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J Neuroophthalmol. Author manuscript; available in PMC 2022 October 11.

Published in final edited form as:

J Neuroophthalmol. 2020 June ; 40(2): 144–147. doi:10.1097/WNO.0000000000000970.

The Case–Control Study in Neuro-Ophthalmology

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A case–control study is an observational epidemiologic study design that compares the prevalence of a risk factor or treatment exposure between 2 groups: those with a particular disease or condition of interest (cases), and a similar group that is at risk for this disease or condition but does not have it (controls). Because cases can be pooled across different centers and years of study, case–control studies are particularly well suited for studying rare diseases, which is frequently the case in neuro-ophthalmology. However, their inherently retrospective nature makes it challenging to establish temporality and to distinguish between association and causation. They are also susceptible to recall, selection, and confounding biases. It is therefore important for neuro-ophthalmologists to be familiar with the principles of case–control study design to critically appraise the neuro-ophthalmic epidemiologic literature. In this article, presented as a companion to Lin et al's "Idiopathic Intracranial Hypertension and Anemia: A Matched Case–Control Study" (1) and Rueløkke et al's "Optic Disc Drusen Associated Anterior Ischemic Optic Neuropathy: Prevalence of Comorbidities and Vascular Risk Factors" (2), we review the basics of case–control study design and highlight several common pitfalls in case–control studies for readers to consider when evaluating new studies.

STUDY DESIGN

Cohort and case–control studies both assess the association between an exposure (cause or risk factor, independent variable) and outcome (effect, dependent variable). In contrast to a prospective cohort study, where a large group of patients with heterogeneous exposures who have not yet experienced a particular outcome is followed over time to determine who

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The authors report no conflicts of interest.

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develops the condition and who does not, case–control studies begin by identifying groups of patients with and without disease. In other words, cohort studies look forward in time, whereas case–control studies look backward in time. Identifying subjects based on outcome is ideal for studying rare diseases that have a low rate of incidence.

A case–control study begins by defining the outcome and exposure of interest. The outcome refers to the disease or condition of interest (or if one is only studying patients with a particular disease, then a prespecified event or result associated with that disease). Study subjects who have the outcome of interest are known as cases, and subjects who are at risk for the outcome (i.e., who were capable of developing it) but do not have it are known as controls. In Lin et al's study of idiopathic intracranial hypertension (IIH) and anemia, the outcome was a diagnosis of IIH according to modified Dandy criteria: cases were IIH patients who were diagnosed at a single eye clinic over a 29-month period. Controls were patients seen at the same center and during the same period for conditions other than IIH. Note that controls are defined by the absence of an outcome rather than the presence of a different outcome: a study that compares the prevalence of risk factors between 2 different diseases (e.g., anemia in IIH vs anemia in NAION) would technically not be considered a case–control study.

Exposure refers broadly to a patient-level or environmental-level characteristic or comorbidity, which can be anything from a genetic risk allele to a predisposing medical condition (in Lin et al's case, anemia), environmental exposure (e.g., smoking), or nonrandomized treatment. Case–control studies are classically retrospective in that assessment of the exposure occurs in hindsight, and the timing of the exposure is specified to occur before developing the outcome of interest. For example, in Rueløkke et al's study of ischemic optic neuropathy, patients were queried about whether they were diagnosed with sleep apnea or vascular risk factors before their diagnosis of ischemic optic neuropathy. However, this does not always occur in case–control studies. For example, Lin et al allowed for the assessment of anemia to occur at the time of IIH diagnosis or up to a year afterward, allowing for more of a cross-sectional design. Case–control studies can also use data from existing cohort studies to create a truly prospective study (these are termed nested case–control studies or case cohort studies and are beyond the scope of this review).

Neuro-ophthalmologists are rare disease specialists. Even conditions such as IIH that are common in neuro-ophthalmic clinical practice are rare at the population level: the estimated incidence of IIH among overweight or obese women aged 20–44 years in the United States is less than 20 new cases per 100,000 individuals per year (3). Case–control designs are thus well suited to the study of neuro-ophthalmic disease. If Lin et al had wanted to use a prospective cohort study design to investigate the association between anemia and the risk of developing IIH in the future, they would have had to recruit over 200,000 new subjects, each with or without anemia, to identify 50 new IIH cases over a 2 year-period. A study of that magnitude would not be feasible because it would require hundreds of personnel and hundreds of millions of dollars. Instead, Lin et al were able to query their patient database and find 50 IIH patients and 50 patients without IIH, in whom they assessed for evidence of exposure to anemia. Because case–control studies are often used to study rare conditions, the availability of cases is typically the limiting factor in sample size determinations.

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STATISTICAL CONSIDERATIONS

The standard measure of association between exposure and outcome in a case–control study is the odds ratio. An odds is a ratio of probabilities, specifically the probability of having the exposure and the probability of not having the exposure. An odds ratio, then, is a ratio of 2 odds (one for cases and one for controls). An odds ratio can best be illustrated using the classic two-by-two table—for example, using data from Table 1 in Lin et al's study, a 2-by-2 table can be created (Table 1).

For IIH, the odds of anemia diagnosis is (9/50)/(41/50) = 0.22, and for controls, the odds of anemia is (6/50)/(44/50) = 0.14; so, the odds ratio is 0.22/0.14 = 1.57. Note that in calculating the odds separately for each group, the individual sample size cancels out, and the equation for odds ratio can be simplified to $(a \times d)/(b \times c)$ as denoted by superscripts. If the odds ratio is greater than one, it indicates that cases have a greater odds of having the exposure, and if the odds ratio is less than one, it indicates the opposite. In this case, an odds ratio of 1.57 means that IIH patients are 57% more likely to have anemia than controls, and hypothesis testing (e.g., chi square test, Fisher exact test, logistic regression) is used to determine whether this is statistically significant (in this case, it was not). Continuous variables such as hemoglobin can be analyzed continuously using *t*-tests or linear regression (as in Lin et al's study) or categorically by defining categories for use in a 2-by-2 table. For example, the exposure of anemia could have been defined as hemoglobin <9 g/dL and compared to unexposed individuals with hemoglobin ≥9 g/dL. Selecting a cutpoint to define exposed and unexposed groups using a continuous variable depends on a number of factors including clinical definitions, sample size calculations, and underlying dose–response relationships.

Note that the odds ratio is technically different from the relative risk that is reported in cohort studies. Relative risk is calculated from a prospective cohort study as the incidence of the outcome in the exposed group divided by the incidence of the outcome in the unexposed group. In other words, relative risk compares the frequency of an outcome between groups according to exposure, and odds ratio compares the frequency of an exposure between groups according to outcome. Relative risk is interpreted as the extent to which a particular exposure increases the risk of developing a particular disease or outcome relative to the baseline population risk; for example, if Lin et al had conducted a prospective cohort study of anemia and IIH and found a relative risk of 1.57, it would mean that patients with anemia are 57% more likely to develop IIH than patients without anemia. In a case–control study, one cannot know the true baseline population risk (i.e., the risk of developing IIH in people without anemia) because the study is being conducted after patients have already developed or not developed the outcome. However, as long as the disease of interest is rare, the odds ratio from a case–control study will approximate the relative risk from a prospective cohort study.

SOURCES OF BIAS

In a case–control study, cases and controls are not randomized to having the exposure, and there is the potential for other differences between groups to confound the association

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between exposure and outcome, resulting in a significant association between the exposure and outcome that may in reality be due to other confounding variables associated with both the exposure and outcome. There are a number of statistical methods that can be used to adjust for potential confounding. One method that is highlighted in Lin et al's study is matching, whereby the case and control groups are balanced according to a particular characteristic, thereby removing it as a potential confounder. In this case, Lin et al matched cases to controls by sex and age to account for the fact that young women are more likely to have anemia and are also the demographic at greatest risk for developing IIH. Paired statistical tests (e.g., paired *t* test, matched chi-square test, conditional logistic regression) must be used to account for the matched structure of the data.

Although confounding is a potential weakness in any observational epidemiologic study, there are several methodologic issues that are of particular concern in case–control studies. One important type of bias is recall bias, which refers to the fact that knowing whether a patient has a disease of interest affects their ability to recall whether they had a previous exposure or not. Recall bias can occur in any retrospective study where the exposure is ascertained after the outcome is already known, and it is most problematic when the exposure is self-reported. For example, Rueløkke et al compared patients with anterior ischemic optic neuropathy who had optic disc drusen (ODD) to those who did not (NA-AION). Patients with NA-AION are often counseled at the time of their diagnosis on the relationship between vascular risk factors such as diabetes, hypertension, hyperlipidemia, smoking, and obstructive sleep apnea and NA-AION, and the theoretical possibility that better control of these risk factors could reduce their risk of fellow eye involvement. If this experience makes it more likely for patients to recall their previous diagnoses of diabetes or other vascular risk factors, there could be greater recall among those patients, and any difference in the prevalence of vascular risk factors in the NA-AION group relative to the ODD group could be exaggerated. In Lin et al's study of anemia and IIH, anemia was measured using a complete blood count (CBC) rather than self-report. Because patient recollection is not involved, recall bias is minimized.

Information Bias

Information bias can result from limited availability of data. This is a consideration in Lin et al's retrospective study, where measuring the exposure depends on the availability of data that have been collected for routine clinical purposes rather than research. Of an initial sample of 95 IIH patients, 45 (47.3%) were excluded due to a lack of available CBC. If these excluded subjects all had undiagnosed anemia, the prevalence of anemia in IIH would actually be 57% (54/95 × 100) instead of 18% (9/50 × 100), and a true association between anemia and IIH would be missed.

Selection Bias

Selection bias can occur as a result of how cases and controls are defined. For cases, rigorous diagnostic criteria (e.g., modified Dandy criteria for IIH in Lin et al's study) are used to ensure that cases have an accurate clinical diagnosis. Inclusion criteria for controls are frequently less clearly defined but are equally important. Specifically, it is important for controls to be representative of the general population of interest, and the method in

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which controls are identified should not be associated with exposure because this would result in selection bias. A famous example of selection bias comes from a case–control study of coffee consumption and pancreatic cancer (4). In this study (published in the *New England Journal of Medicine*), cases (pancreatic cancer patients) and controls (patients without pancreatic cancer) were asked about their coffee consumption, and cases were 2.7 times more likely to report drinking 3 or more cups of coffee daily. This led to widespread fear that coffee caused pancreatic cancer. However, one must ask an important question: from what population was the control group selected? In this case, controls were recruited from gastroenterology clinics, where the same providers were also seeing pancreatic cancer patients, and most control patients had gastroesophageal reflux disease, peptic ulcer disease, and other conditions that could potentially cause them to reduce their coffee consumption to reduce their symptoms. Thus, the prevalence of coffee consumption in the control group was lower than the population of patients with pancreatic cancer, resulting in a spurious association between coffee consumption and pancreatic cancer that subsequent studies have failed to confirm. In Lin et al's study of IIH and anemia, control subjects were selected from patients who were seen at the same eye center for reasons other than IIH and had a CBC collected. If their reasons for seeking ophthalmic care (e.g., dry eye, uveitis) were associated with anemia, then the prevalence of anemia in the control group would not reflect the prevalence of anemia in the general population, and this could cause selection bias. Specifically, if both the IIH and control groups have a significantly increased prevalence of anemia relative to the general population, comparing IIH to controls would fail to demonstrate a significant difference (bias toward the null). Knowing that these conditions are not associated with anemia is reassuring, although the precise indications for checking a CBC in this group remain unclear.

The potential for bias limits the generalizability of case–control study results. Prospective cohort studies protect against information and recall biases, and randomized controlled trials provide ideal control for confounding, so the findings of a case–control study would ideally be confirmed in a prospective observational or interventional study before being implemented into clinical practice, but this is not always feasible.

CONCLUSION

In summary, case–control studies are a popular epidemiologic study design, and because they are ideal for studying rare diseases, they have widespread applications in neuro-ophthalmology. However, it is important for readers to understand how case–control studies are conducted and the potentials for confounding, information, recall, and selection biases to judge the extent to which a study's findings affect true causal relationships that are relevant to the care of their patients.

Acknowledgments

A. G. Hamedani receives funding from the National Institutes of Health (NINDS T32 NS061779-10).

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TABLE 1.

Odds ratio example

	Idiopathic Intracranial Hypertension (n = 50)	Controls (n = 50)
Anemia diagnosis (current or former)	9[a]	6[b]
No anemia diagnosis	41[c]	44[d]