People and eyes: statistical approaches in ophthalmology

I E Murdoch, S S Morris, S N Cousens

Clinical or epidemiological studies in ophthalmology generally involve the examination of eyes for a variety of clinical signs or measurements. Unlike cardiology, hepatology, or many other clinical specialties, however, individuals have two eyes. In addition, unlike kidneys or lungs, both eyes are easily accessible for assessment and are frequently both assessed. In some instances a number of participants in a study may refuse complete assessment in both eyes, or the data from one eye may be unavailable for other reasons, resulting in data sets with information on one eye for some individuals and on two eyes for others.

If information is available on both eyes of the same individual, the findings in the left eye are generally likely to be more similar to those in the right eye of the same individual than to those in another eye from a different individual. This is because a multitude of factors, including environmental and genetic factors, act at the level of the individual and thus have an impact on the probability of the finding occurring in both eyes.

Clearly, however, the degree to which a given finding in the right eye predicts the probability of the same finding in the left eye varies considerably for different conditions. Some conditions characteristically only ever occur in one eye. This may be because the disease is rare. An example of this is choroidal melanoma which occurs in only one eye in 99% of cases. Other examples are concomitant strabismus and visual impairment being typical examples. In these circumstances it is natural to perform analyses at the level of the individual. Similarly, if the disease or intervention only ever occurs in one eye the natural level for the analysis is the individual. An example of such a situation is provided by a study of compliance with patching for amblyopia.

When an analysis based on individuals is performed correlation between observations (that is, individuals) is not a problem and such an analysis is statistically valid. In the above circumstances it is also efficient.

Data for inclusion in analysis using one eye per individual

<table>
<thead>
<tr>
<th>Patients</th>
<th>Right eye</th>
<th>Left eye</th>
<th>Random eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>18 mm Hg</td>
<td>25 mm Hg</td>
<td>18 or 23 mm Hg</td>
</tr>
<tr>
<td>Patient B</td>
<td>Retinopathy</td>
<td>Cataract</td>
<td>Retinopathy or cataract</td>
</tr>
</tbody>
</table>

In ocular disease the rule is for unilateral pathology to favour neither right nor left eyes. Even in ocular trauma, where the dominant eye has been said to be more...
often injured, there is no significant laterality. One possible exception is normal tension glaucoma which may favour left eyes. Studies of this condition which use data from only one eye per individual will need to consider carefully how they choose which eye to study.

For conditions that are equally likely to affect either eye, analyses based on only right eyes, or on only left eyes, or on a randomly selected eye are statistically equivalent. Analyses based on a single eye per individual are convenient in that standard statistical methods can be employed. The major disadvantage of this approach is a loss of information. In the extreme case when data have been collected on both eyes in all individuals and there is no correlation between right and left eye findings, half of all the information collected is unused in the analysis. Thus, the use of data from only one eye per individual is statistically valid but is likely to be inefficient (the power and precision of the analysis are less than optimal).

A second disadvantage of this approach is the potential for bias arising through the choice of which data to use. Often, if data are only available on a single eye in an individual because of incomplete data or for other reasons, that single eye is included in the analysis. Bias could occur if some individuals have data on both eyes, only one of which is “randomly” selected for analysis, while other individuals have data on only one eye which is automatically included (that is, not randomly selected). The non-random selection of eyes can introduce bias.

Similar caveats apply to the choice of the first eye with disease, worse/better eye, or operated eye.

In conclusion, the use of one eye per individual in the analysis means that between eye correlation is not a problem, but that there may be considerable “waste” of available data. In addition, incomplete data collection or selection of eyes for inclusion in a study on clinical grounds may have the potential to introduce bias. This potential bias should be acknowledged and, when possible, its likely extent assessed.

OVERALL SUMMARY OF OCULAR FINDINGS PER INDIVIDUAL

In the review of papers, the data from an individual’s two eyes were pooled in 13 reports. For example, this method was used in the study of therapies for blepharitis and in the investigation of the effect of smoking beedies on cataract development. In a further six reports the average result for the two eyes was taken. For example, the average measurement of corneal surface quality in right and left eyes was taken. For example, the average of measurements increased.) Di...
Generalised estimating equations—the outcome in each eye is modelled as a function of the risk factors and the correlation between the fellow eyes is modelled separately and explicitly.14

If used appropriately, these two approaches give similar results in most, but not all, circumstances. They represent an efficient use of available data.

PAIRED COMPARISON (FELLOW EYE USED AS "CONTROL")

In this case the fellow eye is used as a "control" for the eye of interest. Five of the studies reviewed utilised this approach. Paired designs such as the “double crossover” design advocated by Newcombe and Duff are a particularly powerful approach for comparing the effects of localised treatments on bilateral eye disease. A sign test has been proposed for comparing survivorship curves in clinical trials with correlated or paired data.15 An example of the paired approach applied outside the context of a clinical trial is provided by a study of aqueous flare in cases of choroidal melanoma in which the fellow eye was used as the control to determine if presence of the tumour resulted in increased flare.16

When appropriate, paired designs offer a very powerful approach. To benefit fully from the approach the statistical analysis must take account of the pairing.

Summary

In conclusion, when an observation by its nature involves two eyes, as for blindness, statistical analyses should be conducted on individuals rather than eyes and between eye correlation is not a problem. In other circumstances, if information on only one eye per individual is used in the analysis there is a potential “waste” of information leading to less precise estimates of effect and less power. In addition, bias may be introduced into a study if there is non-random selection of the eye for inclusion in the analysis. The use of an overall summary of ocular findings for an individual may result in “wastage” of information in a similar fashion to the use of only one eye per individual. On the other hand, an analysis of individual eyes with no allowance made for between eye correlation may result in falsely narrow confidence intervals around estimates of effect. Between eyes correlation may be assessed empirically using the kappa statistic or similar means. If between eye correlation is substantial, statistical techniques exist which can utilise all available data while allowing for the correlation. In some circumstances a powerful design may be to use the fellow eye as a “control”.

Two conclusions may be drawn from this review of analytical approaches to the analysis of clinical data in the BrJO. Firstly, the analytical approaches employed in many studies fail to use all the data available. In other words the analysis is less than “optimal”. Secondly, in a proportion of studies, inappropriate statistical methods are used which may lead the investigator to draw inappropriate conclusions. In other words, the analysis is invalid. Ophthalmic data, by their very nature, present particular statistical challenges. We emphasise the need to involve appropriate statistical expertise in the design and analysis of ophthalmic studies.

Mr Murdoch was supported by the Welcome Trust at the time this article was written.

I E MURDOCH

Department of Preventive Ophthalmology, Institute of Ophthalmology, London EC1V 9EL

S S MORRIS

Food Consumption and Nutrition Division, International Food Policy Research Institute, Washington DC, USA

S N COUSENS

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT

Correspondence to: Mr Murdoch.


People and eyes: statistical approaches in ophthalmology

I E MURDOCH, S S MORRIS and S N COUSENS

doi: 10.1136/bjo.82.8.971

Updated information and services can be found at:
http://bjo.bmj.com/content/82/8/971

These include:

References
This article cites 17 articles, 8 of which you can access for free at:
http://bjo.bmj.com/content/82/8/971#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

- Epidemiology (1075)
- Eye Lids (60)
- Lens and zonules (807)
- Muscles (254)
- Neurology (1355)
- Vision (627)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/