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

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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.

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 sole 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 included after reviewing titles and abstracts, which process is shown in Figure 1.
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.

Fig. 1. Flow chart outlining the literature search and evaluation process of published meta-analyses and systematic reviews. MA, meta-analysis.
| 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 | I² % | Publication bias |
|------------|----------------------|----------------------------------------|--------------------------------------------------------------------------------------|------------------|-----------------|--------------|---------------|-------------|----------------|-------|-----------------|
| Dietary intake |                      |                                        |                                                                                     |                  |                 |              |               |             |                |       |                  |
| Vitamin A  | Ramdas et al. [65]    | Cross-sectional, cross-sectional case-control, prospective cohort | 5                                      | 940/123,697      | Pool OR        | REM          | 0.45 (0.30–0.68) | 0.02   | 0              | NR   |                  |
| Vitamin B1 | Ramdas et al. [65]    | Cross-sectional cohort, 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 cohort, cross-sectional case-control, prospective cohort | 4                                      | 849/121,135      | Pool OR        | REM          | 0.39 (0.23–0.67) | 0.2    | 0              | NR   |                  |
| Vitamin E  | Ramdas et al. [65]    | Cross-sectional cohort, cross-sectional case-control, prospective cohort | 5                                      | 940/123,697      | OR              | REM          | 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     | Pool OR      | 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) |
| Zhou et al. [59] | Current smoking | Cohort, case-control                  |                                                                                     | 6                | NR              | Pool RR      | 0.97 (0.81–1.16) | 0.74   | 38             | Funnel plot symmetry |
| Past smoking |                       |                                        |                                                                                     | 6                |                 |              | 0.97 (0.83–1.13) | 0.66   | 46             |                  |
| Statin     | McCann et al. [58]   | <2 years                               | Cross-sectional, case-control, cohort   | 4                | 583,615        | Pool OR      | 0.96 (0.94–0.99) | 0.005  | 0             | Funnel plots symmetry |
|           |                      | >2 years                               |                                                                                     | 3                |                 |              | 0.70 (0.46–1.06) | 0.09   | 73             |                  |
| Diseases   |                      |                                        |                                                                                     |                  |                 |              |               |             |                |       |                  |
| Diabetes   | Zhao et al. [55]      | Cross-sectional, case-control, longitudinal cohort | 47                                     | 2,981,342        | Pool RR        | REM          | 1.48 (1.29–1.71) | NR     | 82.30          | Egger test (p < 0.001) |
| Zhao and Chen [64] |                     | Prospective cohort                     |                                                                                     | 7                | 2,445,203      | Pool RR      | 1.36 (1.24–1.50) | NR     | 30             |                  |
| Hyperlipidemia | Pertl et al. [62]   | Case-control                           |                                                                                     | 17               | 1,391/25,575   | Pool mean absolute difference | 14.2  | 66.20          | Funnel plot symmetry |
| Wang and Bao [67] |                      | Cross-sectional, case-control, cohort   |                                                                                     | 18               | 2,721,615      | Pool OR      | 1.37 (1.16–1.61) | NR     | 97.00          | Egger test (p 0.751) |
| Hypertension | Zhao et al. [52]     | Cross-sectional, case-control, longitudinal cohort | 27                                     | 2,333,996        | Pool OR        | REM          | 1.16 (1.05–1.28) | NR     | 34.50          | Funnel plots symmetry |
| Bae et al. [49] | Cross-sectional, cohort |                                                                                     |                                                                                     | 16               | 60,084         | Pool OR      | 1.22 (1.08–1.37) | NR     | 7.50           | Egger test (p 0.90) |
| Nocturnal dip in blood pressure | Bowe et al. [53]     | Systolic blood pressure                 | Retrospective cohort                                                       | 4                | 259            | OR           | 3.32 (1.84–6.00) | <0.0001 | 0            | NR   |                  |
|           |                      | Diastolic blood pressure                |                                                                                     |                  |                 |              | 2.09 (1.20–3.64) | 0.009  | 0            | NR   |                  |
| Hypothyroidism | Wang et al. [63]     | Cross-sectional, case-control, cohort   |                                                                                     | 11               | 381,695        | Pool OR      | 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 | Pool OR      | 1.41 (1.11–1.79) | 0.006  | 73.00          |                  |
|           |                      | Case-control                            |                                                                                     | 6                | 1,032/7,039    | Pool OR      | 1.96 (1.37–2.80) | 0.002  | 0.00          | NR   |                  |
| Liu et al. [57] | Case-control      |                                                                                     |                                                                                     | 3                | 711/6,709      | Pool OR      | 2.46 (1.32–4.59) | 0.005  | 0            | Begg’s test Pr | 0.348 |
| Cohort     |                      |                                                                                     |                                                                                     | 3                | 2,281,281      | Pool OR      | 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, n | Case/control, N | Metric of MA | Effects model | ES (95% CI)    | Effect p value | I² % |Publication bias |
|----------------------------------|-----------------------------|---------------------------|-----------------------|------------------|-----------------|--------------|---------------|----------------|----------------|-------|-----------------|
| H. pylori 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 (p 0.347) |
| Myopia                           | Xiong et al. [51]           | > –3.00D                  | 11                    | 45,996           | Pooled OR       | FEM          | 1.52 (1.23–1.88) | NR             | 7.30   | Egger test (p 0.74) |
| Myopia                           | Xiong et al. [51]           | ≤ –3.00D                  | 11                    | 467,008          | Pooled RR       | FEM          | 2.41 (1.91–3.03) | 0              | 0              | Egger test (p 0.272) |
| Migraine                         | Xu et al. [66]              | Case-control, cohort      | 11                    | 161,978          | RR              | FEM          | 0.92 (0.89–0.94) | NR             | 89.00 | Egger test (p 0.01) |
| Alzheimer’s disease              | Tsilis et al. [50]          | Non-demented participants | 8                     | 162,790          |                 | REM          | 0.94 (0.92–0.96) | 89.40          | Egger test (p < 0.001) |
| Alzheimer’s disease              | Tsilis et al. [50]          | With dementia             | 9                     | 162,790          |                 | REM          | 0.94 (0.92–0.96) | 89.40          | Egger test (p < 0.001) |
| Biomarkers                       |                             |                           |                       |                  |                 |              |               |                 |                 |       |                 |
| Plasma tHcy                      | Li et al. [56]              | NTG                       | 4                     | 149/148          | Pooled WMD      | REM          | 1.16 (–0.13, 2.45) | 0.08           | 72    | NR               |
|                                    | Xi et al. [48]              | POAG                      | 12                    | 546/535          | WMD             | REM          | 2.05 (0.63–3.47) | 0.005          | 94.40 | NR               |
| Serum folic acid                 | Li et al. [56]              | NTG                       | 2                     | 90/82            | Pooled WMD      | REM          | –0.62 (–1.96, 0.74) | 0.37           | 52    | NR               |
|                                    | Xi et al. [48]              | POAG                      | 6                     | 222/252          | WMD             | FEM          | 0.34 (–0.37,1.05) | 0.344          | 0     | NR               |
| Serum vitamin B12                | Li et al. [57]              | NTG                       | 6                     | 222/249          | WMD             | FEM          | 0.93 (–31.116, 29.249) | 0.952          | 0     | Funnel plots symmetry |
| Serum vitamin B6                  | Li et al. [56]              | NTG                       | 2                     | 90/82            | Pooled WMD      | REM          | –16.79 (–46.09, 25.51) | 0.63           | 0     | NR               |
|                                    | Li et al. [57]              | POAG                      | 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                      | 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                    | 1,213/1,055      | MD              | NR          | −1.54 (−1.58, −1.41) | <0.00001       | 78    | NR               |
|                                    |                             | CCT                       |                         |                  |                 | FEM          | −8.49 (−11.36, −5.62) | p <0.00001     | 60    |                 |
|                                    |                             | Normally active group      | 7                     | 124              |                 | REM          | −2.340 (−3.305, −1.375) | 91.80          |                 |                 |

MA, meta-analysis; OR, odds ratio; RR, relative risk; MD, mean difference; WMD, weighted mean differences; 95% CI, 95% confidence interval; FEM, fixed-effects model; REM, random-effects model; IOP, intraocular pressures; 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; OSAS, obstructive sleep apnea syndrome; H. pylori, Helicobacter pylori; tHcy, homocysteine.
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

| 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  | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | N   | Y   | N   | Critically low |
| Bonovas et al. [47]      | Y  | N  | N  | Y  | Y  | Y  | PY | PY | N  | Y   | Y   | Y   | N   | N   | N   | Critically low |
| Zhou et al. [59]         | Y  | PY | Y  | Y  | Y  | Y  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | N   | Moderate |
| McCann et al. [58]       | Y  | PY | Y  | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | N   | N   | N   | Low |
| Zhao et al. [55]         | Y  | PY | Y  | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Low |
| Zhao and Chen [64]       | Y  | PY | Y  | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Critically low |
| Pertl et al. [62]        | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | N   | N   | N   | Critically low |
| Wang and Bao [67]        | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Low |
| Zhao et al. [52]         | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Critically low |
| Bowe et al. [53]         | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | N   | N   | N   | Critically low |
| Bae et al. [49]          | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Low |
| Wang et al. [63]         | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | N   | N   | Low |
| Shi et al. [54]          | Y  | N  | PY | Y  | Y  | Y  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Liu et al. [57]          | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Doulberis et al. [82]    | Y  | PY | Y  | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Low |
| Xiong et al. [51]        | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Low |
| Xu et al. [66]           | Y  | N  | PY | Y  | Y  | Y  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Tsilis, et al. [50]      | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Li et al. [56]           | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Xu et al. [48]           | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | N   | N   | N   | Critically low |
| Li et al. [57]           | Y  | N  | PY | Y  | Y  | N  | PY | PY | N  | Y   | Y   | Y   | Y   | Y   | Y   | Critically low |
| Gaspar et al. [60]       | Y  | N  | PY | N  | N  | N  | N  | N  | N  | N   | N   | N   | N   | N   | N   | Critically low |
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 nondiabetic 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 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–
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2.13) [63]. Thvlum 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 (I², 89%; I²heterogeneity < 0.001) and exhibited substantial publication bias (Egger’s p ≤ 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])
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 µm [−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 × 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 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 development 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.

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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.

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