Author Response: Statin Use and Open-Angle Glaucoma: Evidence From Observational Studies

We read with interest the letter titled "Statin Use and Open-Angle Glaucoma: Evidence From Observational Studies" from Ng and colleagues.[1] We would like to thank the authors for the constructive scrutiny of our study design[2] in relation to (1) placement of studies in the meta-analysis, (2) the process of appraising the quality of evidence of the included studies, and (3) appropriateness of inclusion of studies in the systematic review. Below we aim to address the points raised by Ng and colleagues.

1. Placement of studies in the meta-analysis

We thank the authors for raising the discussion regarding our assignment of "suspected glaucoma conversion to open-angle glaucoma (OAG)" as "progression" rather than "incidence." In light of the definition of OAG suspect in the American Academy of Ophthalmology Preferred Practice Pattern Guidelines,[3] we agree that there is room for discussion around this point. We would like to thank the authors for the amended meta-analysis, which includes "suspect to OAG" in the forest plot on incidence of glaucoma and statin use > 2 years. As the authors have noted, development of "outside normal limits" on Humphrey Field Analyzer hemifield measurement should be classified as "incidence of OAG" rather than "progression"; therefore we have added the results of De Castro et al.[4] to the forest plot on incidence of glaucoma and statin use > 2 years (Fig. 1). For the purposes of our analysis, controls were the "did not take statins" ($n = 39$) and "aspirin only" ($n = 13$) groups. Those who took statins were the "statins only" ($n = 12$) and "statins + aspirin" ($n = 12$) groups. We also added "suspect to OAG" analysis to the forest plot on incidence of glaucoma and statin use ≤ 2 years (Fig. 2).

2. The process of appraising the quality of evidence of the included studies

We thank the authors for the revision of the Newcastle Ottawa Scale (NOS) scores for the cohort studies and accept most of their interpretations. However, we have given a mark to De Castro et al.[4] for "demonstration that outcome of interest was not present at start of study" because eligible participants had "no visual field defect" at baseline but had hemifield defects when they became OAG cases (Table 1). It is debatable that De Castro et al.[4] should not be given a mark for "ascertainment of exposure" because a documented medical history could be interpreted as a secure record; however, we have agreed with the authors' conservative approach. In the case–control study NOS scores, a study received a mark for "additional factors the studies control for" only if diabetes and other ocular parameters were controlled for as suggested by the authors for cohort studies (Table 2). The cutoff point for the presence of bias was changed from ≤7 to <6 because ≤7 would exclude all the studies from the meta-analysis. The figure <6 was chosen because the mean of the NOS scores of the six studies included in the meta-analyses was 6.

3. Appropriateness of inclusion of studies in the systematic review

We accept that the case–control study by Owen et al.[10] defined cases based on diagnostic codes for glaucoma, prescription for glaucoma medications, and ocular hypertension, and this was described in our study (Table 3 in the article). We agree that there is a lack of information on the proportion of cases with diagnostic code for ocular hypertension. We also accept that ocular hypertension is not a subtype of glaucoma and therefore there is a valid argument for the exclusion of the study from the meta-analyses. However, we believe that discussion of the results in the systematic review and exploration of the implications of removing these results in sensitivity analyses would be pragmatic given the relative lack of studies identified.

We agree that the cross-sectional study by Khawaja et al.[12] was not able to infer a causal relationship between statin use and IOP due to its cross-sectional design. However, we disagree that this is justification for the study to be excluded from the systematic review. The identification of concurrent beta-blocker therapy as the explanation for the association between statin therapy and IOP is an important finding.

SENSITIVITY ANALYSIS

A revised sensitivity analysis was conducted following the changes to the NOS scoring and changes to the studies that were included in the forest plots. To address the issue of ocular hypertension in the case mix in the case–control study by Owen et al.,[10] sensitivity analysis was performed on meta-analyses that included the results of this study. Removal of Owen et al.[10] from the meta-analysis of glaucoma incidence in statin exposure for ≤2 years resulted in no change to the statistical significance of the result (with Owen et al.,[10] odds ratio [OR] 0.96, 95% confidence interval [CI] 0.94, 0.98; without Owen et al.,[10] OR 0.96, 95%CI 0.93, 0.98). Removal of

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
McGwin et al. (greater than 24m)	-0.5125	0.2189	5.1%	0.60 [0.39, 0.92]	
Stein et al. (no OAG to OAG)	-0.0797	0.0304	47.6%	0.92 [0.87, 0.98]	
Stein et al. (suspect to OAG)	-0.0973	0.0357	44.8%	0.91 [0.85, 0.97]	
Marcus et al.	-0.7765	0.3537	2.1%	0.46 [0.23, 0.92]	
De Castro et al.	-0.7419	0.6995	0.5%	0.48 [0.12, 1.88]	
Total (95% CI)			100.0%	0.88 [0.80, 0.97]	

Heterogeneity: Tau² = 0.00; Chi² = 8.46, df = 4 (P = 0.08); I² = 53%
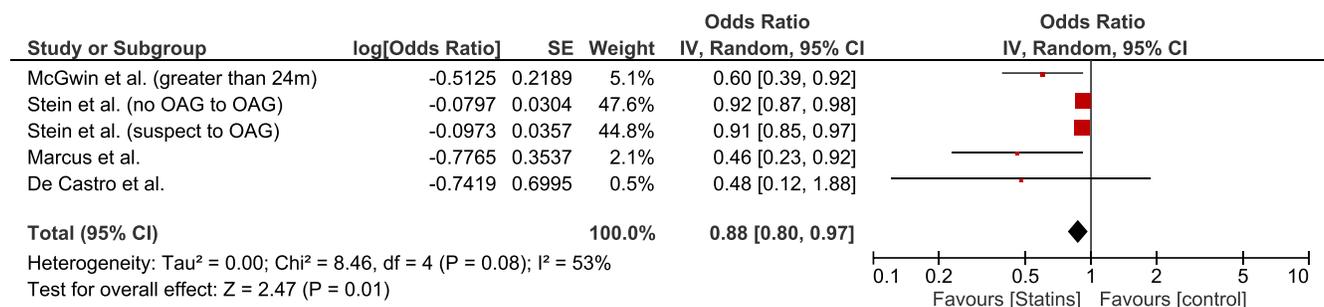Test for overall effect: Z = 2.47 (P = 0.01)

FIGURE 1. Forest plot of incidence of glaucoma and statin use > 2 years versus control. Marcus et al.[7]: Upper limit of 95%CI (0.92) is not exactly equivalent to upper limit of 95%CI in Table 3 of original article (0.94) due to rounding in meta-analysis software.
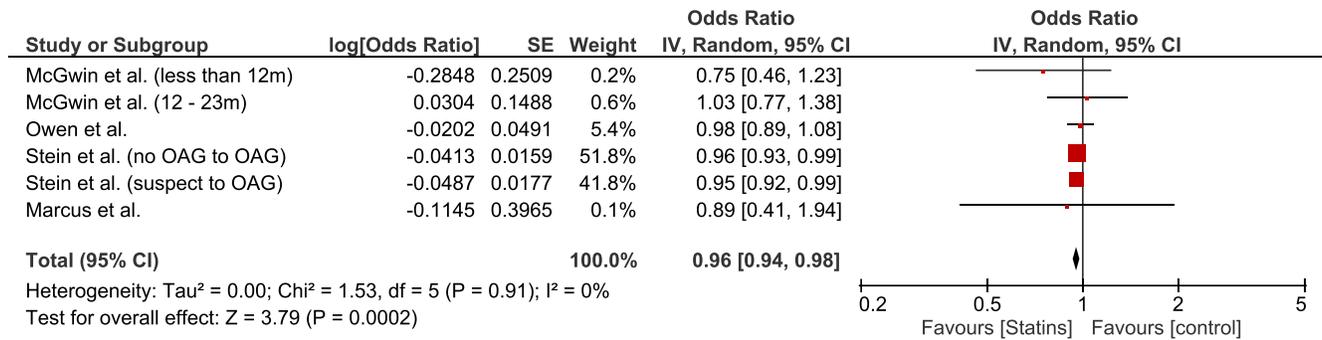
Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
McGwin et al. (less than 12m)	-0.2848	0.2509	0.2%	0.75 [0.46, 1.23]	
McGwin et al. (12 - 23m)	0.0304	0.1488	0.6%	1.03 [0.77, 1.38]	
Owen et al.	-0.0202	0.0491	5.4%	0.98 [0.89, 1.08]	
Stein et al. (no OAG to OAG)	-0.0413	0.0159	51.8%	0.96 [0.93, 0.99]	
Stein et al. (suspect to OAG)	-0.0487	0.0177	41.8%	0.95 [0.92, 0.99]	
Marcus et al.	-0.1145	0.3965	0.1%	0.89 [0.41, 1.94]	
Total (95% CI)			100.0%	**0.96 [0.94, 0.98]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.53, df = 5 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.79 (P = 0.0002)

0.2   0.5   1   2   5
Favours [Statins]   Favours [control]

FIGURE 2.   Forest plot of incidence of glaucoma and statin use ≤ 2 years versus controls. McGwin et al.[9] (12–23 months): Upper limit of 95%CI (1.38) is not exactly equivalent to upper limit of 95%CI in Table 3 of original article (1.39) due to rounding in meta-analysis software.

TABLE 1.   Newcastle-Ottawa Scale: Cohort Studies

Domain	DeCastro et al.[4] 2007	Iskedjian et al.[5] 2009	Leung et al.[6] 2010	Marcus et al.[7] 2012	Stein et al.[8] 2012
Selection					
Representativeness of the exposed cohort	No description of the derivation of the cohort (university-based eye center) (0)	Somewhat representative of the average patient receiving prescription benefits in Regie de l'assurance maladie du Quebec (1)	No description of the derivation of the cohort (university-based eye center) (0)	No description of the derivation of the cohort (0)	Selected group of users (0)
Selection of the nonexposed cohort	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)	Drawn from the same community as the exposed cohort (1)
Ascertainment of exposure	Medication history collected from medical records and confirmed by phone call (0)	Secure record (1)	Secure record (1)	Secure record (1)	Secure record (1)
Demonstration that outcome of interest was not present at start of study	Yes (1)	Yes (1)	No/NA (progression as the only outcome) (0)	Yes (1)	Yes (1)
Comparability					
Study controls for the most important factor*	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Study controls for any additional factor†	DM, CCT, IOP, refractive error (1)	No (0)	DM, CCT, IOP (1)	IOP, myopia (0)	DM (0)
Outcome					
Ascertainment of outcome	Independent assessment (1)	Record linkage (1)	Independent assessment (1)	Independent assessment (1)	Record linkage (1)
Was follow-up long enough for outcomes to occur?	Yes (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)
Adequacy of follow-up of cohort	Complete follow-up—all subjects accounted for (1)	Complete follow-up—all subjects accounted for (1)	Subject lost to follow-up unlikely to introduce bias: 0.4% lost to follow-up (1)	Complete follow-up—all subjects accounted for (1)	Complete follow-up—all subjects accounted for (1)
Total score	7	8	7	7	7

CCT, central corneal thickness; DM, diabetes mellitus; IOP, intraocular pressure.
* If the study adjusted for age, one mark was scored.
† If the study adjusted for diabetes mellitus and relevant ocular parameters (central corneal thickness, intraocular pressure, or refractive error), one mark was scored.

TABLE 2. Newcastle-Ottawa Scale: Case–Control Studies

Domain	McGwin et al.[9] 2004	Owen et al.[10] 2010	Chen et al.[11] 2015
Selection			
Is case definition adequate?	Yes, e.g., record linkage or based on self-reports (0)	Yes, e.g., record linkage or based on self-reports (0)	Yes, e.g., record linkage or based on self-reports (0)
Representativeness of cases	Potential for selection bias or not stated (0)	Consecutive or obviously representative series of cases (1)	Potential for selection bias or not stated (0)
Selection of controls	Hospital controls (0)	Community controls (1)	Community controls (1)
Definition of controls	No history of disease, endpoint (1)	No history of disease, endpoint (1)	No history of disease, endpoint (1)
Comparability			
Comparability of cases and controls on the basis of design or analysis			
Most important factor study controls for*	Age (1)	Year of birth (1)	Age (1)
Study controls for any additional factor†	Diabetes (0)	Diabetes (0)	Diabetes (0)
Exposure			
Ascertainment of exposure	Secure record (1)	Secure record (1)	Secure record (1)
Same method of ascertainment for cases and controls	Yes (1)	Yes (1)	Yes (1)
Nonresponse rate	Same rate for both groups (1)	Same rate for both groups (1)	Same rate for both groups (1)
Total	5	7	6

CCT, central corneal thickness; DM, diabetes mellitus; IOP, intraocular pressure.

* If the study adjusted for age, one mark was scored.

† If the study adjusted for diabetes mellitus and relevant ocular parameters (central corneal thickness, intraocular pressure, or refractive error), one mark was scored.

Owen et al.[10] from the meta-analysis of glaucoma incidence in statin therapy not stratified by length of exposure also resulted in no change to the statistical significance of the result (with Owen et al.,[10] OR 0.94, 95%CI 0.83, 1.06; without Owen, et al.[10] OR 0.86, 95%CI 0.66, 1.12). McGwin et al.[9] was removed from the meta-analyses in which it was included because it scored <6 in NOS. Removal of the two McGwin et al.[9] results from the meta-analysis of glaucoma incidence in statin exposure for ≤2 years resulted in no difference to the overall estimate, which remained OR 0.96 (95%CI 0.94, 0.98). Removal of McGwin et al.[9] from the meta-analysis of glaucoma incidence in statin exposure for >2 years resulted in a small change to the overall estimate but no change to the statistical significance of the result (with McGwin et al.,[9] OR 0.88 95%CI 0.80, 0.97; without McGwin et al.,[9] OR 0.91, 95%CI 0.84, 0.98). Removal of both McGwin et al.[9] and Owen et al.[10] from the meta-analysis of glaucoma incidence in statin exposure for ≤2 years resulted in no change to the statistical significance of the result (without both, OR 0.96, 95%CI 0.93, 0.98). Removal of both McGwin et al.[9] and Owen et al.[10] from the meta-analysis of glaucoma incidence in statin therapy not stratified by length of exposure resulted in no change to the statistical significance of the result despite the change in the overall estimate and precision (without both, OR 0.79, 95%CI 0.43, 1.45).

CONCLUSIONS

Analysis of the data with inclusion of "suspect to OAG" as "incidence" rather than "progression" supports our initial conclusion that short-term statin therapy is associated with reduced incidence of glaucoma. However, the reanalysis following the suggestions by Ng et al.[1] has revealed that long-term statin therapy may be also associated with reduced incidence of glaucoma. As in our initial review we recommend caution when interpreting the results of the meta-analysis because the results of the heavily weighted Stein et al.[8] study are susceptible to misclassification bias and its generalizability is limited to the population with hyperlipidemia. We would again like to thank Ng and colleagues for bringing to our attention some of the limitations of the original analysis and their valuable expertise.

Paul McCann
Ruth E. Hogg
Augusto Azuara-Blanco

Centre for Public Health, Queens University Belfast, Belfast, United Kingdom.
E-mail: pmccann45@qub.ac.uk

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