## A Meta-Analysis of Glaucoma Risk in Hyperlipidemic Individuals: A Critical Problem in Design

Because glaucoma is the leading cause of irreversible visual impairment and is usually undetectable until advanced stages,[1] investigations on modifiable factors associated with glaucoma risk are warranted. The recent article by McCann et al.,[2] which reported on a meta-analysis of observational studies evaluating the effects of statins on glaucoma, demonstrated that "short-term statin use is associated with a reduced incidence of glaucoma." This is, to our knowledge, the first comprehensive review of statin use and glaucoma risk, but its implication would be limited because it is uncertain whether hyperlipidemia itself increases the risk of developing glaucoma.

We conducted a meta-analysis focused on studies that investigated the association between hyperlipidemia and glaucoma following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. A systematic literature search of PubMed, EMBASE, and the Cochrane Library was performed independently by two investigators. The search terms were "lipid-related," "glaucoma related," and "outcome-related." The inclusion criteria were obviously defined exposure to lipid abnormalities, reported glaucoma incidence, and reported relative risk or odds ratio. Through a rigorous searching process (Supplementary Fig. S1), three relevant studies[3–5] were included in the final analysis (Supplementary Table S1). Pooled odds ratios demonstrated that hyperlipidemia did not increase the incidence of glaucoma (relative risk, 1.40; 95% confidence interval [CI], 0.73–2.68; Fig.); there was no evidence of publication bias (Egger's test, $P$ for bias = 0.370).

In our analysis, all of the included studies did not refine the effects of hyperlipidemia from those of lipid-lowering drugs (i.e., mixed results as a metabolic component or not considered a drug effect; this may have contributed to the high heterogeneity). This flaw was also the same in the study of McCann et al.[2] If the opposite directions in these two meta-analyses are true, the effect sizes would be underestimated in both studies. To understand the role of lipid dysregulation and its control of glaucoma risk, a clear definition of case (hyperlipidemic individuals not taking lipid-lowering drugs) and control groups in the cohort or case–control studies, if not the randomized controlled trials, must be done. In addition, a tight connection to other metabolic abnormalities (e.g., hypertension, type 2 diabetes, or obesity)[6] should be considered when designing a study and/or analyzing the data.

Apart from the indirect hypothesis of statin's neuroprotective action,[7] there have been very few basic research studies indicating that lipid abnormalities alone increase intraocular pressure or the risk of glaucoma. A plausible mechanism is that excess intraorbital fat and increased blood viscosity in obesity, usually clustered with lipid abnormalities, may disturb the aqueous outflow capacity, which consequently increases the intraocular pressure.[8,9] Clinically, beyond the simple snapshot association,[10] a recent large retrospective study demonstrated a significant longitudinal relationship between cholesterol levels and intraocular pressure.[11] However more well-designed clinical studies to explore the role of hyperlipidemia and collaborative basic research are warranted. Such studies will provide a rationale for cooperative care of patients by ophthalmologists and metabolic physicians.

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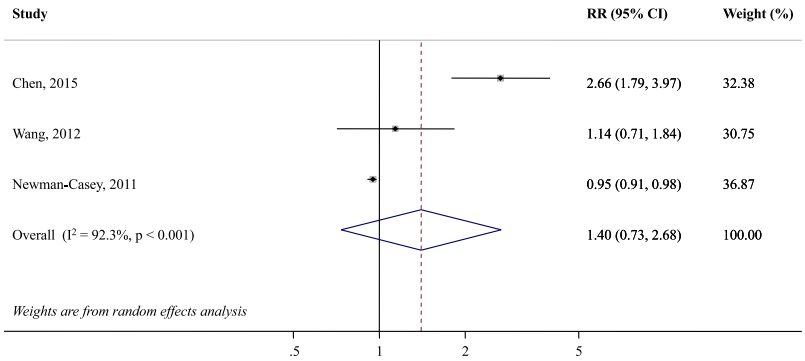


**Figure.** Forest plot showing the impact of hyperlipidemia on glaucoma risk. RR, relative risk.





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