Hallucinations: A Meta-Analysis

Shiming Wang1 and Xianyi Bao2
1Aier Eye Hospital Group, Ningbo Aier Guangming Eye Hospital, Ningbo, China
2Aier Eye Hospital Group, Wuhan Aier Eye Hospital, Wuhan, China

CORRESPONDENCE: Shiming Wang, Aier Eye Hospital Group, Ningbo Aier Guangming Eye Hospital, 8 Huancheng North Road, Ningbo, Zhejiang Province 315020, China; shimingwangMD@163.com.
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PURPOSE. Previous studies reported that hyperlipidemia and blood lipid levels were associated with glaucoma, ocular hypertension (OHT), and intraocular pressure (IOP). However, studies aimed at investigating this association have yielded conflicting results. Therefore, to shed light on these inconclusive findings, we performed multiple distinct meta-analyses to clarify the association between hyperlipidemia and blood lipid levels with glaucoma, OHT, and IOP.

METHODS. A systematic literature search from Embase, Web of Science, and PubMed was performed to identify relevant studies. To assess the association between hyperlipidemia and glaucoma, we used the pooled odds ratio (OR) with 95% confidence interval (CI). When we assessed the association between blood lipid levels and IOP levels, the pooled mean difference in IOP associated with a 10 mg/dL increase in the blood lipid level was estimated. The pooled difference in IOP was also estimated between patients with and without hyperlipidemia. All the papers that assessed the correlation between hyperlipidemia and glaucoma, between blood lipid levels and IOP levels, and between hyperlipidemia and IOP were included in this meta-analysis.

RESULTS. We detected a marked association between hyperlipidemia and glaucoma (OR = 1.37; 95% CI = 1.16–1.61), with significant heterogeneity among studies. However, hyperlipidemia was not significantly associated with glaucoma in our analysis of only cross-sectional studies, studies that reported only on hypercholesterolemia patients, studies that were conducted only in North America and Europe, or studies in which normal-tension glaucoma (NTG) patients were included only in the subgroup analyses. The pooled results showed that an increase of 10 mg/dL in blood triglyceride levels would increase the IOP by 0.016 mm Hg (95% CI = 0.009–0.024), with evident heterogeneity between studies (P < 0.001; I² = 92.0%). The pooled results showed that the blood total cholesterol and low-density lipoprotein-cholesterol (LDL-c) level both had a significant association with IOP. When compared to the patients with nonhyperlipidemia, those with hyperlipidemia had a significantly higher IOP of 0.51 mm Hg (95% CI = 0.18–0.83) (P = 0.001 for heterogeneity; I² = 81.6%).

CONCLUSIONS. The evidence suggests that hyperlipidemia is significantly associated with an increased risk of glaucoma and that hyperlipidemia and the increased blood lipid levels are associated with increased IOP.

Keywords: hyperlipidemia, blood lipid level, glaucoma

Glaucoma, a multifactorial condition characterized by a progressive optic neuropathy and distinctive visual field loss, has become the most common cause of irreversible blindness worldwide.1,2 Quigley et al.3 estimated that by 2020, 79.6 million people will suffer from glaucoma, and 74% will have primary open-angle glaucoma (POAG). The exact mechanism by which the anatomic and functional damage occurs in patients with POAG remains unknown. Established risk factors include elevated intraocular pressure (IOP),4 as well as old age,5 ethnic background,2 and family history of glaucoma.6 However, other potential risk factors for glaucoma may exist, and these should be explored to develop interventions that can reduce the incidence of this disorder.

Recent epidemiologic studies have suggested that hyperlipidemia may be associated with glaucoma, although the findings have been contradictory. For example, Newman-Casey et al.7 found that individuals with hyperlipidemia had a reduced risk of developing POAG when compared to those with no hyperlipidemia. However, several studies have also shown a positive correlation between hyperlipidemia and development of this disorder. For instance, the study by Lin and colleagues,8 which used the National Health Insurance Database, indicated that hyperlipidemia increases the odds of developing POAG. The increased blood lipid level has also been proposed as a risk factor for elevated IOP, but the results from published studies examining this correlation have also been inconsistent.9,10

At present, the pathogenesis of POAG is not fully understood. Establishing a clearer understanding of the association between hyperlipidemia and POAG may therefore provide insights into the pathophysiology of this disease. For this reason, we first conducted multiple distinct meta-analyses...
of the available published literature to clarify whether hyperlipidemia and blood lipid levels are associated with an increased risk of glaucoma and elevated IOP.

METHODS

Search Strategy

The study was performed according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology guidelines. A systematic literature search was performed using the Embase, Web of Science, and PubMed databases to identify relevant studies published up to July 2018. The following keywords were used: “hypercholesterolemia,” “hypertriglyceridemia,” “blood fat,” “blood lipid,” “lipid blood level,” “TG,” “triglyceride,” “triglycerides,” “glycerin triurate,” “cholesterin,” “cholesterol,” “cholestone,” “hyperlipemia,” “high density lipoprotein cholesterol,” “HDL-c,” “low density lipoprotein cholesterol,” “LDL-c,” “LDL cholesterol,” “intraocular pressure,” “ocular tension,” “eye internal pressure,” “eye pressure,” “intraocular hypertension,” “glaucoma,” and “intraocular tension.” Additional information was obtained by searching Google Scholar. We also screened the reference lists of all retrieved trials to identify studies not yet included in the computerized databases. The search did not restrict the language, methodological filter, or publication year.

Inclusion and Exclusion Criteria

In the present meta-analysis, we aimed to identify all relative studies reporting a correlation between hyperlipidemia or blood lipid levels with glaucoma, ocular hypertension (OHT), or IOP levels. The following inclusion criteria were met in the present meta-analysis: (1) Individuals were older than 18 years of age; (2) study design: cohort, case-control, or cross-sectional study; (3) odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) estimates with their 95% confidence intervals (CIs) were provided; (4) sufficient data were provided to calculate ORs, RRs, or HR values; or (4) sufficient data were provided to calculate the weighted mean differences (WMD) with their 95% CI for changes in IOP. The following exclusion criteria were also considered: (1) studies conducted in animals; (2) reports that were letters, reviews, case reports, or abstracts, or reports that had incomplete data; (3) studies not reporting glaucoma, OHT, or IOP as outcomes; (4) studies not using hyperlipidemia and lipid blood levels as exposures. If multiple publications from the same study population were available, then duplicate analyses were checked and only the most recent publication was included. The study endpoints in this meta-analysis were IOP, OHT, and POAG. If studies did not report POAG separately from other types of glaucoma, we used the results for glaucoma as endpoints. If studies reported an association between hyperlipidemia and glaucoma, we used hyperlipidemia as the exposure. If studies reported an association between hypercholesterolemia or hypertriglyceridemia and glaucoma, we considered hypercholesterolemia or hypertriglyceridemia to represent hyperlipidemia and separated it in the subgroup analysis.

Data Extraction and Quality Assessment

The following information was extracted by two independent reviewers (S.W. and X.B.): first author, publication year, sources of research population, study period, study design, age of subjects, gender proportions, sample size, measure and range of exposure, method of ascertaining exposure, measure and range of outcome, definition of outcome, adjusted variables, and reported measures of association with corresponding 95% CIs or standard errors (SE). Discrepancies between reviewers were resolved by consensus or adjudication by a third reviewer. The study quality was assessed by two reviewers (S.W. and X.B.) using the methods described by Sanderson et al. and Viswanathan et al. This quality assessment method contains 15 items involving criteria and evaluation of design and data analysis for observational studies. In brief, the methods used for selecting study subjects, the methods used for measuring outcomes and exposure; and the methods used to control for confounding, potential conflicts of interest, and the risk of bias associated with different designs were examined (Table 1). Any discrepancies were addressed by discussion to reach a consensus.

Statistical Analyses

These meta-analyses were conducted using the Stata software package (Version 12.0; Stata Corp., College Station, TX, USA). We performed a separate meta-analysis for each combination of exposure (hyperlipidemia and blood lipid level) and outcome (glaucoma, IOP, and OHT) to combine the potential association. For binary outcomes, we assessed the correlation between hyperlipidemia and glaucoma by estimating the pooled OR (ORs, HRs, and RR were all referred to as ORs) with 95% CI using the random-effects model. For continuous outcomes, the pooled mean difference in IOP associated with an increase in 10 mg/dL of blood lipid level was estimated. The pooled mean difference in IOP was also estimated between patients with and without hyperlipidemia. For studies reporting correlation coefficients with SIs, we converted the SIs to 95% CIs. When the included studies provided estimates of effect size from different multivariate models, we included the result from the model with the largest number of adjusted variables. We evaluated the presence of among-studies heterogeneity using the $I^2$ and $I^2$ tests. For the $I^2$ test, $P < 0.1$ was considered to represent significant heterogeneity. For $I^2$, a value >50% indicated significant heterogeneity. We conducted a stratified analysis when assessing the association between hyperlipidemia and glaucoma on the basis of the study design (case-control, cross-sectional, nested case-control/cohort study), exposure (hyperlipidemia, hypercholesterolemia, hypertrigliceridemia), geographical area (North America, Asia, Europe), or age (younger, older). For studies assessing POAG (IOP level above 22 mm Hg) normal open anterior chamber angle; the presence of glaucomatous optic nerve head change and corresponding visual field change on automated static perimetry), normal tension glaucoma (NTG) (IOP level below 22 mm Hg; normal open anterior chamber angle; the presence of glaucomatous optic nerve head change and corresponding visual field change on automated static perimetry), glaucoma, the number of adjusted variables (more than three factors), less than or equal to three factors), the sample size (>10,000, ≤10,000), and the publication year (≤2014, >2014). A meta-regression analysis with a random-effects approach was also performed when assessing the association between hyperlipidemia and glaucoma, where studies were weighted by a combination of their between-study variance and the degree of heterogeneity. The reliability of the outcomes of the meta-analysis was determined by a sensitivity analysis performed by omitting each individual study one at a time. Finally, publication biases were detected using the Begg’s and Egger’s tests and assessed using Begg’s funnel plots.
TABLE 1. Quality Criteria and Evaluation of Design and Data Analysis for Observational Studies

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
<th>Other: CD, NA, NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the research question or objective in this paper clearly stated?</td>
<td></td>
<td></td>
<td>CD</td>
</tr>
<tr>
<td>2. Was the study population clearly specified and defined?</td>
<td></td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>3. Was the study population representative of the general population?</td>
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<td></td>
<td>NR</td>
</tr>
<tr>
<td>4. Was the participation rate of eligible persons at least 50%?</td>
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<tr>
<td>5. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?</td>
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<td>6. Were sample size justification, power description, or variance and effect estimates provided?</td>
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<tr>
<td>7. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?</td>
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<tr>
<td>8. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?</td>
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<tr>
<td>9. Were the exposure measures (independent variables) clearly defined, objective, valid, reliable, and implemented consistently across all study participants?</td>
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<tr>
<td>10. Was (were) the exposure(s) assessed more than once over time?</td>
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<tr>
<td>11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?</td>
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<tr>
<td>12. Were the outcome assessors blinded to the exposure status of participants?</td>
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<tr>
<td>13. Was the statistical analysis appropriate?</td>
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<tr>
<td>14. Was loss to follow-up after baseline 20% or less?</td>
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<tr>
<td>15. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?</td>
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</table>

CD, cannot determine; NA, not applicable; NR, not reported.

RESULTS

Literature Search

A total of 8317 papers were identified through literature searches of the three databases. Of these, 1621 were duplicate publications and were removed. A further 6696 papers were also excluded following title and abstract review. Of the remaining 42 publications retained for further assessment and a full-text review, 15 papers were excluded for the following reasons: absence of a normal control (n = 1); hyperlipidemia or blood lipid level were not exposures (n = 8); insuffi cient data to calculate the effect size (n = 5); or glaucoma, IOP, or OHT were not outcomes (n = 1). The remaining 27 articles were included in this meta-analysis. One additional study was included after searching for references. Ultimately, 28 studies, including 13 cross-sectional, 9 cohort or nested case-control, and 5 case-control studies were included in the present meta-analysis. Of these studies, 18 studies reported on the relationship between hyperlipidemia (hyperlipidemia or hypertriglyceridemia or hypercholesterolemia) and glaucoma, and 10 studies reported on the relationship between hyperlipidemia and IOP changes. We also treated this as two studies. The detailed process of data selection is described in Figure 1.

Characteristics of Studies and Quality Assessment

Table 2 displays the characteristics of the included studies. These studies were performed in seven countries: the United States, Japan, Portugal, France, Turkey, Chinese Taiwan, and Korea. The sample sizes in the included studies ranged from 162 to 2,182,315. Thus, in this meta-analysis, a total of 2,721,615 subjects were included in studies that assessed the association between hyperlipidemia and glaucoma; 46,629 subjects were included in studies that assessed the association between blood triglyceride levels and IOP; and 17,857 subjects were included in studies that assessed the association between hyperlipidemia and OHT. The definition of outcome and exposure varied across the studies, as summarized in Table 3. Table 4 displays the adjusted variables of the included studies. A detailed quality assessment of all the included studies is displayed in Table 5. This assessment showed that the quality of the cohort/nest case-control studies was good, but it was only fair for the cross-sectional and case-control studies.

Glucoma

Figure 2 shows the pooled effect estimates and the heterogeneity tests of the association between hyperlipidemia and glaucoma. Using the random-effects model, the 18 included studies (21 databases) indicated a significant association between hyperlipidemia and glaucoma (OR = 1.37; 95% CI = 1.16–1.61) with a significant heterogeneity across studies (P < 0.001; I² = 97%). Because of the significant heterogeneity detected in these comparisons, a series of prespecified stratified analyses was performed, based on study design, exposures, geographical...
area, outcomes, number of adjusted variables, sample size, and publication year. In the stratified analysis based on study design, the subgroups of case-control (OR = 1.51; 95% CI = 1.23-1.86) and nested case-control/cohort (OR = 1.50; 95% CI = 1.06-2.11) showed a significant association between hyperlipidemia and glaucoma. However, the cross-sectional design (OR = 1.21; 95% CI = 0.98-1.49) did not reveal this association. Some of the included studies reported on the association between hyperlipidemia and glaucoma, some on the association between high triglyceride and glaucoma, and some on the association between high total cholesterol, high LDL-c, and low HDL-c and glaucoma. The high triglyceride condition was defined as hypertriglyceridemia, and the high total cholesterol, high LDL-c, and low HDL-c were defined as hypercholesterolemia. The next subgroup analyses were performed according to exposure. The results showed that both hyperlipidemia and hypertriglyceridemia had a significant association with glaucoma, but this association was not found in the hypercholesterolemia subgroup. When based on geographical area, the positive relationship between hyperlipidemia and glaucoma was found only in the Asian subgroup and not in the North American and European subgroups. Notably, we found that when stratified by outcome, the NTG subgroup, unlike the glaucoma and POAG subgroups, did not reveal this association (OR = 1.19; 95% CI = 0.84-1.69). For other subgroup analyses, all the subgroups showed a marked association between hyperlipidemia and the risk of glaucoma. However, obvious heterogeneity still existed among most of the subgroups. We conducted a subsequent meta-regression to identify the sources of this heterogeneity but we failed to find any source.
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Location</th>
<th>Population</th>
<th>Recruitment/ Follow-Up Year</th>
<th>Design</th>
<th>Mean Age or Range, Year</th>
<th>Male, %</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girkin (2004)^44</td>
<td>United States</td>
<td>Patients drawn from the Birmingham, Alabama Department of Veterans Affairs Medical Center</td>
<td>1997–2001</td>
<td>Nested case–control</td>
<td>69</td>
<td>100</td>
<td>6,487</td>
</tr>
<tr>
<td>Chen (2005)^9</td>
<td>Chinese Taiwan</td>
<td>Residents participating in private health examination</td>
<td>2001–2002</td>
<td>Cross-sectional</td>
<td>Male: 49.0 Female: 51.1</td>
<td>53</td>
<td>1,271</td>
</tr>
<tr>
<td>Motsko (2008)^54</td>
<td>Portugal</td>
<td>Ingenux Labrix Database</td>
<td>2001–2004</td>
<td>Case–control</td>
<td>&gt;60</td>
<td>38.3</td>
<td>18,912</td>
</tr>
<tr>
<td>Lin (2010)^8</td>
<td>Chinese Taiwan</td>
<td>National Health Insurance Research Database</td>
<td>2005</td>
<td>Case–control</td>
<td>62.7</td>
<td>52.2</td>
<td>306,692</td>
</tr>
<tr>
<td>Lin (2010)^55</td>
<td>Chinese Taiwan</td>
<td>Longitudinal Health Insurance Database</td>
<td>1997–2001</td>
<td>Cohort</td>
<td>69.4</td>
<td>46.0</td>
<td>2,313</td>
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<tr>
<td>Imai (2010)^32</td>
<td>Japan</td>
<td>Health checkup programs at Murakami Memorial Hospital</td>
<td>2004–2008</td>
<td>Cross-sectional</td>
<td>46.0</td>
<td>57.4</td>
<td>14,003</td>
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<tr>
<td>Ishikawa (2011)^52</td>
<td>Japan</td>
<td>Annual community health checkup project</td>
<td>2007</td>
<td>Case-control</td>
<td>54.7</td>
<td>54.1</td>
<td>710</td>
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<tr>
<td>Newman-Casey (2011)^17</td>
<td>United States</td>
<td>The i3 InVision Data Management database</td>
<td>2001–2007</td>
<td>Cohort</td>
<td>54.5</td>
<td>43</td>
<td>2,182,315</td>
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<td>Lin (2012)^48</td>
<td>Chinese Taiwan</td>
<td>Participants who underwent a self-funded health examination</td>
<td>2008</td>
<td>Cross-sectional</td>
<td>Male: 49.2 Female: 50.0</td>
<td>57.6</td>
<td>10,491</td>
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<td>Kim (2014)^54</td>
<td>Korea</td>
<td>Glaucoma screening program at the Gangnam Health Care Center of Seoul National University Hospital</td>
<td>2010–2011</td>
<td>Cross-sectional</td>
<td>52.8</td>
<td>56.9</td>
<td>18,240</td>
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<tr>
<td>Aptel (2014)^67</td>
<td>France</td>
<td>Observatoire Sommeil de la Fédération Francaise de Pneumologie</td>
<td>2009–2012</td>
<td>Cohort</td>
<td>≥50</td>
<td>68.0</td>
<td>9,850</td>
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<tr>
<td>Chen (2014)^48</td>
<td>Chinese Taiwan</td>
<td>National Health Insurance Research Database</td>
<td>2000–2009</td>
<td>Cohort</td>
<td>45.1</td>
<td>77.8</td>
<td>12,640</td>
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<td>Sahinoglu-Keskek (2014)^41</td>
<td>Turkey</td>
<td>Adana Numune Training and Research Hospital</td>
<td>2013</td>
<td>Cross-sectional</td>
<td>NA</td>
<td>41.6</td>
<td>162</td>
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<td>Fujisawa (2015)^69</td>
<td>Japan</td>
<td>The Hisayama Study</td>
<td>2007</td>
<td>Cohort</td>
<td>&gt;40</td>
<td>44.6</td>
<td>2,254</td>
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<td>Shim (2015)^52</td>
<td>Korea</td>
<td>Patients drawn from department of ophthalmology outpatient service at Kangbuk Samsung Hospital</td>
<td>2013–2014</td>
<td>Cross-sectional</td>
<td>20–88</td>
<td>54.3</td>
<td>315</td>
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<tr>
<td>Chen (2016)^60</td>
<td>Chinese Taiwan</td>
<td>Taiwan’s National Health Insurance program</td>
<td>1995–2011</td>
<td>Cohort</td>
<td>56.7</td>
<td>51.6</td>
<td>17,550</td>
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<tr>
<td>Chen (2016)^51</td>
<td>Chinese Taiwan</td>
<td>National Health Insurance Research Database</td>
<td>2000–2010</td>
<td>Cohort</td>
<td>45.1</td>
<td>26.5</td>
<td>88,029</td>
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<tr>
<td>Ko (2016)^55</td>
<td>United States</td>
<td>National Health and Nutrition Examination Survey</td>
<td>2005–2008</td>
<td>Cross-sectional</td>
<td>Glaucoma: 68.1 No glaucoma: 56.4</td>
<td>47.5</td>
<td>5,746</td>
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<td>Yokomichi (2016)^10</td>
<td>Japan</td>
<td>Residents of Yamanashi Prefecture, Japan</td>
<td>1999–2009</td>
<td>Cohort</td>
<td>Male: 54.3 Female: 54.8</td>
<td>50.6</td>
<td>20,007</td>
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<tr>
<td>Lee (2017)^50</td>
<td>Chinese Taiwan</td>
<td>Participants who underwent physical checkup</td>
<td>2011–2014</td>
<td>Cross-sectional</td>
<td>48</td>
<td>66.7</td>
<td>1,041</td>
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<td>First Author (Year)</td>
<td>Outcome</td>
<td>Outcome Definition/Measurement</td>
<td>Exposure</td>
<td>Exposure Definition/Measurement</td>
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<tr>
<td>Girkin (2004)44</td>
<td>POAG</td>
<td>Cases of glaucoma were defined using the ICD-9-CM code 365.1.</td>
<td>Hyperlipidemia</td>
<td>ICD-9-CM code: 272</td>
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<td>Chen (2005)9</td>
<td>IOP</td>
<td>Noncontact tonometer</td>
<td>Blood triglyceride levels</td>
<td>Triglycerides measured by a biochemical autoanalyzer</td>
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<tr>
<td>Lin (2010)8</td>
<td>POAG</td>
<td>One or more of the following ICD-9-CM codes: 365.1–365.11, only patients who had at least three consensus OAG diagnoses were included.</td>
<td>Hyperlipidemia</td>
<td>Medical records</td>
<td></td>
<td></td>
<td></td>
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<td>Lin (2010)45</td>
<td>POAG</td>
<td>One or more of the following ICD-9-CM codes: 365.1–365.11</td>
<td>Hyperlipidemia</td>
<td>ICD-9-CM code: 272</td>
<td></td>
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<tr>
<td>Imai (2010)32</td>
<td>OHT</td>
<td>High ocular tension was defined as right-eye IOP of &gt;21 mm Hg without optic disc abnormalities or history of receiving any antiglaucoma therapy.</td>
<td>Hypertriglyceridemia, hypercholesterolemia</td>
<td>Triglycerides ≥ 150 mg/dL, HDL &lt; 40 mg/dL in men or HDL &lt; 50 mg/dL in women</td>
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<tr>
<td>Ishikawa (2011)52</td>
<td>POAG</td>
<td>Diagnosis of glaucoma was made based on optic disc appearance, including CDR, rim width, nerve fiber layer defect, the visual field test, and the clinical records that were obtained through screening and definitive examinations.</td>
<td>Hypercholesterolemia</td>
<td>Hypercholesterolemia defined when cholesterol levels were greater than the upper limit of the normal range (220 mg/dL)</td>
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<td>Lee (2012)46</td>
<td>IOP</td>
<td>Noncontact tonometer</td>
<td>Blood triglyceride levels</td>
<td>Medical records</td>
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<td>Lin (2012)35</td>
<td>IOP</td>
<td>Noncontact tonometer</td>
<td>Blood triglyceride levels</td>
<td>Laboratory testing</td>
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<tr>
<td>Kim (2014)34</td>
<td>NTG</td>
<td>NTG diagnosis was made for eyes with all of the following: (1) IOP level below 22 mm Hg without optic disc abnormalities; (2) normal open anterior chamber angle; (3) the presence of glaucomatous optic nerve head change and corresponding visual field change on automated static perimetry.</td>
<td>Hypertriglyceridemia, hypercholesterolemia</td>
<td>Hypertriglyceridemia (triglyceride level ≥ 150 mg/dL); low level of HDL (HDL &lt; 40 mg/dL in men or HDL &lt; 50 mg/dL in women)</td>
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<td>Aptel (2014)47</td>
<td>Glaucoma</td>
<td>Glaucoma diagnosis was collected in the database only for patients who had been examined by an ophthalmologist.</td>
<td>Hypertriglyceridemia</td>
<td>Medical information from database</td>
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<td>Kim (2014)35</td>
<td>IOP</td>
<td>Goldmann applanation tonometry</td>
<td>Blood triglyceride levels, blood HDL-c level, blood LDL-c level, Blood total cholesterol level</td>
<td>Biochemistry tests of blood</td>
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<td></td>
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<td>Chung (2014)53</td>
<td>POAG</td>
<td>ICD-9-CM code: 365.1 or 365.11</td>
<td>Hyperlipidemia</td>
<td>NA</td>
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<tr>
<td>Kim (2014)35</td>
<td>POAG</td>
<td>The presence of an open angle; nonglaucomatous optic disc (vertical and horizontal cup:disc ratio &lt;0.7, and intereye difference of vertical and horizontal cup:disc ratio &lt;0.2); absence of optic disc hemorrhage or retinal nerve fibre layer defect; optic disc satisfying the ISNT rule.</td>
<td>Blood HDL-c level</td>
<td>Blood HDL-c levels measured using a Hitachi 7600-110 chemistry analyzer</td>
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<tr>
<td>Chen (2014)48</td>
<td>Glaucoma</td>
<td>The major event of the research was glaucoma diagnosed based on ICD-9-CM 365 (365.1, 365.2, and 365.9).</td>
<td>Hyperlipidemia</td>
<td>ICD-9-CM code: 272</td>
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<tr>
<td>Sahinoglu-Keskek (2014)11</td>
<td>IOP</td>
<td>Noncontact tonometer.</td>
<td>Hyperlipidemia</td>
<td>Fasting triglyceride and high HDL levels analyzed with a Roche C-501 by using homogeneous colorimetric enzyme test. Triglyceride ≥ 150 mg/100 mL considered hyperlipidemia.</td>
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<td>Outcome</td>
<td>Outcome Definition/Measurement</td>
<td>Exposure</td>
<td>Exposure Definition/Measurement</td>
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<tr>
<td>Fujiwara (2015)49</td>
<td>IOP</td>
<td>Noncontact tonometer.</td>
<td>Hyperlipidemia</td>
<td>Serum total cholesterol levels determined enzymatically. Hypercholesterolemia defined as total cholesterol levels of 220 mg/dL or higher.</td>
<td></td>
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<tr>
<td>Shim (2015)52</td>
<td>NTG</td>
<td>Presence of a typical glaucomatous optic disc abnormality, including rim thinning or notching in the inferior or superior temporal area of the optic nerve head; corresponding glaucomatous visual field loss, including paracentral scotoma, arcuate scotoma, or a nasal step; a diurnal IOP measurement less than 21 mm Hg without medication; an open anterior chamber angle on gonioscopy; and no apparent secondary cause of glaucomatous optic neuropathy</td>
<td>Hypercholesterolemia</td>
<td>Laboratory blood tests</td>
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<tr>
<td>Chen (2016)50</td>
<td>POAG</td>
<td>ICD-9-CM code: 365.11. Exfoliative glaucoma or secondary glaucoma was excluded; only patients who had POAG diagnosis at least three times during the period were selected into POAG group.</td>
<td>Hyperlipidemia</td>
<td>ICD-9-CM code: 272</td>
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</tr>
<tr>
<td>Chen (2016)51</td>
<td>POAG</td>
<td>ICD-9-CM codes: 365.1x Photographs of the optic nerve were obtained using a nonmydriatic fundus camera. All glaucoma cases in the analysis were derived from participants who had at least one eye with CDR ≥ 0.6 on initial grading.</td>
<td>Hypertriglyceridemia, hypercholesterolemia</td>
<td>Fasting measurements for triglyceride and cholesterol levels. HDL &lt; 40 mg/dL in men or 50 mg/dL in women, LDL ≥ 160 mg/dL, and triglycerides ≥ 200 mg/dL</td>
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<tr>
<td>Ko (2016)50</td>
<td>Glaucoma</td>
<td>Hyperlipidemia ICD-9-CM code: 272 Fasting plasma cholesterol, and triglycerides measured using a Hitachi Automatic Analyzer 7600. Serum TGs ≥ 150 mg/dL or treatment for high TGs; HDL cholesterol &lt; 40 mg/dL for men, HDL cholesterol &lt; 50 mg/dL for women, or undergoing treatment for HDL cholesterol abnormalities</td>
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<tr>
<td>Kim (2016)36</td>
<td>POAG</td>
<td>POAG was defined as the presence of an open angle and satisfaction of any one of the following category 1 or 2 criteria: Category 1 required both a visual field defect consistent with glaucoma and either a vertical CDR ≥ 0.7 or a vertical CDR difference ≥ 0.2 between eyes; category 2 required a vertical CDR ≥ 0.9 or a vertical CDR difference ≥ 0.3 between eyes.</td>
<td>Hypertriglyceridemia, hypercholesterolemia</td>
<td>Serum markers assessed from blood samples that were collected in the morning before breakfast</td>
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<tr>
<td>Yokomichi (2016)10</td>
<td>IOP</td>
<td>Noncontact tonometer</td>
<td>Blood triglyceride levels</td>
<td>Medical records based on Korean Classification of Diseases</td>
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<tr>
<td>Rim (2017)37</td>
<td>POAG</td>
<td>The POAG group satisfied the following three criteria more than once in the ophthalmologist visit: (1) diagnosed with “primary open-angle glaucoma” (KCD, H401), (2) received a visual field test, and (3) received prescriptions for antiglaucoma medication.</td>
<td>Hyperlipidemia</td>
<td>ICD-9-CM code: 272</td>
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<td></td>
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<tr>
<td>Lee (2017)38</td>
<td>NTG</td>
<td>Patients diagnosed with NTG (ICD-9-CM: 365.12) on three or more ambulatory care claims or in an inpatient setting were eligible to ensure the validity and reliability of the diagnosis.</td>
<td>Hyperlipidemia</td>
<td></td>
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</table>

**Table 3.** Continued
for the heterogeneity. Detailed information about the subgroups and meta-regression is displayed in Table 6.

A sensitivity analysis was performed by omitting one study at a time and then calculating the pooled OR for the remaining studies. The results of this “leave-one-out” sensitivity analysis showed that the corresponding global estimation was not changed by the deletion of any single study. The pooled ORs obtained after omitting one study at a time ranged from 1.34 to 1.41 (Table 7).

We used Begg’s funnel plot and Egger’s test to detect potential publication bias. The values for \( P_{\text{Begg’s test}} \) and \( P_{\text{Egger’s test}} \) were 0.928 and 0.751, respectively, indicating a low probability of publication bias. The funnel plot for the studies is presented in Figure 3 and is symmetrical, which also indicates a low probability of publication bias.

### Intraocular Pressure and Ocular Hypertension

Five studies (six datasets) provided an association between the blood triglyceride levels and the IOP level. The pooled results showed that an increase of 10 mg/dL in blood triglyceride levels would increase the IOP by 0.016 mm Hg (95% CI = 0.009–0.024) (Fig. 4). Significant heterogeneity was detected across studies for the results of this association (\( I^2 = 92.0\% \)). The sensitivity analysis also showed that the corresponding global estimation was not changed by the deletion of any single study (Table 8). The publication bias analysis showed a low probability of publication bias, with the values of \( P_{\text{Begg’s test}} \) and \( P_{\text{Egger’s test}} \) 0.734 and 0.865, respectively. The association between blood lipid level and IOP level is displayed in Table 9. The pooled results showed that the blood total cholesterol and LDL-c levels both had a significant association with IOP level. However, we failed to detect a similar relationship between the blood HDL-c level and IOP level. When compared to the patients with non-hyperlipidemia, hyperlipidemia patients had a higher 0.51 mm Hg (95% CI = 0.18–0.83), which also showed significant heterogeneity in this meta-analysis (Fig. 5). Only one study reported hyperlipidemia and OHT; thus, we did not pool this effect.

### DISCUSSION

Many risk factors for the development of POAG have been identified, but the investigation continues. A great number of studies have reported an association between hyperlipidemia and glaucoma, or between hyperlipidemia or blood lipid level and IOP; however, no definitive link has yet been established. The aim of the present study was therefore to evaluate these potential correlations. We detected that hyperlipidemia increased the risk of glaucoma and increased the level of IOP. The results showed that both hyperlipidemia and hypertriglyceridemia displayed a significant association with glaucoma. We also found a significant association between blood lipid levels and IOP levels. An increase of 10 mg/dL in the blood triglyceride levels, blood total cholesterol levels, or blood LDL-c levels would increase the IOP by 0.016 mm Hg, 0.032 mm Hg, or 0.050 mm Hg, respectively. However, we should notice that a 100 mg/dL increase in triglycerides, which is a large increase, would increase the IOP level by only 0.16 mm Hg, and a 300 mg/dL increase in triglycerides, a very large increase, would increase the IOP level by only 0.48 mm Hg, which is not clinically significant because the error in measuring the IOP is 1 to 2 mm Hg when using the gold standard Goldmann applanation tonometry. In addition, in this meta-analysis, we also noticed that, when comparing patients with and without hyperlipidemia, the IOP of those without hyperlipidemia was only 0.5 mm Hg lower. Concerning this difference, we considered that although a relationship might exist between hypercholesterolemia and glaucoma, it is so small that it is not likely to be clinically significant. It is much more likely that this relationship occurs due to an unmeasured confounding factor because these findings were all reported in the observational studies.

The evidence demonstrating the association between hyperlipidemia and glaucoma was further validated by performing a series of analyses. Omission of individual studies one at a time and then recalculating the pooled OR for the remaining studies revealed no significant changes in the corresponding estimates, indicating the high stability and reliability of this study. Similarly, the publication bias analysis...
<table>
<thead>
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<th>First Author (Year)</th>
<th>Adjusted Variables</th>
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<tr>
<td>Girkin (2004)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Chen (2005)</td>
<td>Age, SBP, DBP, glucose</td>
</tr>
<tr>
<td>Motsko (2008)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Lin (2010)</td>
<td>Age, gender, monthly income, and level of urbanization of the community in which the patient resided</td>
</tr>
<tr>
<td>Lin (2010)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Imai (2010)</td>
<td>Age, maximum temperature, increased abdominal circumference, elevated fasting glucose level, BP</td>
</tr>
<tr>
<td>Ishikawa (2011)</td>
<td>Age, sex, DBP, IOP, and ocular perfusion pressure</td>
</tr>
<tr>
<td>Newman-Casey (2011)</td>
<td>Age, sex, race, education level, household net worth, region of residence at the time of enrollment in the medical plan, cataract, pseudophakia or aphakia, macular degeneration, diabetic retinopathy, systemic hypotension, sleep apnea, and migraine headache</td>
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<tr>
<td>Lee (2012)</td>
<td>Age, sex, SBP</td>
</tr>
<tr>
<td>Lin (2012)</td>
<td>Age, sex, BMI, waist, SBP, DBP, fasting sugar, and postprandial sugar</td>
</tr>
<tr>
<td>Kim (2014)</td>
<td>Age, sex, impaired glucose tolerance, hypertension, and baseline IOP</td>
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<td>Aptel (2014)</td>
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<td>Kim (2014)</td>
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<td>Age, sex</td>
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<td>Kim (2014)</td>
<td>Age, sex, myopia, fasting blood glucose</td>
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<tr>
<td>Chen (2014)</td>
<td>Age, sex, hypertension, diabetes, CAD, and obstructive sleep apnea</td>
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<td>Fujiiwara (2015)</td>
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</tr>
<tr>
<td>Shim (2015)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Chen (2016)</td>
<td>Age, sex</td>
</tr>
<tr>
<td>Chen (2016)</td>
<td>Age, gender, and comorbidities of diabetes, hypertension, and CAD</td>
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<tr>
<td>Ko (2016)</td>
<td>Age, gender, ethnicity, education, insurance, diabetes duration, BMI, hypertension, obstructive sleep apnea, and current smoker</td>
</tr>
<tr>
<td>Kim (2016)</td>
<td>Age, sex, IOP household income, education level, smoking status, alcohol consumption, and BMI</td>
</tr>
<tr>
<td>Yokomichi (2016)</td>
<td>Age, sex, SBP, DBP, fasting plasma glucose</td>
</tr>
<tr>
<td>Rim (2017)</td>
<td>Age, sex, hypertension, DM, chronic renal failure, atrial fibrillation, residence, income</td>
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<td>Lee (2017)</td>
<td>Age, sex, hypertension, DM, congestive heart failure, ischemic heart disease, atrial fibrilation</td>
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<tr>
<td>Lec (2017)</td>
<td>Age, sex, BMI, smoking status, refractive status, and education level</td>
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<td>Lec (2017)</td>
<td>Age</td>
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</table>

BP, blood pressure; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus.

showed a low probability of publication bias, which also implied the robustness of this meta-analysis.

In the analysis of the association between hyperlipidemia and glaucoma, the subgroup analyses showed that this association existed for case-control and longitudinal designs, but not for cross-sectional design studies. For this reason, we considered that the cross-sectional design is subject to significant selection bias, which could mask a real association. Separate analyses based on different exposures indicated that patients with hypercholesterolemia had no increased risk of glaucoma, which differed from the findings for patients with hyperlipidemia and hypertriglyceridemia. The exact reasons for this difference were not clear, so additional basic research is needed. Among the included studies, some only included patients with POAG, some included patients with NTG, and others included glaucoma without detailing the type. The pooled results suggested that hyperlipidemia increased the risk of POAG and glaucoma incidence but did not influence NTG incidence. NTG is a special type of POAG characterized by a normal IOP, so the pathomechanisms of NTG may differ from those of POAG. We speculate that NTG is less likely to be directly related to hyperlipidemia. Other subgroup analyses based on the number of adjustments for covariates, publication year, and sample size showed that the pooled results of all the different subgroups were consistent with the overall result.

To date, the mechanisms explaining how hyperlipidemia could increase the risk of the progression of glaucoma are unclear. One possible explanation might be that excess blood lipid levels would increase the episcleral venous pressure and blood viscosity, resulting in a consequent decrease in outflow facility. Similarly, a positive association was determined between IOP level and blood lipid level in the present meta-analysis. Therefore, the possible reasons for the association between IOP level and triglyceride level might be the same as those for the association between hyperlipidemia and the risk of glaucoma. This may also explain why hyperlipidemia is related only to POAG and glaucoma, but not to NTG.

Genetic predisposition might be another important reason for this relationship. For example, ABCA1, an ATP-binding cassette (ABC) subfamily A exporter, mediates the cellular efflux of phospholipids and cholesterol to the extracellular acceptor apolipoprotein A-I (apoA-I) for generation of nascent HDL, cavinol 1, which also had been proven involved in the lipid metabolism. Meanwhile, the loci of both of these genes were also detected and had a significant correlation with the risk of POAG. These correlations might imply a potential relationship between hyperlipidemia and glaucoma.

Heterogeneity is always found in a meta-analysis due to variabilities between the included studies. Thus, the assessment of heterogeneity is always a crucial issue in a meta-analysis. The between-studies variability is due to the influence of an indeterminate number of characteristics that vary among the studies, such as those related to the characteristics of the samples, variations in the treatments used, variations in the design quality, and so on. Notably, substantial heterogeneity was detected among the studies in the meta-analysis that assessed the association between hyperlipidemia and glaucoma. We performed several stratified analyses of study design, exposure, geographical area, outcome, and adjustments for covariates, sample size, and publication year to investigate the sources of this heterogeneity. However, substantial heterogeneity still existed in all subgroups. The “leave-one-out” sensitivity analysis also indicated that no single study was the main source of the heterogeneity. Meta-regression also failed to distinguish the exact source of the heterogeneity. Several factors, such as different characteristics of the populations, different quality of the included studies, different methods used to ascertain outcomes and exposure, different sample
sizes, different data collection methods, and other unknown factors, were likely to have contributed to the high degree of heterogeneity in the results. For example, patients with hyperlipidemia are frequently treated with statins, and several studies have reported on the relationship between the use of statins and the risk of glaucoma.\(^{18,22,25}\) Some studies found that individuals with hyperlipidemia who used statins had a reduced risk of POAG, whereas individuals with hyperlipidemia who used non-statin cholesterol-lowering medications did not have a lowered risk of POAG. However, in some of the included studies, some patients used non-statin cholesterol-lowering medications and others used statins to lower their cholesterol levels. Thus, the use or nonuse of statins in hyperlipidemia patients might be the potential confounding factor, and it might also be the source of the heterogeneity. However, detailed information on statin use was not available in the original studies included in the meta-analysis. Thus, we failed to perform an additional analysis of the association between hyperlipidemia and glaucoma, such as in the subgroups based on statin use and no statin use, to clarify if statin use was the source of the heterogeneity. The significant heterogeneity among studies might affect the validity of the pooled results and the conclusions drawn from the meta-analysis. Thus, the conclusions should be interpreted with caution.

This study has several advantages. First, to date, this paper presents the results of a relatively large analysis that explores the association between hyperlipidemia-related exposure and glaucoma-related outcomes. Second, the sensitivity analysis and the publication bias analysis confirmed the reliability and robustness of the pooled results. Third, the study-level data allowed meaningful stratified analyses. This analysis therefore provides the most up-to-date information on the hyperlipidemia and glaucoma relationship.

Despite the strengths of this study, several limitations should also be acknowledged. First, although the results of this meta-analysis may be statistically significant, they are unlikely to be clinically significant. Second, the analysis of the association between blood lipid level (HDL-c, LDL-c, total cholesterol) and IOP level was based on only one or two studies, which precludes drawing a robust conclusion. In the future, larger and more rigorous studies are required to clarify the association between blood lipid level and IOP level. Third, the subjects included in several studies were those who had undergone a self-paid health examination and this could have led to selection bias. We speculated that the participants may represent only some portion of the groups, and that the IOP level and prevalence of glaucoma in these participants may differ from those of the general population. Fourth, the definition of exposure and outcome in some included studies that were entirely dependent on International Classification of Disease (ICD) codes may be less accurate when compared with those obtained through a standardized procedure. Fifth, not all the studies controlled for potential confounding variables such as myopia. For example, myopia is a known risk factor of POAG. A meta-analysis has also proved that individuals with myopia have an increased risk of developing open-angle glaucoma.\(^{60}\) Thus, the association between hyperlipidemia and the glaucomatous process may be

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\(Y\), yes; \(N\), no.
different in subjects with myopia and without myopia. However, detailed information on myopia was not available in the original studies. We cannot perform further analysis of the association between hyperlipidemia and glaucoma such as subgroup based on subjects with and without myopias.

However, the results from subgroup analysis restricted to studies adjusted for more than three covariates or less than three covariates showed a significant association between hyperlipidemia and glaucoma, which suggested the stability of the results. Sixth, our analysis failed to find any significant association between hyperlipidemia and glaucoma in some of the subgroups. The relatively small number of included studies in some subgroups might be the main reason for this result, and the conclusion should be interpreted with caution.

Seventh, in the IOP analysis, most of the studies used a noncontact tonometer to measure the IOP levels; only one study used Goldmann applanation tonometry. While the Goldmann application is the gold standard for measuring IOP, clearly the majority of the data reported in the studies in this meta-analysis were obtained using noncontact tonometry. However, the sensitivity analysis showed that the corresponding global estimation was not changed by the deletion of any single study. Finally, significant heterogeneity was detected among the studies. Although we performed a series of analyses, such as “leave-one-out” sensitivity analyses, subgroup analysis, and meta-regression, we still failed to identify the source of the heterogeneity. The quality of the included studies, the methods used to ascertain outcomes and exposure, and other unknown factors varied across studies and could explain this heterogeneity.

In conclusion, the current limited evidence suggests that hyperlipidemia is significantly associated with an increased risk of glaucoma and that hyperlipidemia and increased blood lipid levels are associated with increased IOP. These study findings provide the clinician with useful information about the treatment of hyperlipidemia to prevent the incidence of glaucoma. Despite these encouraging findings, the inherent limitations of the included studies should be considered, and the conclusions should be interpreted with caution.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. Studies</th>
<th>Random-Effects Model</th>
<th>Overall Effect</th>
<th>Test of Homogeneity</th>
<th>Meta-Regression</th>
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<td>OR 95% CI</td>
<td>Z  P</td>
<td>P  I², %</td>
<td>P</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Case-control</td>
<td>4</td>
<td>1.51 1.23, 1.86</td>
<td>3.89 &lt;0.001</td>
<td>85.63 96.0 &lt;0.001</td>
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<td>Cross-sectional</td>
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<td>1.21 0.98, 1.49</td>
<td>1.75 0.080</td>
<td>34.51 74.0 &lt;0.001</td>
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<tr>
<td>Nested case–control/cohort</td>
<td>7</td>
<td>1.50 1.06, 2.11</td>
<td>2.29 0.020</td>
<td>256.33 98.0 &lt;0.001</td>
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<td>Exposure</td>
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<td>Hyperlipidemia</td>
<td>12</td>
<td>1.40 1.14, 1.71</td>
<td>3.27 &lt;0.001</td>
<td>840.44 98.7 &lt;0.001</td>
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<tr>
<td>Hypercholesterolemia</td>
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<td>0.98 0.326</td>
<td>14.10 71.6 0.007</td>
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<tr>
<td>Hypertriglyceridemia</td>
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<td>1.42 1.04, 1.93</td>
<td>2.19 0.028</td>
<td>7.51 60.1 0.057</td>
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<td>Geographical area</td>
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<td>North America</td>
<td>5</td>
<td>1.35 0.93, 1.95</td>
<td>1.59 0.112</td>
<td>194.92 97.9 &lt;0.001</td>
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</tr>
<tr>
<td>Europe</td>
<td>2</td>
<td>1.55 0.99, 2.45</td>
<td>1.90 0.058</td>
<td>6.65 85.0 0.010</td>
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<tr>
<td>Asia</td>
<td>14</td>
<td>1.35 1.17, 1.56</td>
<td>4.02 &lt;0.001</td>
<td>115.87 88.8 &lt;0.001</td>
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<td>Outcome</td>
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<td>POAG</td>
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<td>822.04 98.7 &lt;0.001</td>
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<td>NTG</td>
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<td>0.96 0.358</td>
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<tr>
<td>Glaucoma</td>
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<td>3.41 0.001</td>
<td>3.64 17.5 0.305</td>
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<td>Adjustment for covariates</td>
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<td>&gt;3 factors</td>
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<td>3.97 &lt;0.001</td>
<td>82.14 91.5 &lt;0.001</td>
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<tr>
<td>Sample size</td>
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<tr>
<td>&gt;10,000</td>
<td>10</td>
<td>1.36 1.09, 1.70</td>
<td>2.71 0.007</td>
<td>831.92 98.9 &lt;0.001</td>
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<tr>
<td>≤10,000</td>
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<td>1.37 1.09, 1.73</td>
<td>2.72 0.006</td>
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<td>Publication year</td>
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<td>1.37 1.16, 1.61</td>
<td>3.15 0.002</td>
<td>55.39 83.8 &lt;0.001</td>
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Table 7. Sensitivity Analysis of the Meta-Analyses of Hyperlipidemia and Glaucoma

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<th>Random-Effects Model</th>
<th>Test of Homogeneity</th>
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<tr>
<td></td>
<td>OR 95% CI</td>
<td>Q  P  I², %</td>
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<td>1.37 1.16, 1.61</td>
<td>690.83 97.0 &lt;0.001</td>
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<td>Girkin (2004)44</td>
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<td>867.73 97.8 &lt;0.001</td>
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<td>Motsko (2008)54</td>
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<td>858.18 97.8 &lt;0.001</td>
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<td>Lin (2010)8</td>
<td>1.34 1.15, 1.56</td>
<td>391.61 95.1 &lt;0.001</td>
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<td>Lin (2010)55</td>
<td>1.39 1.17, 1.64</td>
<td>870.26 97.8 &lt;0.001</td>
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<tr>
<td>Ishikawa (2011)52</td>
<td>1.38 1.16, 1.63</td>
<td>872.19 97.8 &lt;0.001</td>
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<td>Newman-Casey (2011)9</td>
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<td>216.44 91.2 &lt;0.001</td>
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<td>Kim (2014)34</td>
<td>1.38 1.16, 1.64</td>
<td>870.46 97.8 &lt;0.001</td>
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<td>Chen (2016)51</td>
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<td>872.32 97.8 &lt;0.001</td>
</tr>
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<td>Ko (2016)39</td>
<td>1.38 1.17, 1.63</td>
<td>870.78 97.8 &lt;0.001</td>
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<td>1.39 1.17, 1.64</td>
<td>870.35 97.8 &lt;0.001</td>
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<td>1.37 1.15, 1.62</td>
<td>872.36 97.8 &lt;0.001</td>
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<td>Lee (2017)39</td>
<td>1.41 1.19, 1.67</td>
<td>852.25 97.8 &lt;0.001</td>
</tr>
<tr>
<td>Lee (2017)39</td>
<td>1.36 1.15, 1.61</td>
<td>872.15 97.8 &lt;0.001</td>
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</tbody>
</table>
**FIGURE 3.** Funnel plot of the included studies evaluating the association between hyperlipidemia and glaucoma.

**FIGURE 4.** Change in intraocular pressure associated with a 10 mg/dL increase in blood triglyceride level.
Table 8. Sensitivity Analysis of the Meta-Analyses of Change in IOP (mm Hg) Associated With a 10 mg/dL Increase in Blood Lipid Level

<table>
<thead>
<tr>
<th>Study Excluded</th>
<th>OR</th>
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<th>Q</th>
<th>I² (%)</th>
<th>P</th>
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<td>0.009, 0.024</td>
<td>62.19</td>
<td>92.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Chen (man) (2014)</td>
<td>0.016</td>
<td>0.008, 0.024</td>
<td>62.15</td>
<td>93.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chen (woman) (2014)</td>
<td>0.017</td>
<td>0.010, 0.025</td>
<td>60.70</td>
<td>93.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lee (2012)</td>
<td>0.013</td>
<td>0.006, 0.020</td>
<td>52.08</td>
<td>92.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lin (2012)</td>
<td>0.019</td>
<td>0.009, 0.028</td>
<td>59.50</td>
<td>93.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kim (2014)</td>
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<td>0.006, 0.024</td>
<td>14.77</td>
<td>72.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Yokomichi (2016)</td>
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<td>0.009, 0.029</td>
<td>18.99</td>
<td>78.9</td>
<td>0.001</td>
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</table>

Table 9. Change in IOP Associated With a 10 mg/dL Increase in Blood Lipid Level

<table>
<thead>
<tr>
<th>Blood Lipid Level</th>
<th>No. Studies</th>
<th>Random-Effects Model</th>
<th>Overall Effect</th>
<th>Test of Homogeneity</th>
</tr>
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<td></td>
<td></td>
<td>WMD</td>
<td>Z</td>
<td>P</td>
</tr>
<tr>
<td>Blood triglyceride level</td>
<td>5</td>
<td>0.016</td>
<td>0.009, 0.024</td>
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<tr>
<td>Blood HDL-c level</td>
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<td>0.022</td>
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<tr>
<td>Blood total cholesterol level</td>
<td>2</td>
<td>0.032</td>
<td>0.014, 0.050</td>
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<td>Blood LDL-c level</td>
<td>1</td>
<td>0.050</td>
<td>0.011, 0.089</td>
<td>2.51</td>
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</tbody>
</table>

Figure 5. The difference in intraocular pressure comparing patients with hyperlipidemia with those without hyperlipidemia.
**Acknowledgments**

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**References**


