Author Response: Comparison of Risk Factor Profiles for Primary Open-Angle Glaucoma Subtypes Defined by Pattern of Visual Field Loss: True Risk Factors or Arbitrary Definition?

We thank Ratnarajan et al.[1] for their interest in our work[2] and for the opportunity to clarify aspects of the study. First Ratnarajan et al.[1] were concerned that our definitions for the primary open-angle glaucoma (POAG) with paracentral and peripheral visual field (VF) defect groups were arbitrary and that we did not follow predefined international glaucoma guidelines. Importantly, Ratnarajan et al.[1] were concerned that because the paracentral VF defect group included those with paracentral and peripheral VF defects that our results mainly reflected differences in association with later versus earlier diagnosis rather than with different VF loss patterns. To the best of our knowledge, we are not aware of any clear predefined internationally accepted guidelines for distinguishing POAG subtypes by VF patterns. Absent such guidelines, we allowed those with both types of VF defects for the paracentral group because this definition balanced the need for accuracy with statistical power. Our cases were incident POAG cases, with generally mild early VF loss, and in this setting, among those with any paracentral loss, those with isolated paracentral loss only was relatively uncommon (21%), whereas most with clear paracentral loss also had some peripheral VF defects; thus, we included those with isolated as well as early paracentral and peripheral defects to maximize power. However, our definition is supported by several key clinical observations. For example, compared to cases of peripheral VF loss only, our paracentral VF loss group showed lower mean intraocular pressure (IOP), higher cup-to-disk ratio at diagnosis, and significantly (P = 0.0002) more defects in the superior than in the inferior hemifield, which is entirely consistent with reports from studies that have included only those with isolated paracentral VF loss.[3,4] Also, in a recently published computerized machine learning approach to objectively categorize VFs, 13,213 Humphrey VFs were classified into 17 archetypes of VF loss patterns. Interestingly, in the paper by Elze et al.,[5] VF archetype number 14 was most representative of an archetype of paracentral VF loss and indeed included paracentral, Bjerrum region, and nasal step involvement, closely resembling our definition.

A second concern was that VF mean deviation (MD) parameters were not provided in the two groups. When we evaluated a random sample of the paracentral VF loss cases (n = 31) and peripheral VF loss cases (n = 54), we observed that the MD was −4.5 (SD = 3.2) dB in the paracentral VF loss group and −2.7 (SD = 2.4) dB in the peripheral VF loss group, with 74% and 91% considered having mild disease severity (i.e., MD better than −6 dB based on the Hodapp-Anderson-Parrish grading scheme[6]) in the paracentral and peripheral VF groups, respectively; this refutes the claim that our paracentral VF loss group consisted mainly of those with advanced loss. In contrast, in a random sample (n = 18) of cases that we censored in analyses due to advanced loss with both paracentral and peripheral defects, the MD was −10.6, indicative of moderate disease severity, based on the Hodapp-Anderson-Parrish grading scheme.[6]

A third concern was our reliance on self-reporting for glaucoma case confirmation. We agree that this was a limitation, which was mentioned in the Discussion. However, it should be emphasized that although the first step in the case confirmation involves self-reporting, all self-reports were confirmed by a standard confirmation protocol using objective data from medical records. Also, the universal eye examination restriction imposed on all eligible person-time of observation, the standardized protocol for confirmation of self-reports and continued longitudinal follow-up of our cohort of medically trained and motivated health professionals helps to minimize underascertainment of glaucoma.

Ratnarajan et al.[1] commented on the lack of details of eye examination information (especially "IOP measurement [baseline and throughout study time] and VF parameters"). To elaborate, the only eye examination details we sought were those for the specific eye examinations where glaucoma was initially diagnosed; during general cohort follow-up, we simply used participants' self-reports of eye examinations to restrict person-time, and at baseline, we excluded those who self-reported prevalent glaucoma, without requiring any details on eye examinations. For confirming new reports of glaucoma, we used a standardized protocol that relied on eye examination information (via our glaucoma questionnaire or medical records) from the diagnosing physicians. We collected information about maximum untreated IOP at diagnosis, but it was not a part of the case definition, so we did not require a certain type of IOP measurement, although the majority (>95%) were from Goldmann applanation tonometry. A key to case confirmation was presence of reproducible VF defects on reliable tests. For VF defects, the type of perimetry was not restricted; however, full static threshold testing (24-2 or 30-2 VFs) was documented in >95%, and kinetic VFs in <1%. For static threshold or suprathreshold tests, we used the following reliability definitions: fixation loss ≤33%, false positive rate ≤20%, and false negative rate of ≤20%. For kinetic VFs, a VF test was considered reliable unless the examiner noted to the contrary. In addition to VFs, we required (1) that slit lamp biomicroscopy show no signs in either eye of pigment dispersion syndrome, uveitis, exfoliation syndrome, trauma, or rubeosis; (2) that gonioscopy showed that the filtration angle was not occludable in either eye (>70% of cases) or documentation of pupil dilation in a slit lamp exam without subsequent adverse events; and 3) that there were no other conditions that could cause the observed VF defects.

Another issue was the possible bias due to the large proportion of self-report of glaucoma that was excluded in the final analysis. We agree that the confirmation rate was low; however, methodologically, in an observational study setting where underascertainment of disease is a concern, there are two critical requirements: (1) a standardized disease confirmation procedure that is not dependent on exposures and (2) a very high specificity (or low false positives) in outcome definition.[7] When we compared those participants who self-reported glaucoma, confirmed and included in the analysis, with those who self-reported but were not confirmed, we observed similar characteristics (e.g., mean age at self-reported glaucoma and body mass index were virtually identical), minimizing the likelihood of bias.

Ratnarajan et al.[1] described our study as "retrospective," but we respectfully disagree. In epidemiology, the sole distinction between a retrospective and a prospective cohort study is whether the outcome of interest has occurred at the time investigators initiate a study.[8] We clearly indicated that we began our study in 1986, when we determined a subcohort of nurses' health study (NHS) and health professionals' follow-up study (HPFS) participants who were free of glaucoma and categorized them according to baseline exposure, and then we

iovs.arvojournals.org | ISSN: 1552-5783

Investigative Ophthalmology & Visual Science

followed them prospectively to determine who newly developed disease for calculating relative incidence by exposure categories. With questionnaires, we updated our data every two years to start with a disease-free group who were categorized by updated exposure and then followed for new disease; this was repeated for 20+ years. Thus, glaucoma cases occurred after we began the study, making this a prospective study.

Another issue was whether the study was "population-based," as it included "nonrepresentative populations consisting predominately of health professionals." Population-based studies refer to studies with well-defined populations and clear membership criteria,[9] thus, our study was population-based. Also, although we agree that the study population was unique and that this limited generalization of the findings, which we emphasized in the Discussion, it is hard to conceive why biological relationships might differ in these cohorts of health professionals. Indeed, we have observed strong associations with age, family history of glaucoma and African-heritage, which are established glaucoma risk factors. Furthermore, data from a case-control group nested within our cohorts have contributed to the genetic discovery of the 9p21 region in association with POAG,[10] a finding confirmed by other research groups.[11,12] Finally, the inverse associations between BMI and POAG observed in our studies[2,13] is generally consistent with three[14–16] of the 4 papers Ratnarajan et al.[1] quote in their letter.

A concern was that the two cohorts were unbalanced in sample size; indeed, the number of female participants in the NHS was almost double that of male participants in the HPFS. We agree that this imbalance could cause problems if associations differed by cohort/sex; however, before we combined the data from the two cohorts into one dataset to increase statistical power, we used formal statistical tests to assess whether exposure: POAG associations differed by cohort (which they did not). In addition, in Cox models, the analyses were stratified by cohort to allow for different baseline hazards within each cohort.

In epidemiology, consistency across studies is important for causal inference. Therefore, we agree with Ratnarajan et al.[1] that more studies are needed that attempt to differentiate risk factors specific to paracentral as well as peripheral glaucomatous VF defects. Such an approach may yield new insights into glaucoma etiology.

Jae H. Kang[1]
Stephanie J. Loomis[2]
Bernard A. Rosner[1,3]
Janey L. Wiggs[4]
Louis R. Pasquale[1,4]

[1]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States; [3]Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, United States; and the [4]Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, United States
E-mail: nhjhk@channing.harvard.edu

References

1. Ratnarajan G, Hirn C, Normando E, et al. for the Writing Committee for the European Glaucoma Panel. Comparison of risk factor profiles for primary open-angle glaucoma subtypes defined by pattern of visual field loss: true risk factors or arbitrary definition? *Invest Ophthalmol Vis Sci*. 2015;56:6531.
2. Kang JH, Loomis SJ, Rosner BA, Wiggs JL, Pasquale LR. Comparison of risk factor profiles for primary open angle glaucoma subtypes defined by pattern of visual field loss: a prospective study. *Invest Ophthalmol Vis Sci*. 2015;56:2439–2448.
3. Jung KI, Park HY, Park CK. Characteristics of optic disc morphology in glaucoma patients with parafoveal scotoma compared to peripheral scotoma. *Invest Ophthalmol Vis Sci*. 2012;53:4813–4820.
4. Park SC, De Moraes CG, Teng CC, Tello C, Liebmann JM, Ritch R. Initial parafoveal versus peripheral scotomas in glaucoma: risk factors and visual field characteristics. *Ophthalmology*. 2011;118:1782–1789.
5. Elze T, Pasquale LR, Shen LQ, Chen TC, Wiggs JL, Bex PJ. Patterns of functional vision loss in glaucoma determined with archetypal analysis. *J R Soc Interface*. 2015;12.
6. Hodapp E, Parrish RKI, Anderson DR. *Clinical Decisions in Glaucoma*. St. Louis, MO: CV Mosby; 1993.
7. Rothman KJ, Greenland S. *Modern Epidemiology. 2nd ed*. Philadelphia: Lippincott-Raven; 1998:130–131.
8. Hennekens CH, Buring JE. *Epidemiology in Medicine*. Boston: Little, Brown and Co.; 1987.
9. Szklo M. Population-based cohort studies. *Epidemiol Rev*. 1998;20:81–90.
10. Wiggs JL, Yaspan BL, Hauser MA, et al. Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma. *PLoS Genetics*. 2012;8:e1002654.
11. Nakano M, Ikeda Y, Tokuda Y, et al. Common variants in CDKN2B-AS1 associated with optic-nerve vulnerability of glaucoma identified by genome-wide association studies in Japanese. *PLoS One*. 2012;7:e33389.
12. Burdon KP, Macgregor S, Hewitt AW, et al. Genome-wide association study identifies susceptibility loci for open angle glaucoma at TMCO1 and CDKN2B-AS1. *Nat Genet*. 2011;43:574–578.
13. Pasquale LR, Willett WC, Rosner BA, Kang JH. Anthropometric measures and their relation to incident primary open-angle glaucoma. *Ophthalmology*. 2010;117:1521–1529.
14. Leske MC, Connell MS, Wu S-Y, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma. The Barbados Eye Study. *Arch Ophthalmol*. 1995;113:918–924.
15. Ramdas WD, Wolfs RC, Hofman A, de Jong PT, Vingerling JR, Jansonius NM. Lifestyle and risk of developing open-angle glaucoma: the Rotterdam study. *Arch Ophthalmol*. 129:767–772.
16. Gasser P, Stumpfig D, Schotzau A, Ackermann-Liebrich U, Flammer J. Body mass index in glaucoma. *J Glaucoma*. 1999;8:8–11.

Citation: *Invest Ophthalmol Vis Sci.* 2015;56:6532–6533.
doi:10.1167/iovs.15-17944

Investigative Ophthalmology & Visual Science