

The Heritability of Optic Disc Parameters: A Classic Twin Study

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PURPOSE. To examine the roles of genetic and environmental factors in the optic disc in a classic twin study.

METHODS. Five hundred six pairs of twins were recruited to participate from the Twins U.K. Adult Twin Registry at St. Thomas' Hospital, London. Photographs of the optic disc were obtained, and the covariance of optic disc, cup, and rim areas within monozygotic (MZ) and dizygotic (DZ) pairs was compared, and genetic modeling techniques were used to determine the relative contributions of genes and environment to the variation in optic disc parameters in this population.

RESULTS. Mean optic disc, cup, and rim areas were 2.62 (range, 1.06–4.87), 0.98 (range, 0.25–4.72), and 1.64 (range, 1.43–6.16) mm², respectively. The MZ correlations were higher than those of DZ pairs for disc and cup areas (correlation coefficient, 0.73/0.81 and 0.41/0.50 for MZ and DZ twins, respectively). The correlation for optic rim was also higher in MZ (0.62) than in DZ (0.43) pairs. Modeling suggested heritability for the optic disc area of 0.73 and for the optic cup area of 0.66. The heritability of the rim area was lower at 0.34, with a significant shared environmental component of 0.27 and individual factors (including measurement error) explaining 39% of the variance of the rim area.

CONCLUSIONS. This study has demonstrated that genetic effects were important in the determination of optic disc parameters in this twin population, with genetic factors explaining 73%, 66%, and 34% of the variation of optic disc, cup, and rim areas, respectively. Environmental factors also seemed to be important. (*Invest Ophthalmol Vis Sci.* 2008;49:77–80) DOI: 10.1167/iovs.07-0962

Glaucoma is a leading cause of blindness worldwide.¹ There has been considerable research into the genetics of glaucoma and numerous gene loci (GLC1A-I) have been identified,² together with three genes *MYOC*,³ *OPTN*,⁴ and *WDR36*,⁵ which may be involved in the etiology of glaucoma in a small subset of the population. Searching for genes for relatively uncommon complex diseases is difficult. Researchers have

studied intermediate traits (endophenotypes) that are associated with those diseases (such as intraocular pressure and optic disc/cup size in glaucoma), as such traits enable study of a quantitative trait rather than affected/unaffected status. Raised intraocular pressure (IOP) is the strongest known risk factor other than age for glaucoma's development and progression. A genetic basis for IOP has been reported in several twin studies,^{6,7} and familial aggregation^{8,9} studies have showed a modest but significant correlation for IOP between sib, parent-child, and cousin pairs.

Optic disc parameters have also been linked to glaucoma; for example, a smaller rim area has been reported to predict the development of glaucoma in the Ocular Hypertension Treatment Study.¹⁰ There has been little research into the hereditary aspects of optic disc parameters in the general population. Two population-based studies reported a correlation between first-degree family members for optic disc parameters—specifically, optic cup and disc diameter and cup-disc ratio.^{11,12} Previous small studies of optic disc parameters in twins have been concentrated on vertical cup and disc measures and the cup-to-disc ratio.^{12,13} An underpowered twin study suggested a heritability index of 0.6 to 0.8¹³ for diameter of normal physiological cup, but did not use modern genetic modeling techniques. We have already shown a significant heritability of β -peripapillary atrophy, which is associated with glaucoma and myopia, even when shared genetic effects with myopia are removed.¹⁴

Twin studies are an excellent method of studying the relative importance of genetic and environmental influences on a phenotype.¹⁵ Factors such as perfect age matching and more similar environment allow twin studies to calculate the maximum genetic contribution to a trait. We conducted a classic twin study to determine the heritability of optic disc parameters (optic disc, cup, and neural rim areas, as well as vertical cup-disc ratio) in a general population. Covariance of optic disc parameters between MZ and DZ twins was compared by using modern genetic modeling techniques.

METHODS

Five hundred and six pairs of white female twins (226 monozygotic and 280 dizygotic) with mean age of 62 years (range, 49–79)¹⁶ were studied. The twins were initially recruited to participate in the Twins UK Adult Twin Registry, held at St. Thomas' Hospital, London, and were unaware of any hypotheses or proposals for specific studies; only later were they invited to have an eye examination. Our institutional ethics committee approved the study, and all the women gave informed consent. The study adhered to the Declaration of Helsinki. Zygosity was determined by a standardized questionnaire¹⁷ and confirmed by DNA analysis of short tandem repeat polymorphisms in the pairs for which there was any doubt about zygosity. Exclusion criteria included subjects who were unwilling to undertake dilated retinal photography (two twin volunteers) or those with significant congenital optic disc abnormality (one subject). As it was a volunteer population-based study, subjects with glaucoma were included in the analysis.

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Supported by Guide Dogs for the Blind and the Wellcome Trust.

Submitted for publication July 28, 2007; revised September 12, 2007; accepted November 14, 2007.

Disclosure: **P. Healey**, None; **F. Carbonaro**, None; **B. Taylor**, None; **P. Mitchell**, None; **T.D. Spector**, None; **C.J. Hammond**, None

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Optic Disc Grading

Photographs of the optic disc were taken with a Kowa camera (Kowa-Europe, Dusseldorf, Germany) with nonsimultaneous stereo photographs of each disc taken on a 30° width-of-field setting and developed on slide film (Ektachrome 64; Eastman Kodak, Rochester, NY). The same individual took all photographs (CJH) with the same camera, and film was processed by the same company, to ensure as much consistency as possible. The slide photographs were digitized with a slide scanner (CoolScan IV ED; Nikon Corp, Tokyo, Japan). Data from the right eyes of each subject were used. If there was no usable image for an individual's right eye, then data from the left eye were used, if possible.

Optic disc, cup, and neuroretinal rim areas were measured with stereoscopic planimetric software (StereODx, using a Z-screen; StereoGraphics Corp., Beverly Hills, CA).¹⁸ This stereoscopic visualization system has been detailed elsewhere.¹⁹ It consists of a filter that circularly polarizes light from two images on the screen. The component images of the stereopair are alternately displayed on the monitor at 60 Hz to provide flicker-free stereoscopy. These polarized images are then filtered by polarized eyewear worn by the observer. The cursor depth can be adjusted to coincide with Elschnig's rim. Semiautomated tracing of the disc and cup margins is performed while viewing stereographic images of the optic disc, followed by automated area analysis. Both intra- and inter-observer reproducibility was good.¹⁸

All images were graded in the reading center of the University of Sydney Centre for Vision Research (Westmead, NSW, Australia) by the same experienced grader who was masked as to zygosity and clinical information. Queries and discrepancies were adjudicated by one of the authors (PRH). Magnification effects of the eye-camera system were corrected by using spherical equivalent refraction, and coefficients were derived for the specific camera from a model eye. The detailed description of the method by which this was reached, is beyond the scope of this article; however, it is described in greater detail elsewhere.^{20,21}

Analytic Methods

The variance of a phenotype in a population is due to genetic and environmental factors. Most traits or disease occur more commonly in the families of affected individuals than in the general population, but because families share both genes and environment, it is difficult to separate the effects of each. Because identical or MZ twin pairs share the same genes, and nonidentical or DZ twins share on average half of their segregating genes, any greater concordance or correlation between MZ twins can be attributed to this additional genetic sharing. Twin models assume that both MZ and DZ twins share the same common family environment (the equal environment assumption).²²

Data handling and preliminary analyses were undertaken with commercial software (Stata; StataCorp. LP, College Station, TX).²³ The covariance matrices for MZ and DZ twin pairs were used in the Mx genetic modeling program.²⁴ This method is based on comparing the covariances of a measured trait between MZ and DZ twins. The observed phenotypic variance can be divided into additive genetic (A), dominant genetic (D), common environmental (C), and unique environmental (E) components. The common environmental component estimates the contribution of family environment, whereas the unique environmental component estimates the effects that apply only to each individual, including measurement error. The broad-sense heritability, which estimates the extent to which variation in optic disc parameters in a population can be explained by genetic variation, can be defined as the ratio of genetic variance (A + D) to total phenotypic variance (A + D + C + E). The best-fitting model is calculated by the use of the Akaike Information Criterion (AIC). The AIC describes the model with best goodness of fit combined with parsimony (fewest latent variables) and is calculated as $2 \times$ the degrees of freedom—the model fit χ^2 . The sub model with the lowest AIC is the best fitting.

TABLE 1. Demographic Details of Twin Pairs Included in the Glaucoma Study

	MZ	DZ
Twin pairs (<i>n</i>)	196	248
Mean age (SD), y	62.5 (5.7)	61.9 (5.6)
Disc area mean (SD) (mm ²)	2.62 (0.48)	2.62 (0.48)
Disc area correlation (<i>r</i>)	0.73	0.41
Cup area mean (SD) (mm ²)	0.98 (0.40)	0.98 (0.42)
Cup area correlation (<i>r</i>)	0.81	0.50
Rim area mean (SD) (mm ²)	1.64 (0.32)	1.64 (0.31)
Rim area correlation (<i>r</i>)	0.62	0.43

RESULTS

Of the 1012 twin volunteers, 62 (6.1%) individuals were excluded from the full analysis. Of these 19 (1.9%) had poor photographs that were not of sufficient quality for stereographic analysis, 18 (1.8%) had no disc images available, and 25 (2.4%) were not analyzed due to missing digitized images. For each ungraded individual, the corresponding data of their twin was excluded from the analysis, because the analysis involved comparison within pairs of twins. Thus, data were available for analysis of 196 MZ pairs and 248 DZ pairs (mean age: MZ, 62.5 ± 5.7 [SD] MZ; range, 51–75; DZ 61.9 ± 5.6 years; range, 49–79). Eleven subjects had glaucoma (1.1% of the whole cohort), and a further five (0.5%) were referred to local ophthalmology services for further investigation for glaucoma based on clinical examination at the time or on optic disc photography. Exclusion of these subjects did not alter the mean values or their correlations.

Mean optic disc area was 2.62 mm² (95% confidence interval [CI] 1.06–4.87). Mean optic cup and neural rim areas were 0.98 (95% CI: 0.25–4.72) and 1.64 (95% CI: 1.43–6.16) mm², respectively. Values were similar for MZ and DZ twins (Table 1), with a normal distribution (data not shown). There was no significant correlation of any of the optic disc parameters with age ($P > 0.12$) or refractive error (spherical equivalent in diopters; $P > 0.55$).

The MZ and DZ intrapair correlation coefficients are detailed in Table 1 and show that the MZ twin pairs were more highly correlated than the DZ pairs for all three parameters. Correlations were higher for the optic cup area (MZ/DZ 0.81/0.50) than for the optic disc (MZ/DZ 0.73/0.41) and optic rim (MZ/DZ 0.62/0.43) areas. The higher MZ correlations than DZ correlations support a genetic influence on optic disc morphology.

Genetic modeling suggested the best-fitting model for optic disc area to be the AE model, meaning that additive genetic effects and individual environmental effects explained the variance (Table 2). The calculated heritability (b^2) was 0.73 (95% CI: 0.67–0.78) with the remaining proportion of variance due to individual environmental effects of 0.27 (95% CI: 0.22–0.33). For optic cup area the best fitting was the ACE model, with variance explained by genetic effects (heritability b^2 0.66, 95% CI: 0.49–0.84), shared common environment C (proportion of variation 0.16, 95% CI: 0.10–0.32), and individual environmental effects E (0.18, 95% CI: 0.15–0.23). For neural rim area, the ACE model was also best fitting, with a lower heritability b^2 of 0.34 (95% CI: 0.10–0.58), shared environment 0.27 (95% CI: 0.05–0.46), and individual environment 0.39 (95% CI: 0.32–0.48).

As disc area influences the rim area (correlation coefficient, 0.56), the effects of disc area on rim area were removed using the residuals after regressing rim area on disc area. The heritability of this adjusted rim area was not significantly altered, with a heritability b^2 of 0.38 and shared environment explain-

TABLE 2. Model Fitting Results for Univariate Analysis of Optic Disc, Cup, and Rim Areas

Model/Area	χ^2	<i>df</i>	<i>P</i>	AIC
Disc				
ACE	1.957	3	0.581	-4.043
ADE	2.545	3	0.467	-3.455
AE	2.545	4	0.637	-5.455
CE	36.462	4	0	28.462
E	193.602	5	0	183.602
Cup				
ACE	2.484	3	0.478	-3.516
ADE	5.165	3	0.168	-0.0835
AE	5.165	4	0.271	-2.835
CE	58.735	4	0	50.735
E	281.099	5	0	271.039
Rim				
ACE	6.268	3	0.099	0.268
ADE	11.963	3	0.008	5.963
AE	11.963	4	0.018	3.963
CE	13.764	4	0.008	5.764
E	149.401	5	0.00	139.401

A, additive genetic; D, dominant genetic; C, common environment, E, unique environmental effects; χ^2 , goodness-of-fit statistic; *df*, change in degrees of freedom between submodel and full model; *P*, probability that $\Delta\chi^2$ (change in χ^2 comparing submodel with full ADE or ACE and age model) is zero. The best-fit models are highlighted in bold.

ing 0.31 of the variance. The heritability of the rim/disc area ratio (i.e., standardizing disc area to 1) was 0.47 (95% CI: 0.30–0.66) and shared environment influence was 0.36 (95% CI: 0.12–0.45).

DISCUSSION

This study showed a significant genetic component for optic disc and cup areas and a smaller but significant heritability for rim area. From a biological point of view, optic disc area is likely to be largely genetically determined, and, while genetic factors influence rim area, the amount of nerve tissue is more influenced by environmental factors. The heritability estimate of 0.73 for disc area is similar in magnitude to peripapillary atrophy type β (0.70 reported in this cohort).¹⁴ The disc area and cup area heritabilities are higher than those of the vertical disc and cup diameters found in the Beaver Dam Eye Study⁸ (0.57 and 0.55). Apart from measurement differences, these slightly higher heritabilities may be attributable to this being a twin study. Twin-based heritability can be higher because of shared age and more similar environments compared with other sibling and family-based studies.

In this population of twins, it was found that a model including shared family (“common”) environment was the best fitting for both the optic cup and rim areas. This was particularly the case with neural rim area, where common environment explained almost as much variance as genes (0.27 vs. 0.34). This finding is relatively unusual in twin studies. Common environment effects are sometimes explained by twins’ shared age, and age has also been reported to influence rim area in normal individuals.²⁵ However, in this cohort, age accounted for very little of the variation of optic disc parameters, making it a less likely cause of the shared environmental effects detailed in the model. The strongest determinant of rim area previously reported is disc area.^{26–28} Even after adjusting for disc area, the common environmental estimate accounted for 31% to 36% of variance. This result suggests as yet unidentified environmental influences on rim area in otherwise normal individuals. The commonality of this influence in the twins

suggests it occurred at an early age or is perhaps was a maternal factor manifesting before birth.

Rim area has been reported to predict the development of glaucoma in several studies.^{29,30,31} It is known that alcohol abuse in pregnancy is associated with optic nerve hypoplasia,³² and it is likely that other maternal insults reduce the amount of neural tissue in the optic nerve and thus the size of rim (and cup) areas. It has been speculated that dietary factors, such as a diet high in seafood, either prenatally or during a child’s growth, may have played a role in the evolution of the larger human brain.³³ Maternal seafood consumption has been shown to be beneficial for a child’s neurodevelopment.³⁴ Could such factors influence neural rim size and glaucoma risk later in life?

In addition to common environment, individual environmental factors contribute to a substantial amount of variance of rim area. One explanation for this is that, as optic nerve axons are lost with increasing age, environmental factors play a larger part in determining the rim area. But individual environmental effects estimates in these models include measurement error. As rim area was calculated by subtracting the optic cup area from the optic disc area, the chance of error increased and may be the cause of the higher estimate.

Although this study was based on a volunteer twin population, optic disc measurements were similar to those in large population-based studies. The findings for mean optic disc, cup, and rim areas were 2.62, 0.98, and 1.64 mm²; comparable to those of the Baltimore Eye Study,³⁵ which reported mean optic disc, cup, and rim areas to be 2.63, 0.71, and 1.92 mm², respectively. We believe that these twin data are generalizable to the singleton population, as twins have similar morbidity and mortality to the rest of the population.³⁶ Heritability is a population-specific factor and our study applies to this population of British women, which could be different for other populations with different gene pools or environmental circumstances. A possible limitation of twin studies may be the “equal environment” assumption, that MZ and DZ twins share the same common family environment in which they are brought up; however, the assumption generally holds up to testing. A potential limitation could be recruitment bias because the subjects were volunteers. We attempted to minimize bias by the fact that the twins had volunteered for reasons other than eye studies and were subsequently invited for an eye examination, without glaucoma’s being initially specified as an outcome of interest. The prevalence of glaucoma of 1% at the start of the study is comparable to population-based studies, and inclusion or exclusion of these subjects did not significantly alter results.^{37,38,39}

In conclusion, this study has demonstrated that genetic effects are important in determination of optic disc parameters in this twin population, with genetic factors explaining 73%, 66%, and 34% of the variation of the optic disc, cup, and rim areas, respectively. While the lower heritability of rim area may be in part due to a greater chance of measurement error, environmental factors, including unknown shared family factors, are also important in determining neural rim area. These results may lead to the search for genes involved in the development of the optic disc, and maintenance of the neural rim area, to elucidate further our understanding of the mechanisms of glaucoma and the susceptibility of the optic disc to this disorder. Greater understanding about mechanisms may also help to identify disease-modifying agents or environmental interventions to reduce disease in susceptible individuals.

Acknowledgments

The authors thank James Morgan for assistance with the stereoscopic planimetry and Mario Economou for photograph digitization.

References

1. Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol*. 1996;80:389-393.
2. Wiggs JL. Genetic etiologies of glaucoma. *Arch Ophthalmol*. 2007;125:30-37.
3. Stone EM, Fingert JH, Alward WL, et al. Identification of a gene that causes primary open angle glaucoma. *Science*. 1997;275:668-670.
4. Rezaie T, Child A, Hitchings R, et al. Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science*. 2002;295:1077-1079.
5. Monemi S, Spaeth G, DaSilva A, et al. Identification of a novel adult-onset primary open-angle glaucoma (POAG) gene on 5p22.1. *Hum Mol Genet*. 2005;14(6):725-733.
6. Kalenak JW, Paydar F. Correlation of intraocular pressures in pairs of monozygotic and dizygotic twins. *Ophthalmology*. 1995;102:1559-1564.
7. Gottfredsdottir MS, Sverrisson T, Musch DC, Stefansson E. Chronic open-angle glaucoma and associated ophthalmic findings in monozygotic twins and their spouses in Iceland. *J Glaucoma*. 1999;8:134-139.
8. Klein BE, Klein R, Lee KE. Heritability of risk factors for primary open-angle glaucoma: The Beaver Dam Eye Study. *Invest Ophthalmol Vis Sci*. 2004;45(1):59-62.
9. Wolfs RC, Klaver CC, Ramrattan RS, van Duijn CM, Hofman A, de Jong PT. Genetic risk of primary open-angle glaucoma: population-based familial aggregation study. *Arch Ophthalmol*. 1998;116(12):1640-1645.
10. Zangwill LM, Weinreb RN, Beiser JA, et al. Baseline topographic optic disc measurements are associated with the development of primary open-angle glaucoma: the Confocal Scanning Laser Ophthalmoscopy Ancillary Study to the Ocular Hypertension Treatment Study. *Arch Ophthalmol*. 2005;123:1188-1197.
11. Chang TC, Congdon NG, Wojciechowski R, et al. Determinants and heritability of intraocular pressure and cup-to-disc ratio in a defined older population. *Ophthalmology*. 2005;112(7):1186-1191.
12. Armaly MF. Genetic determination of cup-disc ratio of the optic nerve. *Arch Ophthalmol*. 1967;78:35-42.
13. Teikari JM, Airaksinen JP. Twin study on cup/disc ratio of the optic nerve head. *Br J Ophthalmol*. 1992;76(4):218-220.
14. Healey PR, Mitchell P, Gilbert CE, et al. The inheritance of peripapillary atrophy. *Invest Ophthalmol Vis Sci*. 2007;48(6):2529-2534.
15. Martin N, Boomsma D, Machin G. A twin-pronged attack on complex traits. *Nat Genet*. 1997;17:387-392.
16. Hammond CJ, Sneider H, Spector TD, Gilbert CE. Genetic and environmental factors in age related nuclear cataracts in monozygotic and dizygotic twins. *N Engl J Med*. 2000;342:1786-1790.
17. Martin NG, Martin PG. The inheritance of scholastic abilities in a sample of twins. I. Ascertainments of the sample and diagnosis of zygosity. *Ann Hum Genet*. 1975;39:213-218.
18. Morgan JE, Sheen NJ, North RV, et al. Digital imaging of the optic nerve head: monoscopic and stereoscopic analysis. *Br J Ophthalmol*. 2005;89:879-884.
19. Morgan JE, Sheen NJ, North RV, et al. Discrimination of glaucomatous optic neuropathy by digital stereoscopic analysis. *Ophthalmology*. 2005;112:855-862.
20. Bengtsson B, Krakau CE. Correction of optic disc measurements on fundus photographs. *Graefes Arch Clin Exp Ophthalmol*. 1992;30:24-28.
21. Rudnicka AR, Burk RO, Edgar DF, et al. Magnification characteristics of fundus imaging systems. *Ophthalmology*. 1998;105:2186-2192.
22. Kyvik KO. Generalisability and assumptions of twin studies. In: Spector TD, Snieder H, MacGregor AJ, eds. *Advances in Twin and Sib-Pair Analysis*. London: Greenwich Medical Media, Ltd.; 2000: 67-77.
23. StataCorp. *Intercooled Stata for Windows 95, ver. 5.0*. College Station TX: StataCorp.; 1997.
24. Neale MC. *Mx: Statistical Modeling*. 4th ed. Richmond, VA: Dept. of Psychiatry, Medical College of Virginia; 1997.
25. Garway-Heath DF, Wollstein G, Hitchings RA. Aging changes of the optic nerve head in relation to open angle glaucoma. *Br J Ophthalmol*. 1997;81(10):840-845.
26. Caprioli J, Miller JM. Optic disc rim area is related to disc size in normal subjects. *Arch Ophthalmol*. 1987;105:1683-1685.
27. Britton RJ, Drance SM, Schulzer M, Douglas GR, Mawson DK. The area of the neuroretinal rim of the optic nerve in normal eyes. *Am J Ophthalmol*. 1987;103:497-504.
28. Jonas JB, Gusek GC, Naumann GO. Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. *Invest Ophthalmol Vis Sci*. 1988;29:1151-1158.
29. Keltner JL, Johnson CA, Anderson DR, et al. The association between glaucomatous visual fields and optic nerve head features in the Ocular Hypertension Treatment Study. *Ophthalmology*. 2006;113(9):1603-1612.
30. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber layer atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol*. 1991;109:77-83.
31. Jonas JB, Martus P, Horn FK, et al. Predictive factors of the optic nerve head for development or progression of glaucomatous visual field loss. *Invest Ophthalmol Vis Sci*. 2004;45:2613-2618.
32. Pinazo-Duran MD, Renau-Piqueras J, Guerri C, Stromland K. Optic nerve hypoplasia in fetal alcohol syndrome: an update. *Eur J Ophthalmol*. 1997;7(3):262-270.
33. Cunnane SC. Survival of the fittest: the key to human brain evolution. *Med Sci (Paris)*. 2006;22(6-7):659-663.
34. Hibbeln JR, Davis JM, Street C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study). *Lancet*. 2007;7:369:578-585.
35. Varma R, Tielsch JM, Quigley HA, et al. A. Race-, age-, gender-, and refractive error-related differences in the normal optic disc. *Arch Ophthalmol*. 1994;112:1068-1076.
36. Andrew T, Hart DJ, Sneider H, et al. Are twins and singletons comparable?—a study of disease related and lifestyle characteristics in adult women. *Twin Res*. 2001;4(6) 464-477.
37. Klein BE, Klein R, Sponsel WE, et al. Prevalence of glaucoma: the Beaver Dam eye study. *Ophthalmology*. 1992;99:1499-1504.
38. Rudnicka AR, Mt-Isa S, Owen CG, et al. Variations in primary open angle glaucoma prevalence by age, gender and race: a Bayesian meta-analysis. *Invest Ophthalmol Vis Sci*. 2006;47(10):4254-4261.
39. Mitchell P, Smith W, Attebo K, et al. Prevalence of open-angle glaucoma in Australia: the Blue Mountains Eye Study. *Ophthalmology*. 1996;103:1661-1669.