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Statistical approaches in published ophthalmic clinical science papers: a comparison to statistical practice two decades ago

Harrison G Zhang¹ and Gui-shuang Ying²

¹Conestoga High School, Berwyn, Pennsylvania, USA

²Department of Ophthalmology, Center for Preventive Ophthalmology and Biostatistics, The University of Pennsylvania, Philadelphia, Pennsylvania, USA

Abstract

The aim of this study is to evaluate the current practice of statistical analysis of eye data in clinical science papers published in *British Journal of Ophthalmology (BJO)* and to determine whether the practice of statistical analysis has improved in the past two decades. All clinical science papers (n=125) published in *BJO* in January–June 2017 were reviewed for their statistical analysis approaches for analysing primary ocular measure. We compared our findings to the results from a previous paper that reviewed *BJO* papers in 1995. Of 112 papers eligible for analysis, half of the studies analysed the data at an individual level because of the nature of observation, 16 (14%) studies analysed data from one eye only, 36 (32%) studies analysed data from both eyes at ocular level, one study (1%) analysed the overall summary of ocular finding per individual and three (3%) studies used the paired comparison. Among studies with data available from both eyes, 50 (89%) of 56 papers in 2017 did not analyse data from both eyes or ignored the intereye correlation, as compared with in 60 (90%) of 67 papers in 1995 (P=0.96). Among studies that analysed data from both eyes at an ocular level, 33 (92%) of 36 studies completely ignored the intereye correlation in 2017, as compared with in 16 (89%) of 18 studies in 1995 (P=0.40). A majority of studies did not analyse the data properly when data from both eyes were available. The practice of statistical analysis did not improve in the past two decades. Collaborative efforts should be made in the vision research community to improve the practice of statistical analysis for ocular data.

Introduction

A unique characteristic in ophthalmic and vision research is that outcome measurements (eg, visual acuity, intraocular pressure, refractive error) are usually taken from both eyes of a subject. These outcome measurements from both eyes of the same subject tend to be positively correlated.^{1–3} That is, a measurement from one eye is more likely to be similar to

Correspondence to: Dr Gui-shuang Ying, Center for Preventive Ophthalmology and Biostatistics, Department of Ophthalmology, The University of Pennsylvania, Philadelphia, PA 19104, USA; gsyng@pennmedicine.upenn.edu.

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that of the other eye than a measurement from the eye of an unrelated subject. Therefore, data obtained from two eyes of a subject should not be analysed the same way as data measured from two independent subjects due to the presence of the intereye correlation. So, to draw proper conclusions from the data, it is important to account for the intereye correlation while performing statistical analyses. However, many ophthalmologic investigators and vision researchers are not aware of the need to account for the intereye correlation or do not know the proper statistical methods for adjusting for the intereye correlation. Thus, correlated eye data are often analysed improperly by either completely ignoring the intereye correlation or selecting the data from only one eye per subject for analysis.^{4–8} Such inappropriate analyses can lead to biased estimates, decreased statistical power or overestimation of precision.^{9–12}

More than 20 years ago, Thompson reviewed 49 papers published in *British Journal of Ophthalmology (BJO)* during the first 6 months of 1990 and found that 23 (47%) of the papers had some statistical analysis errors, including the misuse of a statistical test.⁸ Murdoch *et al* later evaluated 79 clinical science papers published in *BJO* during the first 6 months of 1995⁷ and found that about one-third of papers only analysed data from one eye although data from both eyes were available, resulting in a waste of information and, thus, less precise estimates of effect and lower power to detect differences. More importantly, about one-fifth of papers in 1995 analysed data from both eyes but completely ignored the intereye correlation, leading to artificially narrower CIs and smaller P values.⁷

In the past two decades, statistical methods for analysing correlated data, such as the mixed effect model and generalised estimating equations,¹³¹⁴ have been developed and integrated into the statistical software (eg, SAS, R, STATA). These methods can be applied to account for the intereye correlation.²³¹⁴¹⁵ Also, several papers in ophthalmology and optometry journals have highlighted the importance of accounting for intereye correlation when analysing correlated eye data.^{2–4715–17} Short courses at professional conferences (eg, Association for Research in Vision and Ophthalmology (ARVO)) and tutorial papers²³ in ophthalmology journals also have been initiated to educate ophthalmology and vision investigators on the appropriate analysis of correlated eye data. It is reasonable to assume that these activities may improve the awareness of the need to adjust for intereye correlation and thus the improved practice of statistical analysis for correlated eye data in published papers.

The purpose of this paper is to evaluate the current practice of statistical methods for the analysis of correlated eye data by reviewing clinical science papers published in *BJO* from January to June 2017 and to determine whether the practice of analysis of correlated eye data has been improved in the past two decades by comparing to the previous findings from reviewing papers in *BJO* 1995 by Murdoch *et al*.⁷

Methods

We reviewed all clinical science papers published in *BJO* during the first 6 months (January–June) of 2017. The papers were downloaded and reviewed by the first author (HGZ). The

senior author (GsY) subsequently verified the first author's review results and made any necessary corrections.

For each paper, we determined the number of subjects and eyes included for analysis, the type of primary outcome data (continuous, categorical) and the statistical analysis approach used for analysing the primary outcome data. Our determination of statistical approach for primary outcome was based on either the description of statistical analysis in the 'Methods' section, any information in table footnotes or the statistical results presented in the 'Results' section. To facilitate the direct comparison of our findings with previous findings of Murdoch *et al*,⁷ we grouped the practice of statistical analysis for the primary outcome into the same five categories (table 1): (1) analysis at individual level because of nature of observation; (2) one eye per individual included into analysis; (3) overall summary of ocular findings per individual; (4) analysis at ocular level and (5) paired comparison.⁷ To evaluate whether the statistical analysis practice varied across countries, we also recorded the country of corresponding author. All review results were recorded in an Excel spreadsheet and imported into SAS V.9.4 for statistical analyses.

We performed descriptive analyses for frequency distributions of statistical analysis methods used by considering all papers together, by type of data and by country of the corresponding author. We used the χ^2 test for comparing findings between *BJO* 2017 papers and *BJO* 1995 papers.⁷

Results

We reviewed a total of 125 *BJO* clinical science research papers published within the first 6 months of 2017. We excluded 13 papers from case series studies that did not require statistical comparison. The findings from our review of the remaining 112 papers, along with previous findings from Murdoch *et al*'s review of 79 papers in *BJO* 1995,⁷ are presented in table 1. Of the 112 papers, half of them analysed data at individual level because of nature of observation, 16 (14%) studies only analysed data from one eye, one study used the overall summary of ocular finding per individual for analysis, 36 (32%) studies analysed data from both eyes at ocular level and three (3%) studies used the paired comparison (eg, fellow eye as control).

Among 16 studies that only analysed data from one eye, nine (56%) studies used the 'clinical selection' criteria (either worse eye or first disease eye), three (19%) studies used the random selection of an eye for analysis, two (13%) studies selected same eye (either all left eyes or all right eyes) for analysis and two (13%) studies performed analysis on the left eye and right eye separately.

Among 36 studies that analysed data from both eyes of a subject, only three (8%) studies adjusted for the intereye correlation and the remaining 33 (92%) studies completely ignored the intereye correlation, as compared with 16 (89%) of 18 studies that ignored the intereye correlation in 1995 ($P=0.40$).

Among studies with primary outcome data available from both eyes in some or all subjects, we considered the statistical analysis approach inappropriate when either: (1) only one eye

data or average of two eyes was analysed or (2) both eyes data were analysed but the intereye correlation was not adjusted for. We found that 50 (89%) of 56 studies did not analyse data properly, as compared with 60 (90%) of 67 papers in 1995 ($P=0.96$).

Among these 112 papers in 2017, the primary outcome was a continuous measure in 77 (69%) studies and a categorical measure in 35 (31%) studies (table 2). Among studies with primary outcome data available from both eyes in some or all subjects, statistical analysis was not appropriate in 38 (86%) of 44 studies with continuous primary outcome and not appropriate in all 12 (100%) studies with categorical primary outcome. In particular, when data from both eyes were analysed, 24 (89%) of 27 studies with a continuous primary outcome and all nine (100%) studies with a categorical primary outcome did not account for the intereye correlation.

When studies were analysed by the country of the corresponding author, the statistical analyses were not appropriate in 11 (85%) of 13 studies in North American countries, 26 (90%) of 29 studies in European countries, 12 (92%) of 13 studies in Asian countries and one (100%) study in Oceanian countries ($P=0.90$).

Discussion

This study evaluated the current practice of statistical analysis of eye data for studies published in *BJO* from January to June 2017. We found that among studies with data available from both eyes, statistical analysis was suboptimal in the majority (89%) of them, no matter whether the outcome measure was continuous or categorical. This suboptimal practice is widespread across countries around the world.

When outcome measures from both eyes are available and two eyes are in the same comparison groups, the investigators should first check the magnitude of intereye correlation to help decide the appropriate statistical method for analysing data from both eyes. If there exists a high degree of intereye correlation, utilising data obtained from the second eye may not add much statistical information, and analysing data from one eye only using simple statistical tests (eg, t-test for means or χ^2 test for proportions) may be acceptable. If there exists a low degree intereye correlation, analysis of data obtained from both eyes should be performed even though ignoring the intereye correlation may not have a substantial impact on the resulting CIs and P values. When outcome measures from both eyes are moderately correlated, the proper statistical analysis should analyse data from both eyes and account for their intereye correlation.

In this review, we found that many studies only analysed data from one eye even when data from both eyes are available, and this practice did not change significantly in the past 20 years (29% in this study as compared with 40% in 1995, $P=0.18$). Analysing data from only one eye can result in waste of information, less precise estimates of effect and lower power in detecting differences compared with analysis of data from two eyes. The decrease in precision and statistical power inversely depends on the intereye correlation, that is, the lower intereye correlation, the more decrease in statistical power. Among studies with analysis of data from both eyes, the majority of studies (92% in 2017 and 89% in 1995) did

not account for intereye correlation. The impact of ignoring the intereye correlation on statistical inference is dependent on whether the two eyes of a subject are in the same comparison group or not. When two eyes of a subject are in the same comparison group, failure to adjust for positive intereye correlation can falsely make the CIs too narrow and P values too small. However, when two eyes of a subject are in two different comparison groups, failure to adjust for positive intereye correlation can falsely make the CIs too wide and P values too large. These inappropriate statistical analyses (either only analysing data from one eye or ignoring the intereye correlation) can lead to the invalid conclusions from the study.

When ocular measures are available from both eyes, researchers are challenged on how to analyse the correlated eye data. In the past two decades, many steps have already been taken to improve the practice of statistical analysis for eye data including short courses in vision research conferences (eg, ARVO), statistical papers calling for the appropriate analysis of eye data^{2-4,7,15-17} and tutorial papers on how to use statistical softwares to analyse the eye data.²³ The statistical procedures for analysis of correlated eye data also have been easily available in the statistical packages (SAS, R, STATA). However, this study did not find much improvement in the statistical analysis of correlated eye data over the past two decades. This could be due to study investigators being unaware of the need to adjust for the intereye correlation or not knowing how to analyse the correlated eye data as it is less straightforward than the analysis of independent data using standard tests, for example, two group t-test for means, χ^2 test for proportions, etc. Continuing education on the appropriate analysis of correlated eye data is needed through the short courses in professional conferences, tutorial papers in ophthalmology journals and the instructional review of manuscripts by the statistical experts for ophthalmology journals. More importantly, the ophthalmic and vision researchers should seek collaborations with biostatistical experts in the design and statistical analyses for their ophthalmologic and vision studies.

The results from this review of *BJO* papers are in line with the results from review of papers in other ophthalmology and optometry journals. Karakosta *et al* reviewed 161 research articles published in five ophthalmology journals (*American Journal of Ophthalmology*, *Acta Ophthalmologica*, *The Journal of Cataract & Refractive Surgery*, *Retina*, and *Journal of Glaucoma*) in the first 2 months of 2008. Among 42 papers that reported results from both eyes, only two papers adjusted for the intereye correlation, and 31 (74%) papers did not make any adjustment for the intereye correlation.⁵ Amstrong *et al* reviewed 230 articles published in three optometry journals (*Ophthalmic and Physiological Optics*, *Optometry and Vision Science* and *Clinical and Experimental Optometry*) during 2009–2012. He found that among 82 papers with data available from both eyes, 18 (22%) papers analysed data from one eye only, 10 (12%) papers analysed data from both eyes separately, 15 (18%) papers analysed data from both eyes with fellow eye data as control, 10 (12%) papers analysed data from both eyes and adjusted for the intereye correlation and 29 (35%) papers analysed data from both eyes but did not adjust for the intereye correlation.⁴ This widespread and suboptimal statistical analysis of correlated eye data calls for the ophthalmic and vision research community to take action to improve the practice of statistical analysis for ocular studies.

This study is unique in that we evaluated the practice of statistical analysis in recent papers in the same journal and used the same approach as Murdoch *et al*'s evaluation of papers published more than two decades ago. We found that the practice of statistical analysis did not improve in past two decades, consistent with the findings from evaluation of papers published in other ophthalmic and vision journals. Collaborative efforts should be made in vision research community to improve the statistical analysis of eye data.

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Table 1

Analysis approaches employed in clinical science papers published in January–June 1995 versus January–June 2017

Approaches	Papers published in 2017 (n=112), n (%)	Papers published in 1995 (n=79)*, n (%)
Analysis at level of individual because of nature of observation	56 (50.0)	12 (15.2)
Unilateral disease or therapy or imaging	44 (39.3)	9 (11.4)
Disease entity requires both eyes for diagnosis	12 (10.7)	3 (3.8)
One eye per individual included in analysis	16 (14.3)	25 (31.6)
Random selection of eye for inclusion	3 (2.7)	5 (6.3)
Right/left selection of eye for inclusion	2 (1.8)	7 (8.9)
'Clinical selection' criteria—worse eye, first eye with disease, etc.	9 (8.0)	13 (16.5)
Analysis of left eye and right eye separately	2 (1.8)	
Overall summary of ocular findings per individual	1 (0.9)	19 (24.1)
'Pooled' findings	0 (0.0)	13 (16.5)
Average taken of results in the two fellow eyes	1 (0.9)	6 (7.6)
Analysis at ocular level	36 (32.1)	23 (29.1)
No correction for correlation between eyes	33 (29.5)	16 (20.3)
Correction for correlation between eyes	3 (2.7)	2 (2.5)
Paired comparison (fellow eye used as 'control')	3 (2.7)	5 (6.3)

* From table 1 of paper by Murdoch *et al.*⁷

Table 2

Analysis approaches employed in clinical science papers published in January–June 2017 by type of data

Approaches	Continuous measure (n=77), n (%)	Categorical measure (n=35), n (%)
Analysis at level of individual because of nature of observation	33 (42.9)	23 (65.8)
Unilateral disease or therapy or imaging	29 (37.7)	15 (42.9)
Disease entity requires both eyes for diagnosis	4 (5.2)	8 (22.9)
One eye per individual included in analysis	13 (16.9)	3 (8.7)
Random selection of eye for inclusion	3 (3.9)	0 (0.0)
Right/left selection of eye for inclusion	2 (2.6)	0 (0.0)
‘Clinical selection’ criteria—worse eye, first eye with disease, etc.	7 (9.1)	2 (5.7)
Analysis of left eye and right eye separately	1 (1.3)	1 (2.9)
Overall summary of ocular findings per individual	1 (1.3)	0 (0.0)
‘Pooled’ findings	0 (0.0)	0 (0.0)
Average taken of results in the two fellow eyes	1 (1.3)	0 (0.0)
Analysis at ocular level	27 (35.1)	9 (25.7)
No correction for correlation between eyes	24 (31.2)	9 (25.7)
Correction for correlation between eyes	3 (3.9)	0 (0.0)
Paired comparison (fellow eye used as ‘control’)	3 (3.9)	0 (0.0)