The Role of Ocular Perfusion Pressure in Glaucoma Cannot Be Studied With Multivariable Regression Analysis Applied to Surrogates

Ocular perfusion pressure (OPP) is not easily directly measurable, and the difference between blood pressure and intraocular pressure (IOP) has been suggested as a simple surrogate of OPP.[1] We write in relation to publications in this journal[2,3] and elsewhere[4] that have reported a significant association between OPP surrogates and glaucoma. We argue that these findings are based on incorrect interpretation of multivariable regression models, and that these simple surrogates cannot be used to examine the role of OPP in glaucoma. We illustrate this by theoretically reviewing the interpretation of coefficients in multivariable regression models, and then demonstrating the issue using a simulated dataset.

Interpretation of regression coefficients is straightforward in univariable regression. As an example, consider the setting of a cross-sectional study. A univariable logistic regression model examining whether IOP is associated with the prevalence of glaucoma would be as follows:

$$\log(\text{odds of glaucoma}) = \alpha + \beta * \text{IOP} \quad (1)$$

With IOP considered as a continuous variable, the interpretation of e^{β} would be the odds ratio (OR) for a diagnosis of glaucoma per mm Hg increase in IOP. Coefficient α is the constant term and rarely presented or interpreted in analyses.

The interpretation of regression coefficients becomes more complicated in the setting of multivariable regression. Consider the situation of examining the association of both IOP and age with glaucoma:

$$\log(\text{odds of glaucoma}) = \alpha + \beta_1 * \text{IOP} + \beta_2 * \text{age} \quad (2)$$

The interpretation of $e^{\beta 1}$ would now be the OR for glaucoma per mm Hg increase in IOP, *while holding age constant*. The last part of this interpretation is crucial, and this is what makes multivariable regression an effective method for adjusting for potentially important confounders.

Now consider the situation of examining the association between OPP surrogates and glaucoma. An example of an OPP surrogate is diastolic ocular perfusion pressure (DOPP), calculated from diastolic blood pressure (DBP) and IOP:

$$\text{DOPP} = \text{DBP} - \text{IOP} \quad (3)$$

To examine the association between DOPP and glaucoma, a univariable logistic regression model would be as follows:

$$\log(\text{odds of glaucoma}) = \alpha + \beta * \text{DOPP} \quad (4)$$

The interpretation of e^{β} is simply the OR for a diagnosis of glaucoma per mm Hg increase in DOPP.

In an attempt to determine if the association between DOPP and glaucoma is independent of IOP, some investigators have put both terms into the same multivariable regression model. For example:

$$\begin{aligned}\log(\text{odds of glaucoma}) &= \alpha + \beta_1 * \text{DOPP} + \beta_2 * \text{IOP} \\ &= \alpha + \beta_1(\text{DBP} - \text{IOP}) + \beta_2 * \text{IOP} \quad (5)\end{aligned}$$

Now the interpretation of $e^{\beta 1}$ is not so simple. It is the OR for a diagnosis of glaucoma per mm Hg increase in DOPP, *while holding IOP constant*. If IOP is to be held constant, the only way for DOPP (= DBP − IOP) to increase is for the DBP component to increase. This means that $e^{\beta 1}$ represents the OR for glaucoma per mm Hg increase in DBP, adjusted for IOP. It does *not* represent the OR per mm Hg increase in DOPP (a common misinterpretation; see below). Similarly, $e^{\beta 2}$ represents the OR for glaucoma per mm Hg increase in IOP, while holding DOPP constant. This is equivalent to the OR per mm Hg increase in both IOP *and* DBP together. It does *not* represent the OR per mm Hg increase in IOP. The main problem in interpretation results from IOP forming part of two terms in the same regression model.

This can also be illustrated by simply looking at the mathematical model equations. With DBP and IOP in the logistic regression (model A), the equation is as follows:

$$\log(\text{odds of glaucoma}) = \alpha + \beta_{1A} * \text{DBP} + \beta_{2A} * \text{IOP} \quad (6)$$

With DOPP and IOP in the logistic regression model (model B), the equation is as shown in Equation 5, and can be rearranged to be in the same format as Equation 6 (model A):

$$\begin{aligned}\log(\text{odds of glaucoma}) &= \alpha + \beta_{1B}(\text{DBP} - \text{IOP}) + \beta_{2B} * \text{IOP} \\ &= \alpha + \beta_{1B} * \text{DBP} + (\beta_{2B} - \beta_{1B}) * \text{IOP} \quad (7)\end{aligned}$$

It is therefore clear what the regression coefficients for model B represent: β_{1B} is equivalent to the coefficient for DBP in an IOP-adjusted model (β_{1A}); β_{2B} is equivalent to the addition of the coefficients for DBP and IOP in a model containing both terms ($\beta_{1A} + \beta_{2A}$).

We further illustrate the issue in a simulated population-based dataset. For this purpose, a random baseline probability for a diagnosis of glaucoma was attributed to 5000 participants. This probability was subsequently modified by several risk factors, including IOP with an increase in risk of 12% per mm Hg.[5] IOP and DBP were added as normally distributed random numbers with mean and standard deviation values taken from the literature.[6] A threshold was set to derive a realistic glaucoma prevalence of 1.2%.[7] DOPP was calculated as (DBP − IOP). Table 1 shows the results from a multivariable logistic regression model for prevalent glaucoma, with DOPP and IOP both in the model. Coefficients are presented to the full number of decimal places given in the software output (Stata Statistical Software, Release 12; StataCorp, College Station, TX).

Table 2 presents the results from a multivariable logistic regression model for prevalent glaucoma, now with DBP and IOP both in the model (i.e., DBP in the model rather than DOPP).

The OR for DOPP in the IOP-adjusted model (Table 1) is exactly the same as for DBP in an IOP-adjusted model (Table 2), as are the 95% confidence intervals and *P* values. Moreover, log(1.005653) plus log(1.232978) equals log(1.239948), which illustrates the equivalence of β_{2B} and $\beta_{1A} + \beta_{2A}$. This phenomenon remains unchanged when other covariables are adjusted for, when using the open source programming

Table 1. Results From a Multivariable Logistic Regression Model With Glaucoma Status as the Dependent Variable and DOPP and IOP as Continuous Explanatory Variables

	Odds Ratio	95% CI	*P* Value
DOPP, mm Hg	1.005653	0.9785898, 1.033465	0.685
IOP, mm Hg	1.239948	1.126622, 1.364673	<0.001

CI, confidence interval.

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Table 2. Results From a Multivariable Logistic Regression Model With Glaucoma Status as the Dependent Variable and DBP and IOP as Continuous Explanatory Variables

	Odds Ratio	95% CI	*P* Value
DBP, mm Hg	1.005653	0.9785898, 1.033465	0.685
IOP, mm Hg	1.232978	1.124384, 1.352060	<0.001

language R (R Foundation for Statistical Computing, Vienna, Austria), or when applying Cox regression to longitudinal data.

This difficulty in interpretation applies whether perfusion pressure is entered as a continuous variable or considered in categories (as, for example, derived from tertiles). Changing from one category of perfusion pressure to another while holding IOP constant represents a change in blood pressure only. However, the coefficients no longer represent a constant or specific amount of change in blood pressure (as they do when the variables are continuous), as this depends on which perfusion pressure category an individual lies in, and where within that category. An alternative way of interpreting the coefficient of a perfusion pressure category in an IOP-adjusted model would be the log OR between an individual in that category and an individual in the referent group, with both individuals having the same IOP. The only way these two individuals can be in different perfusion pressure categories while having the same IOP is to have different blood pressures.

Lower systolic ocular perfusion pressure (SOPP), mean ocular perfusion pressure (MOPP), and DOPP were reported as significant risk factors for incident open-angle glaucoma (OAG) in the Barbados Eye Studies.[4] However, the relative risks reported were derived from regression models adjusted for IOP, and therefore more represent risk for decrease in blood pressure than perfusion pressure. Of note is that the investigators presented relative risks for both perfusion pressure and blood pressure.[4] These should have been identical, for example for DOPP and DBP. However, they were not. The reason for this discrepancy is not clear, but it may be that the analyses were carried out on slightly different subsets of participants. Lower DOPP and MOPP were reported as significantly associated with prevalent OAG in the Singapore Malay Eye Study.[2] Again, however, this conclusion is unjustified given that it is based on interpretation of the coefficients for DOPP and MOPP in IOP-adjusted models (therefore reflecting risk associated with DBP and mean arterial pressure instead). Similarly, low SOPP, MOPP, and DOPP were reported to be associated with prevalent OAG in the Los Angeles Latino Eye Study, which was unfounded based on IOP-adjusted regression models.[3] What is clear from these studies is that blood pressure seems to be consistently associated with glaucoma, independently from its association with IOP.

The difficulty in interpreting coefficients of related variables in the same multivariable model is well recognized in the field of nutritional epidemiology. Interpreting coefficients for a specific nutrient intake is complicated in models adjusted for total energy intake.[8,9] For example, the coefficient for fat intake in a model adjusted for total energy intake represents risk for swapping fat intake for other nutrients of equal energy, not the risk for increasing fat intake.

The optimal statistical method for examining the association between IOP containing surrogate measures of OPP and glaucoma remains to be determined. As shown above, adjusting for IOP in a model means that little information can be derived regarding perfusion pressure-related risk. However, not adjusting for IOP is also problematic. If a perfusion pressure term is significant in an unadjusted model, it will not be possible to determine if this is due to OPP per se or just related to the IOP component. Ramdas and colleagues showed that the unadjusted association between MOPP/SOPP/DOPP and incident glaucoma remained even when the blood pressure component of MOPP/SOPP/DOPP was replaced with random values.[6] Furthermore, after they repeated the process 30 times (with different sets of random values), the magnitudes of association were largely distributed within the 95% confidence interval of the original hazard ratio. This strongly suggests that it is the IOP component of the perfusion pressure measurement that drives any significant association with glaucoma in unadjusted models, certainly within the Rotterdam cohort.

In summary, the strength of IOP as a risk factor for glaucoma precludes any useful interpretation of OPP surrogates (blood pressure − IOP) in unadjusted analyses, and adjusting for IOP changes the interpretation of regression coefficients such that they no longer reflect risk attributed to the perfusion pressure measure. Is it time to abandon the use of this type of surrogate measure of OPP? At the very least, the current interpretation of findings is confused and does not appear to be furthering the understanding of glaucoma.

Anthony P. Khawaja[1]
David P. Crabb[2]
Nomdo M. Jansonius[3,4]

[1]Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom; [2]Department of Optometry and Visual Science, City University London, London, United Kingdom; [3]Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; and [4]Department of Epidemiology, Erasmus Medical Center, Rotterdam, The Netherlands.
E-mail: anthony.khawaja@gmail.com

References

1. Tielsch JM, Katz J, Sommer A, et al. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch Ophthalmol*. 1995;113:216–221.
2. Zheng Y, Wong TY, Mitchell P, et al. Distribution of ocular perfusion pressure and its relationship with open-angle glaucoma: the Singapore Malay Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51:3399–3404.
3. Memarzadeh F, Ying-Lai M, Chung J, et al. Blood pressure, perfusion pressure, and open-angle glaucoma: the Los Angeles Latino Eye Study. *Invest Ophthalmol Vis Sci*. 2010;51:2872–2877.
4. Leske MC, Wu S-Y, Hennis A, et al. Risk factors for incident open-angle glaucoma: the Barbados Eye Studies. *Ophthalmology*. 2008;115:85–93.
5. Marcus MW, Müskens RPHM, Ramdas WD, et al. Cholesterol-lowering drugs and incident open-angle glaucoma: a population-based cohort study. *PLoS One*. 2012;7:e29724.
6. Ramdas WD, Wolfs RCW, Hofman A, et al. Ocular perfusion pressure and the incidence of glaucoma: real effect or artifact? The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2011;52:6875–6881.
7. Wolfs RC, Borger PH, Ramrattan RS, et al. Changing views on open-angle glaucoma: definitions and prevalences–The Rotterdam Study. *Invest Ophthalmol Vis Sci*. 2000;41:3309–3321.
8. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr*. 1997;65:1220S–1228S, discussion 1229S–1231S.
9. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17–27.

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