# Randomisation, confounding & observational methods in ophthalmic epidemiology

BY SKANDA RAJASUNDARAM, DALIA ABDULHUSSEIN, CHRISTOPHER BENTLEY AND MINAK BHALLA

## Randomisation and confounding

Understanding the relationship between an exposure and an outcome of interest is the central challenge in ophthalmic epidemiology. The exposure may be aetiological, taking the form of a putative risk biological factor, or therapeutic, in the form of a proposed treatment. Randomised controlled trials (RCTs) sit at the top of the canonical hierarchy of evidence, primarily because the process of randomisation helps balance measured and unmeasured confounders across both exposed and unexposed arms [1,2]. Given a large enough sample size, the two arms will, on average, tend to differ in only one respect: allocation to receive or not to receive the exposure under investigation. Consequently, we can attribute any differences in outcomes in the exposed vs. unexposed arms as being a causal effect of the exposure itself. In other words, we can attribute causality to the exposure because the very process of randomisation minimises bias due to confounding.

## The role of observational studies in ophthalmology

In practice, however, RCTs are extremely resource-intensive in terms of time, money and personnel. We could not feasibly perform an RCT for every possible exposure-outcome relationship of ophthalmological interest. Indeed, for many aetiological exposures, it would be unethical to perform an RCT. Take, for example, attempting to measure the effects of any exposure that we have good prior evidence or reasonable inclination to believe, has harmful effects: smoking, diabetes, hyperlipidaemia, raised intra-ocular pressure (IOP), corneal thinning, prior ophthalmic surgery. Clearly, it would be unethical to take a population of people and randomise half to receive an intervention that increased their intra-ocular pressure, simply because we wanted to measure the causal effect of raised IOP. Yet the clinical imperative to understand the downstream clinical sequalae of raised IOP is no less pertinent. Accordingly, despite the inherent vulnerability to confounding – amongst a range of other biases – we are left to observe differences in IOP that arise naturally in the population. We then look for factors associated with raised IOP that might cause the raised IOP in the first place, as well as ocular sequelae that might result as a consequence of the raised IOP. Ethics, economics and effort explain why observational studies continue to be essential tools for studying exposure-outcome relationships in Ophthalmological research. Moreover, a well-designed observational study can be highly informative. We illustrate this below using a recent study published in JAMA Ophthalmology.

## An illustrative example

Bai et al. conducted a retrospective cohort analysis of medical records in Olmsted County, Minnesota, to evaluate the risk of diabetes-associated ocular complications (DAOCs) amongst children with Type 2 Diabetes Mellitus (T2DM) vs. Type 1 Diabetes Mellitus (T1DM) during a 50-year period [3]. The study was motivated by the increasing prevalence of T2DM diabetic retinopathy in children and the relative paucity of evidence guiding the screening and management of T2DM diabetic retinopathy in comparison to that of T1DM diabetic retinopathy. In comparison to children with T1DM, there was a 1.88-fold increased risk of developing any diabetic retinopathy, a 2.33-fold increased risk of developing proliferative diabetic retinopathy and a 4.06-fold increased risk of requiring pars plana vitrectomy in children with T2DM, based on their univariate Cox regression analyses. The authors suggest that these results may warrant the need for ophthalmoscopic examination of children with T2DM at least as frequently, if not more frequently, than children with T1DM in order to prevent diabetes-associated ocular complications (DAOCs).

Firstly, it's important to acknowledge the merits in this study. The study investigates a clinically important question for which little published data currently exist. That such an analysis was possible is a testament to the consistent record-keeping over a 50-year period in Olmsted County. However, there are a number of important limitations, some of which have been discussed previously [4]. For example, Kaplan-Meier estimates were unstable beyond 15 years of follow-up owing to the small numbers of children with T2DM, insufficient duration of follow-up and participants dropping out of the study (e.g. moving away from Olmsted County) [4].

Consequently, the longer-term estimates of DAOC risk, arguably the most important estimates given the progressive and chronic nature of T2DM, are least reliable. Further, the authors' attempts to control for confounding due to differences in HbA1c levels between T1DM and T2DM populations is hampered by unstandardised recording of HbA1c prior to 1996, as highlighted by Sun. More importantly, however, attempting to statistically adjust for one parameter of possible differences in disease severity between two exposure groups, even if perfectly measured, addresses only one aspect of possible confounding. Bai et al. also produce sex and ethnicity-adjusted risk estimates. This approach does nothing to address known confounders that cannot feasibly be included as co-variates in a multivariable model and, more importantly, does nothing to account for the multitude of unknown confounders that may be exacerbating or attenuating the apparent difference in rates of DAOCs in children with T2DM vs T1DM. By definition, unknown confounders are unknown, and even the most elaborate statistical models are helpless to address them. Indeed, given the small event rate, as reflected by the presence of only 17 of the 64 children with T2DM developing any DAOC over the 50-year period, the presence of only a small degree of confounding can markedly skew final point estimates toward

the exposure of interest (T2DM), comparator group (T1DM) or null. Moreover, we cannot know in which direction unknown confounding will skew are estimates because, again, it is unknown.

## Concluding remarks

Bai et al. deserve credit for investigating the diabetes-associated ocular sequalae amongst the largest sample and longest follow-up of children diagnosed with T2DM. Nevertheless, ophthalmologists should remain aware that despite yielding statistically significant associations, non-randomised studies are inherently incapable of demonstrating causality between ophthalmological exposures and outcomes of interest, and their clinical implications should be interpreted accordingly [1,2].

### References


1. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. *N Engl J Med* 2020;**382(7)**:674-8.
2. Sedgwick P. Randomised controlled trials: understanding confounding. *BMJ* 2015;**351**:h5119.
3. Bai P, Barkmeier AJ, Hodge DO, Mohney BG. Ocular sequelae in a population-based cohort of youth diagnosed with diabetes during a 50-year period. *JAMA Ophthalmol* 2021;**140(1)**:51-7.
4. Sun JK. The growing need to understand diabetic retinopathy outcomes in youth. *JAMA Ophthalmol* 2021;**140(1)**:57-8.



**AUTHORS**

**Skanda Rajasundaram, BA (Oxon), BMBCh,**

Imperial College Ophthalmology Research Group

**Dalia Abdulhussein, BSc, MBBS,**

Imperial College Ophthalmology Research Group

**Professor Christopher Bentley,**

Consultant Ophthalmic Surgeon, St. Mary's Hospital, London, UK.

**Minak Bhalla,**

Senior Registrar at the Western Eye Hospital, London, UK.


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