–2.80]) and 9 cross-sectional studies (pooled OR [95% CI]: 1.41 [1.11–1.79]) that showed that obstructive sleep apnea syndrome (OSAS) was associated with glaucoma. Liu et al. [57] also reported a significant association between OSAS and glaucoma, including 3 case-control studies (OR [95% CI]: 2.46 [1.32–4.59]) and 3 cohort studies (OR [95% CI]: 1.43 [1.21–1.69]). This association can be explained by 2 major theories. One is that the collapse of the upper airway during sleep in OSAS patients would cause repeated or prolonged hypoxia attacks, thus reducing the supply of oxygen to the optic nerve [80]. Another is that the sympathetic tone occurring in OSAS patients during sleep would increase ocular pressure [81].

Infection with *Helicobacter pylori*

H. pylori infection had a significant association with glaucoma (OR [95% CI]: 2.08 [1.48–2.93]) [82]. *H. pylori* infection and the gastrointestinal microbiota dysbiosis could release inflammatory cytokines, resulting in inducible release of nitric oxide (NO) synthase and NO production and formation of reactive nitrogen species, such as peroxynitrite [83]. These molecules could promote nitrosative stress, mitochondrial injury, neurotoxicity, optic nerve degeneration, and retinal ganglionic cell apoptosis in the eye. NO could also modify vasoactive activity and contribute to unstable intraocular arterial perfusion pressure and transient ischemia-reperfusion injury, resulting in elevated IOP [83].

Myopia

Myopia increased the risk of OAG (pooled OR [95% CI]: 1.52 [1.23–1.88] in low-degree myopia and pooled OR [95% CI]: 2.41 [1.91–3.03] in middle-/high-degree myopia) [51]. The MA of 11 cross-sectional studies included 45,996 participants. High myopia is related to a decreased scleral collagen accumulation, scleral thinning, and reduced scleral tissue [84], which is similar to glaucoma optic nerve-fiber layer damage [7]. Furthermore, scleral remodeling is associated with matrix metalloproteinases that could regulate extracellular matrix metabolism of the trabecular meshwork and then affect IOP [85].

Migraine

Migraine increased the risk of POAG (pooled RR [95% CI]: 1.24 [1.12–1.37]) in 8 case-control studies but not in 3 cohort studies [66]. The analysis included 11 primary studies with 467,008 participants. One possible mechanism of this effect is vascular regulation, which exists in the pathogenesis of glaucoma and migraine [86, 87]. Flammer et al. [88] assumed that a common vasospastic mechanism may be the cause of the relationship between migraine and POAG.

Alzheimer's Disease

Alzheimer's disease did not increase the risk of glaucoma (nondementia participants RR [95% CI]: 0.92 [0.89–0.94], dementia participants RR [95% CI]: 0.94 [0.92–0.96]) [50]. However, the analysis was very heterogeneous (I^2 , 89%; $p_{\text{heterogeneity}} < 0.001$) and exhibited substantial publication bias (Egger's $p \leq 0.01$). Thus, the association between glaucoma and Alzheimer's disease is still not clear.

Biomarkers

Plasma Homocysteine

Elevated plasma homocysteine (tHcy) levels are associated with POAG (WMD [95% CI]: 2.05 [0.63–3.47]) [48] but are not associated with normal-tension glaucoma (NTG) (pooled WMD [95% CI]: 1.16 [–0.13, 2.45]) [56]. tHcy has been discovered as one of the possible risk factors for a multitude of ocular diseases [89]. Studies have shown that increased plasma tHcy levels may induce apoptosis of retinal ganglion cells [90] and cause vascular endothelial inflammation [91, 92]. For NTG, plasma tHcy may be different in ethnic populations [56], and the number of participants included was low.

Serum

Folic acid, serum vitamin B12, serum vitamin B6, serum vitamin D, serum folic acid, serum vitamin B12, serum vitamin B6, and serum vitamin D were not associated with POAG or NTG. The comprehensive results suggested that there was no difference in serum folic acid levels (WMD [95% CI]: 0.34 [–0.37, 1.05]) [48] or NTG (pooled WMD [95% CI]: –0.62 [–1.98, 0.74]) between POAG patients and controls [56]. Li et al. [61] found no differences in serum vitamin B12 levels between POAG patients and controls (WMD [95% CI]: 0.933 [–31.116, 29.249]) and NTG (WMD [95% CI]: 6.652 [–35.473, 48.777]). Serum vitamin B6 was not associated with POAG (WMD [95% CI]: 2.792 [–3.793, 9.377]) [61] or NTG (pooled WMD [95% CI]: –16.79 [–86.09, 52.51])

Table 3. Strength of epidemiological evidence for risk and protective environmental factors for glaucoma

Evidence	Criteria used	Decreased risk	Increased risk
Moderate	>1,000 cases Significant summary associations ($p < 1 \times 10^{-3}$) per random-effects calculations	NA	Hyperlipidemia, nocturnal dip in blood pressure, infection with <i>H. pylori</i> , OSAS, and corneal properties
Weak	All other associations with $p \leq 0.05$	Dietary intake of vitamin A and C and short-term statin use	Hypertension, hypothyroidism, migraine, plasma tHcy, diabetes, and myopia
No	All associations with $p > 0.05$	Dietary intake of vitamin B and E and cigarette smoking Alzheimer's disease, serum folic acid, serum vitamin B12, serum vitamin B6, and serum vitamin D	

OSAS, obstructive sleep apnea syndrome; tHcy, homocysteine.

[56]. There was also no significant difference in the levels of serum vitamin D between POAG patients and controls (WMD [95% CI]: 2.488 [−5.120, 0.145]) [61].

Others

Corneal Properties

CCT and corneal hysteresis (CH) are associated with glaucoma. The analysis suggests that CH was significantly lower in glaucoma patients than in controls (MD [95% CI]: −1.54 mm Hg [−1.68, −1.41]), and CCT was also lower in glaucoma patients than in controls (MD [95% CI]: −8.49 μ m [−11.36, −5.62]) [60]. Lower CH values are related to the thinner retinal nerve-fiber layer, the larger linear cup/disk ratio, the higher optic-disc defects degree, and the lower visual field index [93]. CCT was an effective predictor for the development of POAG [94] because it is related to a thin lamina, which may be less rigid than a thicker lamina and could be more susceptible to IOP fluctuations [95].

Grading of the Level of Evidence of Associations

Table 3 summarizes the grading of the level of evidence of associations. Five factors (hyperlipidemia, nocturnal dip in blood pressure, infection with *H. pylori*, obstructive sleep apnea syndrome, and corneal properties) showed a moderate increase in the risk of epidemiological evidence. No factor showed a moderate protective effect. Six risk factors (hypertension, hypothyroidism, migraine, plasma tHcy, diabetes, and myopia) and 3 protective factors (dietary intake of vitamin A, dietary intake of vitamin C, and short-term statin use) showed weak epidemiological evidence. Nine factors (dietary intake of vitamin B, dietary intake of vitamin D, dietary intake of vitamin E, cigarette smoking, Alzheimer's disease, serum folic acid, serum vitamin B12, serum vitamin B6, and serum vitamin D) showed no significant risk or protective estimates.

Discussion

In this umbrella review of MAs, we provide a comprehensive review and critical assessment of environmental factors associated with glaucoma. A total of 22 factors, including dietary intake, exposure to toxic environmental factors and drugs, diseases, biomarkers, and others, were examined. Among these, the epidemiological evidence of 5 risk factors was moderate, and the epidemiological evidence of 6 risk factors and 3 protective factors was weak. Five factors (hyperlipidemia, nocturnal dip in blood pressure, infection with *H. pylori*, obstructive sleep apnea syndrome, and corneal properties) were supported by evidence with moderate strength epidemiological credibility, as expressed by >1,000 cases and significant summary associations ($p < 1 \times 10^{-3}$) per random-effects calculations. In these studies, the summary ESs were relatively large for nocturnal dip in blood pressure, infection with *H. pylori*, and obstructive sleep apnea syndrome (OR >2).

To the best of our knowledge, our umbrella review provides the first systematic and comprehensive evaluation of the evidence for environmental factors affecting glaucoma. The quality of MA methods varies widely. We used the AMSTAR 2 to assess the methodological quality of the included MAs. The most common cause of quality deterioration was the lack of protocol and absence of a list of excluded studies. Until recently, registering the protocol was a rare occurrence. We ranked the epidemiological evidence according to prespecified criteria; however, evidence of a correlation does not equate to causation because the studies are principally observational studies.

Most of the MAs examined had significant heterogeneity, and some had small-study effects. Heterogeneity might be caused by a range of confounders, such as different races, different qualities of the included studies, different criteria used to ascertain outcomes and expo-

sure, different sample sizes, different methods of data collection, and other unknown factors. The reported associations with glaucoma need to be prudently interpreted, especially for MAs that have large heterogeneity and obvious small-study effects, and the largest study is more conservative than the summary effect.

Although this umbrella review contained multiple nonocular factors, there were also some other factors reported in individual studies not in MAs. Glaucoma risk increases with age [96]. Males are more likely to develop POAG [94]. African Americans have a higher prevalence of POAG than Whites [97], and Asian populations have a higher prevalence of primary angle-closure glaucoma than Whites [98]. Moreover, nicotinamide supplementation can improve inner retinal function in glaucoma patients [99]. About the influencing factors of the ocular, a study shows that low ocular perfusion pressure increases the risk of glaucoma [42].

This umbrella review has some limitations. First, we did not reanalyze the summary estimates and 95% CIs, nor did we search for the primary studies included in the MA. Thus, some research data are missing. Second, some reports of evidence for an association do not equate to causation, such as corneal properties. However, it can be a good predictor of glaucoma. In addition, short-term statin use could decrease the risk of glaucoma, but long-term statin use did not provide any benefit for glaucoma. Fourth, some mechanisms are not clear, such as, it is not clear whether treatment for hyperlipidemia reduces the risk of glaucoma or statin itself, and the underlying mechanism of the relationship between diabetes and POAG was not clear. Hyperglycemia causes impairment of microcirculation and vascular autoregulation, which results in reduced nutrient and oxygen supply to RGC axons [100]. Additionally, hyperglycemia of the aqueous humor can impair the outflow system of the aqueous humor and finally result in POAG [101]. Fifth, although we found that vitamin A and vitamin C intake might be associated with a lower risk of glaucoma, it remains unclear how long the most appropriate duration of vitamin A and vitamin C consumption is. Additional well-designed interventional and cohort studies are needed to address these limitations in the future.

Conclusions

This umbrella review provides evidence that dietary intake, exposure to toxic environmental factors and drugs, diseases, and biomarkers influence the develop-

ment of primary glaucoma. These results contribute to our understanding of the potential induction and potential safeguarding of glaucoma, providing valuable information for developing new prevention strategies and understanding the pathogenesis of this intractable disease.

Statement of Ethics

All analyses were based on previous published studies, and thus, no ethical approval and patient consent are required.

Conflict of Interest Statement

No conflicting relationship exists for any author.

Funding Sources

This study was funded by the National Major Scientific Equipment program (Grant No. 2012YQ12008005). The sponsor or funding organization had no role in the design or conduct of this research.

Author Contributions

W.L. and N.L. designed the study; W.L. and J.P. searched the literature and extracted data; Z.L., S.C., and Y.Q. ran the analysis; N.L. and M.W. revised the essay. N.L. had primary responsibility for final content. All the authors critically reviewed the important intellectual content of the manuscript and passed the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

References

- 1 Kapetanakis VV, Chan MP, Foster PJ, Cook DG, Owen CG, Rudnicka AR. Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *Br J Ophthalmol*. 2016;100(1):86–93.
- 2 Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology*. 2014;121(11):2081–90.
- 3 Chan EW, Li X, Tham YC, Liao J, Wong TY, Aung T, et al. Glaucoma in Asia: regional prevalence variations and future projections. *Br J Ophthalmol*. 2016;100(1):78–85.

- 4 van Koolwijk LM, Bunce C, Viswanathan AC. Gene finding in primary open-angle glaucoma. *J Glaucoma*. 2013;22(6):473–86.
- 5 Asefa NG, Neustaeter A, Jansonius NM, Snieder H. Heritability of glaucoma and glaucoma-related endophenotypes: systematic review and meta-analysis protocol. *BMJ open*. 2018;8(2):e019049.
- 6 O'Brien JM, Salowe RJ, Fertig R, Salinas J, Pistilli M, Sankar PS, et al. Family history in the primary open-angle African American glaucoma genetics study cohort. *Am J Ophthalmol*. 2018;192:239–47.
- 7 Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *Jama*. 2014;311(18):1901–11.
- 8 Fechtner RD, Weinreb RN. Mechanisms of optic nerve damage in primary open angle glaucoma. *Surv Ophthalmol*. 1994;39(1):23–42.
- 9 Bell K, Funke S, Grus FH. [Autoimmunity and glaucoma]. *Ophthalmologie*. 2019;116(1):18–27.
- 10 Jiang S, Kametani M, Chen DF. Adaptive immunity: new aspects of pathogenesis underlying neurodegeneration in glaucoma and optic neuropathy. *Front Immunol*. 2020;11:65.
- 11 Xu H, Zhai R, Zong Y, Kong X, Jiang C, Sun X, et al. Comparison of retinal microvascular changes in eyes with high-tension glaucoma or normal-tension glaucoma: a quantitative optic coherence tomography angiographic study. *Graefes Arch Clin Exp Ophthalmol*. 2018;256(6):1179–86.
- 12 Casson RJ. Possible role of excitotoxicity in the pathogenesis of glaucoma. *Clin Exp Ophthalmol*. 2006;34(1):54–63.
- 13 Benoist d'Azy C, Pereira B, Chiambaretta F, Dutheil F. Oxidative and anti-oxidative stress markers in chronic glaucoma: a systematic review and meta-analysis. *PLoS One*. 2016;11(12):e0166915.
- 14 Ashwinbalaji S, Haribalanaganes R, Krishnasdas S, Muthukkaruppan V, Senthilkumari S. SB772077B (SB77) alleviated the aqueous outflow resistance mediated by cyclic mechanical stress in perfused human cadaveric eyes. *Sci Rep*. 2020;10(1):10202.
- 15 Leske MC, Wu SY, Hennis A, Honkanen R, Nemesure B. Risk factors for incident open-angle glaucoma: the Barbados eye studies. *Ophthalmology*. 2008;115(1):85–93.
- 16 Kyari F, Abdull MM, Wormald R, Evans JR, Nolan W, Murthy GV, et al. Risk factors for open-angle glaucoma in Nigeria: results from the Nigeria national blindness and visual impairment survey. *BMC Ophthalmol*. 2016;16:78.
- 17 Wurster P, Harris A, Gonzalez AC, Adjei S, Verticchio Vercellin A, Mathew S, et al. Risk factors for open-angle glaucoma in persons of Latin American descent. *J Glaucoma*. 2020;29(3):217–25.
- 18 Ioannidis J. Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews. *Br J Sports Med*. 2017;51(20):1456–8.
- 19 Ioannidis JP. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ*. 2009;181(8):488–93.
- 20 Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- 21 Solmi M, Correll CU, Carvalho AF, Ioannidis JPA. The role of meta-analyses and umbrella reviews in assessing the harms of psychotropic medications: beyond qualitative synthesis. *Epidemiol Psychiatr Sci*. 2018;27(6):537–42.
- 22 Dragioti E, Solmi M, Favaro A, Fusar-Poli P, Dazzan P, Thompson T, et al. Association of antidepressant use with adverse health outcomes: a systematic umbrella review. *JAMA Psychiatry*. 2019;76(12):1241–55.
- 23 Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. *Gastroenterology*. 2019;157(3):647–59. e4.
- 24 Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol*. 2015;14(3):263–73.
- 25 Zhou M, Wang W, Huang W, Zhang X. Diabetes mellitus as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *PLoS One*. 2014;9(8):e102972.
- 26 Barbosa-Breda J, Abegão-Pinto L, Van Keer K, Jesus DA, Lemmens S, Vandewalle E, et al. Heterogeneity in arterial hypertension and ocular perfusion pressure definitions: towards a consensus on blood pressure-related parameters for glaucoma studies. *Acta Ophthalmol*. 2019;97(4):e487–92.
- 27 Thvilum M, Brandt F, Brix TH, Hegedüs L. The interrelation between hypothyroidism and glaucoma: a critical review and meta-analyses. *Acta Ophthalmol*. 2017;95(8):759–67.
- 28 Huon LK, Liu SY, Camacho M, Guilleminault C. The association between ophthalmologic diseases and obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath*. 2016;20(4):1145–54.
- 29 Wu X, Liu H. Obstructive sleep apnea/hypopnea syndrome increases glaucoma risk: evidence from a meta-analysis. *Int J Clin Exp Med*. 2015;8(1):297–303.
- 30 Zhang Y, Wu Y. The association between obstructive sleep apnea/hypopnea syndrome and glaucoma: a meta analysis. *Zhonghua Shiyang Yanke Zazhi/Chin J Experiment Ophthalmol*. 2016;34(7):630–4.
- 31 Zeng J, Liu H, Liu X, Ding C. The relationship between *Helicobacter pylori* infection and open-angle glaucoma: a meta-analysis. *Invest Ophthalmol Vis Sci*. 2015;56(9):5238–45.
- 32 Wan H, Wang Q, Guo Y, Liu S. Association between *Helicobacter pylori* infection and primary open angle glaucoma: a meta analysis. *Zhonghua Shiyang Yanke Zazhi/Chin J Experiment Ophthalmol*. 2016;34(7):639–44.
- 33 Marcus MW, de Vries MM, Junoy Montolio FG, Jansonius NM. Myopia as a risk factor for open-angle glaucoma: a systematic review and meta-analysis. *Ophthalmology*. 2011;118(10):1989–94. e2.
- 34 Black RJ, Hill CL, Lester S, Dixon WG. The association between systemic glucocorticoid use and the risk of cataract and glaucoma in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLoS One*. 2016;11(11):e0166468.
- 35 Rong SS, Tsui LY, Ma L, Li J, Pang CPC, Chen LJ. Cigarette smoking increases intraocular pressure and risk of primary open-angle glaucoma: a systematic review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2016;57(12):2576.
- 36 Bae HW, Kang EM, Seong GJ, Kim CY. Association between open-angle glaucoma and hypothyroidism: a meta-analysis. *Invest Ophthalmol Vis Sci*. 2017;58(8):3714.
- 37 Ziemssen F, Lagrèze W, Voykov B. [Secondary diseases in high myopia]. *Ophthalmologie*. 2017;114(1):30–43.
- 38 Li M, Wang M, Guo W, Wang J, Sun X. The effect of caffeine on intraocular pressure: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(3):435–42.
- 39 Valenzuela CV, Liu JC, Vila PM, Simon L, Doering M, Lieu JEC. Intranasal corticosteroids do not lead to ocular changes: a systematic review and meta-analysis. *Laryngoscope*. 2019;129(1):6–12.
- 40 Wang HY, Tseng PT, Stubbs B, Carvalho AF, Li DJ, Chen TY, et al. The risk of glaucoma and serotonergic antidepressants: a systematic review and meta-analysis. *J Affect Disord*. 2018;241:63–70.
- 41 Roddy G, Curnier D, Ellemberg D. Reductions in intraocular pressure after acute aerobic exercise: a meta-analysis. *Clin J Sport Med*. 2014;24(5):364.
- 42 Kim KE, Oh S, Baek SU, Ahn SJ, Park KH, Jeoung JW. Ocular perfusion pressure and the risk of open-angle glaucoma: systematic review and meta-analysis. *Sci Rep*. 2020;10(1):10056.
- 43 Ramdas WD. The relation between dietary intake and glaucoma: a systematic review. *Acta Ophthalmol*. 2018;96(6):550–6.
- 44 Jain V, Jain M, Abdull MM, Bastawrous A. The association between cigarette smoking and primary open-angle glaucoma: a systematic review. *Int Ophthalmol*. 2017;37(1):291–301.
- 45 Edwards R, Thornton J, Ajit R, Harrison RA, Kelly SP. Cigarette smoking and primary open angle glaucoma: a systematic review. *J Glaucoma*. 2008;17(7):558–66.
- 46 Lois N, Abdelkader E, Reglitz K, Garden C, Ayres JG. Environmental tobacco smoke exposure and eye disease. *Br J Ophthalmol*. 2008;92(10):1304–10.

- 47 Bonovas S, Filioussi K, Tsantes A, Peponis V. Epidemiological association between cigarette smoking and primary open-angle glaucoma: a meta-analysis. *Public Health*. 2004; 118(4):256–61.
- 48 Xu F, Zhao X, Zeng SM, Li L, Zhong HB, Li M. Homocysteine, B vitamins, methylenetetrahydrofolate reductase gene, and risk of primary open-angle glaucoma: a meta-analysis. *Ophthalmology*. 2012;119(12):2493–9.
- 49 Bae HW, Lee N, Lee HS, Hong S, Seong GJ, Kim CY. Systemic hypertension as a risk factor for open-angle glaucoma: a meta-analysis of population-based studies. *PLoS One*. 2014; 9(9):e108226.
- 50 Tsilis AG, Tsilidis KK, Pelidou SH, Kitsos G. Systematic review of the association between Alzheimer's disease and chronic glaucoma. *Clin Ophthalmol*. 2014;8:2095–104.
- 51 Xiong Q, Zeng XT, Cai XJ, Li ZL, Li ZH, Li S. Association between myopia and open-angle glaucoma: a meta-analysis. *Chin J Evid-Based Med*. 2014;14(5):618–24.
- 52 Zhao D, Cho J, Kim MH, Guallar E. The association of blood pressure and primary open-angle glaucoma: a meta-analysis. *Am J Ophthalmol*. 2014;158(3):615–e9.
- 53 Bowe A, Grünig M, Schubert J, Demir M, Hoffmann V, Kütting F, et al. Circadian variation in arterial blood pressure and glaucomatous optic neuropathy: a systematic review and meta-analysis. *Am J Hypertens*. 2015; 28(9):1077–82.
- 54 Shi Y, Liu P, Guan J, Lu Y, Su K. Association between glaucoma and obstructive sleep apnea syndrome: a meta-analysis and systematic review. *PLoS One*. 2015;10(2):e0115625.
- 55 Zhao D, Cho J, Kim MH, Friedman DS, Guallar E. Diabetes, fasting glucose, and the risk of glaucoma: a meta-analysis. *Ophthalmology*. 2015;122(1):72–8.
- 56 Li J, Xu F, Zeng R, Gong H, Lan Y. Plasma homocysteine, serum folic acid, serum vitamin B12, serum vitamin B6, MTHFR, and risk of normal-tension glaucoma. *J Glaucoma*. 2016;25(2):e94–8.
- 57 Liu S, Lin Y, Liu X. Meta-analysis of association of obstructive sleep apnea with glaucoma. *J Glaucoma*. 2016;25(1):1–7.
- 58 McCann P, Hogg RE, Fallis R, Azuara-Blanco A. The effect of statins on intraocular pressure and on the incidence and progression of glaucoma: a systematic review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2016;57(6):2729.
- 59 Zhou Y, Zhu W, Wang C. The effect of smoking on the risk of primary open-angle glaucoma: an updated meta-analysis of six observational studies. *Public Health*. 2016;140:84–90.
- 60 Gaspar R, Pinto LA, Sousa DC. Corneal properties and glaucoma: a review of the literature and meta-analysis. *Arq Bras Oftalmol*. 2017; 80(3):202–6.
- 61 Li S, Li D, Shao M, Cao W, Sun X. Lack of association between serum vitamin B(6), vitamin B12, and vitamin D levels with different types of glaucoma: a systematic review and meta-analysis. *Nutrients*. 2017;9(6):636.
- 62 Pertl L, Mossböck G, Wedrich A, Weger M, Königsbrügge O, Silbernagel G, et al. Triglycerides and open angle glaucoma: a meta-analysis with meta-regression. *Sci Rep*. 2017;7(1): 7829.
- 63 Wang S, Liu Y, Zheng G. Hypothyroidism as a risk factor for open angle glaucoma: a systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186634.
- 64 Zhao YX, Chen XW. Diabetes and risk of glaucoma: systematic review and a meta-analysis of prospective cohort studies. *Int J Ophthalmol*. 2017;10(9):1430–5.
- 65 Ramdas WD, Schouten JSAG, Webers CAB. The effect of vitamins on glaucoma: a systematic review and meta-analysis. *Nutrients*. 2018;10(3):359.
- 66 Xu C, Li J, Li Z, Mao X. Migraine as a risk factor for primary open angle glaucoma: a systematic review and meta-analysis. *Medicine*. 2018;97(28):e11377.
- 67 Wang S, Bao X. Hyperlipidemia, blood lipid level, and the risk of glaucoma: a meta-analysis. *Invest Ophthalmol Vis Sci*. 2019;60(4): 1028–43.
- 68 Faustino JF, Ribeiro-Silva A, Dalto RF, Souza MM, Furtado JM, Rocha Gde M, et al. Vitamin A and the eye: an old tale for modern times. *Arq Bras Oftalmol*. 2016;79(1):56–61.
- 69 Nita M, Grzybowski A. Smoking and eye pathologies. A systemic review. Part I. Anterior eye segment pathologies. *Curr Pharm Des*. 2017;23(4):629–38.
- 70 Nita M, Grzybowski A. Smoking and eye pathologies. A systemic review. Part II. Retina diseases, uveitis, optic neuropathies, thyroid-associated orbitopathy. *Curr Pharm Des*. 2017;23(4):639–54.
- 71 Chiotoroiu SM, Pop de Popa D, Ștefăniu GI, Secureanu FA, Purcărea VL. The importance of alcohol abuse and smoking in the evolution of glaucoma disease. *J Med Life*. 2013;6(2): 226–9.
- 72 Cheng AC, Pang CP, Leung AT, Chua JK, Fan DS, Lam DS. The association between cigarette smoking and ocular diseases. *Hong Kong Med J*. 2000;6(2):195–202.
- 73 Tamaki Y, Araie M, Nagahara M, Tomita K. Acute effects of cigarette smoking on tissue circulation in human optic nerve head and choroid-retina. *Ophthalmology*. 1999;106(3): 564–9.
- 74 Martin G, Duez H, Blanquart C, Berezowski V, Poulain P, Fruchart JC, et al. Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL apoA-I. *J Clin Invest*. 2001;107(11):1423–32.
- 75 McGwin G Jr, McNeal S, Owsley C, Girkin C, Epstein D, Lee PP. Statins and other cholesterol-lowering medications and the presence of glaucoma. *Arch Ophthalmol*. 2004;122(6): 822–6.
- 76 Khawaja AP, Chan MP, Broadway DC, Garway-Heath DF, Luben R, Yip JL, et al. Systemic medication and intraocular pressure in a British population: the EPIC-Norfolk Eye study. *Ophthalmology*. 2014;121(8):1501–7.
- 77 Hennis A, Wu SY, Nemesure B, Leske MC. Hypertension, diabetes, and longitudinal changes in intraocular pressure. *Ophthalmology*. 2003;110(5):908–14.
- 78 Xu L, Wang H, Wang Y, Jonas JB. Intraocular pressure correlated with arterial blood pressure: the Beijing eye study. *Am J Ophthalmol*. 2007;144(3):461–2.
- 79 Smith KD, Tevaarwerk GJ, Allen LH. An ocular dynamic study supporting the hypothesis that hypothyroidism is a treatable cause of secondary open-angle glaucoma. *Can J Ophthalmol*. 1992;27(7):341–4.
- 80 Lin CC, Hu CC, Ho JD, Chiu HW, Lin HC. Obstructive sleep apnea and increased risk of glaucoma: a population-based matched-cohort study. *Ophthalmology*. 2013;120(8): 1559–64.
- 81 Faridi O, Park SC, Liebmann JM, Ritch R. Glaucoma and obstructive sleep apnoea syndrome. *Clin Exp Ophthalmol*. 2012;40(4): 408–19.
- 82 Doulberis M, Papaefthymiou A, Polyzos SA, Bargiotas P, Liatsos C, Srivastava DS, et al. Association between active *Helicobacter pylori* infection and glaucoma: a systematic review and meta-analysis. *Microorganisms*. 2020; 8(6).
- 83 Papaefthymiou A, Doulberis M, Katsinelos P, Liatsos C, Polyzos SA, Kotronis G, et al. Impact of nitric oxide's bidirectional role on glaucoma: focus on *Helicobacter pylori*-related nitrosative stress. *Ann N Y Acad Sci*. 2020; 1465(1):10–28.
- 84 Gentle A, Liu Y, Martin JE, Conti GL, McBrien NA. Collagen gene expression and the altered accumulation of scleral collagen during the development of high myopia. *J Biol Chem*. 2003;278(19):16587–94.
- 85 Guo MS, Wu YY, Liang ZB. Hyaluronic acid increases MMP-2 and MMP-9 expressions in cultured trabecular meshwork cells from patients with primary open-angle glaucoma. *Mol Vis*. 2012;18:1175–81.
- 86 Plange N, Remky A, Arend O. Colour Doppler imaging and fluorescein filling defects of the optic disc in normal tension glaucoma. *Br J Ophthalmol*. 2003;87(6):731–6.
- 87 Nosedà R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain*. 2013; 154(Suppl 1):S44–53.
- 88 Flammer J, Konieczka K, Flammer AJ. The primary vascular dysregulation syndrome: implications for eye diseases. *EPMA J*. 2013; 4(1):14.
- 89 Ajith TA, Ranimenon . Homocysteine in ocular diseases. *Clin Chim Acta*. 2015;450:316–21.
- 90 Navneet S, Zhao J, Wang J, Mysona B, Barwick S, Ammal Kaidery N, et al. Hyperhomocysteinemia-induced death of retinal ganglion cells: the role of Müller glial cells and NRF2. *Redox Biol*. 2019;24: 101199.

- 91 Wu X, Zhang L, Miao Y, Yang J, Wang X, Wang CC, et al. Homocysteine causes vascular endothelial dysfunction by disrupting endoplasmic reticulum redox homeostasis. *Redox Biol.* 2019;20:46–59.
- 92 Leng YP, Ma YS, Li XG, Chen RF, Zeng PY, Li XH, et al. l-Homocysteine-induced cathepsin V mediates the vascular endothelial inflammation in hyperhomocysteinaemia. *Br J Pharmacol.* 2018;175(8):1157–72.
- 93 Liang L, Zhang R, He LY. Corneal hysteresis and glaucoma. *Int Ophthalmol.* 2019;39(8):1909–16.
- 94 Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol.* 2002;120(6):714–30; discussion 829–30
- 95 Belovay GW, Goldberg I. The thick and thin of the central corneal thickness in glaucoma. *Eye.* 2018;32(5):915–23.
- 96 Suzuki Y, Iwase A, Araie M, Yamamoto T, Abe H, Shirato S, et al. Risk factors for open-angle glaucoma in a Japanese population: the Tajimi study. *Ophthalmology.* 2006;113(9):1613–7.
- 97 McMonnies CW. Glaucoma history and risk factors. *J Optom.* 2017;10(2):71–8.
- 98 Cho HK, Kee C. Population-based glaucoma prevalence studies in Asians. *Surv Ophthalmol.* 2014;59(4):434–47.
- 99 Hui F, Tang J, Williams PA, McGuinness MB, Hadoux X, Casson RJ, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. *Clin Exp Ophthalmol.* 2020;48(7):903–14.
- 100 Chopra V, Varma R, Francis BA, Wu J, Torres M, Azen SP. Type 2 diabetes mellitus and the risk of open-angle glaucoma the Los Angeles Latino eye study. *Ophthalmology.* 2008;115(2):227–32.e1.
- 101 Sato T, Roy S. Effect of high glucose on fibronectin expression and cell proliferation in trabecular meshwork cells. *Invest Ophthalmol Vis Sci.* 2002;43(1):170–5.