Case-Control Studies in Neurosurgery: The Issue of Effect Estimates

Nathan A. Shlobin[1], Victor Volovici[2-4], M. Kamran Ikram[4,5]

■ OBJECTIVE: **Clinical research questions are commonly answered using a case-control design. The decision to use this design is usually justified due to low cost, feasibility, and ease of execution. However, the case-control design presents challenges in execution, selection of cases/controls, and interpretation of effect measures (odds ratios, among others). In this paper, we clarify for a neurosurgical audience the design and appropriate effect size measures obtained from case-control studies.**

■ METHODS: **A narrative review was conducted of published literature on the topic. The future implementation of such studies was discussed and highlighted with several examples from neurosurgical practice.**

■ RESULTS: **In a case-control design, participants are selected for a study based on their outcome status. Some participants have the outcome of interest (cases), whereas others do not (controls). Controls can be selected from a variety of sources, such as the general population, relatives/friends, or hospital patients without the disease under investigation. The most important criterion is that these controls come from the same study base as cases. Furthermore, it is essential to realize that measures of association obtained from a case-control study depend on the sampling strategy of the controls and, as such, have equivalent counterparts available from cohort studies. We delineate traditional case-control, case-cohort, and incidence density–sampled case-control studies and their applicability to common conditions encountered in daily neurosurgical practice (e.g., glioblastoma, aneurysms, and epilepsy).**

■ CONCLUSIONS: **Neurosurgeons must understand the types of case-control studies and their associated effect measures to properly conduct research and incorporate research findings into clinical practice.**

INTRODUCTION

Classically, a case-control study is an observational study design in which groups with and without a known outcome are identified and then compared with respect to their exposure status, leading to the well-known effect measure of odds ratio.[1-3] Usual arguments in favor of case-control studies are that they can be conducted within a short time period, require low sample sizes, are useful in investigating outcomes that are rare or have a long latency period, and enable examination of multiple exposures.[4-6] Accordingly, case-control studies have become increasingly common within neurosurgery due to their low cost, feasibility, and ease of execution compared to prospective cohort studies and randomized controlled trials.[1] However, disadvantages of case-control studies include susceptibility to bias, in particular selection bias.[4,5,7] Similarly, case-control studies that are poorly designed or improperly interpreted can lead to inaccurate conclusions regarding risk factors for a disease.[1] Besides these pros and cons of case-control studies, another misconception that lingers on in the field of neurosurgery is that a case-control study is somehow the opposite of a cohort design.

In our modern epidemiological thinking, these designs are not opposite of each other. A case-control study is a cohort design in which the investigator—instead of examining the full cohort—efficiently samples a control group. Hence, it is important to realize that every case-control study is embedded within an

Key words
- Case-control studies
- Cohort study
- Epidemiology
- Incidence ratio
- Neurological surgery
- Odds ratio
- Risk ratio

Abbreviations and Acronyms
GBM: Glioblastoma multiforme
SAH: Subarachnoid hemorrhage

From the [1]Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA; [2]Department of Neurosurgery, [3]Center for Medical Decision Making, Department of Public Health, [4]Department of Epidemiology, and [5]Department of Neurology, Erasmus MC, Rotterdam, The Netherlands

To whom correspondence should be addressed: Victor Volovici, M.D., Ph.D. [E-mail: v.volovici@erasmusmc.nl]

Nathan A. Shlobin and Victor Volovici contributed equally and are co—first authors.

Citation: World Neurosurg. (2022) 163:e187-e191.
https://doi.org/10.1016/j.wneu.2022.03.097

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

underlying "cohort." When this underlying cohort is readily identifiable, we also refer to this design as a "nested" case-control study. Furthermore, while the odds ratio is the principal effect size measure utilized in case-control studies in practice, there has been some confusion in the literature regarding its interpretation.[8,9] In this paper, we clarify the design of a case-control study, give an overview of the appropriate effect size measures derived from such a study, and describe its applicability to neurosurgical research.

DESIGN OF A CASE-CONTROL STUDY

In a case-control design, participants are selected for a study based on their outcome status. Some participants have the outcome of interest (cases), whereas others do not have the outcome of interest (controls). The investigator observes the exposure status in both of these groups. The definition of a case should be made as specifically as possible, for example, the definition of the disease based on multiple criteria, which all should be included in order to define a case. Controls can be selected from a variety of sources, such as the general population, relatives/friends, or hospital patients without the disease under investigation. The most important criterion for the selection of cases is that they should come from the same "study base" (the underlying cohort) as that of the cases.[10,11] If well-executed, a case-control study is a more efficient study design in which one already has the outcomes of interest (perhaps collected over a long period of time), which may be used to answer a research question by selecting an appropriate control group. It goes without saying that running an equivalent cohort study would be less efficient, in terms of costs, logistics, and manpower.

MEASURES OF EFFECT IN CASE-CONTROL STUDIES

In their 2008 study examining 150 case-control studies published in top-tier general medicine, epidemiology, and clinical specialist journals, Knol et al. determined that 90% of studies reported an odds ratio, whereas the study designs employed allowed for a more accurate interpretation, such as risk ratios or incidence rate ratios.[8] More recently, a study examining 20 case-control studies published in leading medical journals by Labrecque et al. in 2020 found that only 20% used study designs that estimated the (disease) odds ratio, while 65% used a study design that estimated the incidence ratio.[9] Two studies claiming estimates could be interpreted as incidence rate ratios but reported odds ratios as their primary parameter.[9] These studies indicate that the study design, most notably the sampling strategy for controls, determines which parameter the study estimates.[8,9] In order to understand the link between odds ratios and various other measures of association, we need to go back to our primary research question. In our scientific endeavors, our primary interest is in a comparison—ceteris paribus—between exposed and nonexposed groups (or treatment/placebo). In a laboratory experiment, this situation can be controlled by the researcher. However, in research conducted in human subjects, we try to emulate this by conducting a randomized clinical trial. Nevertheless, due to ethical, financial, and other restrictions, we may not be able to conduct trials in all situations. Hence, many of our (causal) inferences are based on observational studies.

Despite its limitations due to potential biases, this same principle of comparing exposed and nonexposed individuals (e.g., treated/untreated) is also used in cohort studies. In a cohort design, we could use different measures of effect, including incidence rate ratios or cumulative incidence ratios. Yet another option—although not common practice in cohort studies—is to use the "disease odds ratio" as our effect measure, as this encapsules the comparison of the odds in favor of the outcome in the exposed group compared to the odds in favor of the outcome in the nonexposed group.[9] It is important to realize that these 3 effect measures, typical for cohort studies, have equivalent counterparts in the case-control setting.

This point has already been explained by many pre-eminent epidemiologists[10,11] and reiterated by Labrecque et al., namely that this equivalence depends on the sampling strategy used in a case-control design.[9] The usual case-control study conducted in a hospital setting, in which the sampling is done "at the end of follow-up," calculates a case/noncase exposure odds ratio that equals the disease odds ratio.[9] In contrast, the case-cohort study design, in which sampling is done "at the beginning of follow-up," allows the calculation of a case/cohort exposure odds ratio that is equivalent to the risk ratio.[9] Lastly, incidence density–sampled case-control studies use sampling on person-time to calculate the case/person-time exposure odds ratio, which is equal to the incidence rate ratio.[9] Case-control studies with underlying open cohorts that match on time and are conducted in populations with constant prevalence of the exposure also estimate incidence rate ratios.[9] **Table 1** provides a two-by-two table for a fully enumerated cohort. **Table 2** indicates the types of case-control studies and their respective effect size measures.

CHALLENGES OF FUTURE RESEARCH FOR SELECTED NEUROSURGICAL CONDITIONS

The following conditions and diseases are commonly investigated within the field of neurosurgery. Besides the clinical trials and cohort designs, these conditions can very well be studied using case-control designs.

Glioblastoma

Glioblastoma multiforme (GBM) occurs with an annual age-adjusted incidence rate of 3.19 per 100,000 individuals.[12] GBM comprises 57% of all gliomas and 48% of all primary malignant central nervous system tumors.[12] GBM has a poor prognosis due to its rapidly growing, aggressive nature, with a median survival of <2 years, despite advances in multimodal therapy and supportive care.[13-15] Clinical trials are a common mode of investigation for GBM but suffer from long induction times, low patient participation, and loss to follow-up.[16-18] The relatively low population prevalence of GBM, cost, time requirements, and potentially long latency period add further impediments.

Case-control studies may be particularly useful for GBM. For studies examining a potential novel biomarker for GBM, individuals with GBM can be designated as "cases" and those without GBM as "controls." These groups could then be compared based on the absence or presence of the biomarker to calculate the disease odds ratio. Given that biopsy samples from most patients are relatively easily available and collected in many centers for

Table 1. A Two-By-Two Table for a Fully Enumerated Cohort

Exposure Status	Outcome: Yes at the End of Follow-Up	Outcome: No at the End of Follow-Up	Total At the Start of Follow-Up	Person-Time During Follow-Up
Yes	A	B	$a + b$	PT_1
No	C	D	$c + d$	PT_0

Reproduced from Labrecque et al. 2020, with permission.
Depending on the sampling strategy, the "controls" are sampled from one of the last 3 columns with sampling fraction f.
PT_0, person-time unexposed; PT_1, person-time exposed.

research purposes, addressing the exposure issue—the absence or presence of the biomarker—should be straightforward. The challenge in these situations is the selection of proper controls, given that cases of GBM are always well-defined through pathology reports or immunohistochemistry. Avoiding selection bias to the extent possible and selecting controls as "randomly" as possible from the underlying source population determine the validity case-control study. This makes it necessary for neurosurgeons to be well cognizant of study design issues and to prepare a "pool" of potential controls to sample for future studies.

Aneurysms

The prevalence of unruptured intracranial aneurysms is 3.2%, with a mean age of 50 years and occurring more commonly in men.[19,20] Unruptured aneurysms account for 80%–85% of nontraumatic subarachnoid hemorrhages (SAHs).[21] SAH is associated with in-hospital mortality of 21.5% and 30-day mortality as high as 45%.[22-24] The risk of rupture increases with aneurysm size, patient age, cigarette smoking, autosomal dominant polycystic kidney disease, atherosclerosis, and familial predisposition, but may decrease with use of aspirin.[25-29] Aneurysms located in the vertebrobasilar region, particularly in the basilar tip, and in the posterior communicating artery have the highest risk of rupture.[20] The incidence rate of aneurysm rupture is 0.9 per 100,000 person-years, and the cumulative incidence of SAH over a 30-year period is 36.9%, though loss to follow-up may be high.[30-32] Many existing prospective cohort studies and clinical trials seek to evaluate factors associated with aneurysm rupture in various populations and examine the efficacy and safety of medical, endovascular, and surgical therapies.[33,34] However, the feasibility of these studies is often limited by the low prevalence in the general population, cost of surveillance of aneurysms, low cumulative incidence and long latency period for aneurysm rupture, and loss to follow-up.

In this case, again case-control studies may be useful. For example, studying risk factors (e.g., sex, blood pressure, biomarkers) for aneurysm rupture may be studied by identifying individuals with aneurysm rupture as "cases" and those with an unruptured aneurysm as "controls." Again, the crucial point to be aware of is that both cases and controls are identified from the same underlying cohort. Another challenge in such a study is changing exposures to potential confounders such as smoking and worsening atherosclerotic disease burden.[35] It is important for neurosurgeons to realize that these issues in case-control design are similar to the situation that one would have encountered when conducting a cohort study with time-varying confounders during follow-up. Last but not least, it is important to realize that, in the particular case of cerebral aneurysms, "controls" will always have a lower risk of rupture, as the aneurysms perceived to have a higher risk will already be treated. This issue should be accounted for at the beginning of study design.

Table 2. Types of Case-Control Studies and Effect Size Measures

Cohort Study	Case-Control Study	Sampling Strategy
Disease odds ratio (DOR) $\frac{a/b}{c/d}$	Case/noncase exposure OR $\frac{a/c}{b\ x\ f/d\ x\ f}$	Cumulative incidence sampling *"controls sampling at the end of follow-up"*
Cumulative incidence ratio (CIR) $\frac{a/(a+b)}{c/(c+d)}$	Case-source exposure OR $\frac{a/c}{(a+b)xf/(c+d)xf}$	Case cohort sampling *"controls sampling at the beginning of follow-up"*
Incidence rate ratio (IRR) $\frac{a/PT_1}{c/PT_0}$	Case–person-time OR $\frac{a/c}{PT_1xf/PT_0xf}$	Incidence rate sampling *"controls sampling during follow-up"*

f is the sampling fraction.
OR, odds ratio; PT_0, person-time unexposed; PT_1, person-time exposed.

Epilepsy

The point prevalence of active epilepsy is 6.4 per 1,000, while the lifetime prevalence is 7.6 per 1000 people, and the annual cumulative incidence of epilepsy is 67.8 per 100,000 people.[36] Epilepsy is associated with increased mortality relative to the general population[37-39] due to sudden unexpected death in epilepsy, accidents, suicide, etiologies and comorbidities such as neoplasia and vascular disease, and hospital-related and iatrogenic complications including pneumonia.[37-39] Although the proportion of people with epilepsy undergoing surgery is increasing, epilepsy surgery may be underutilized.[40,41] Prospective studies regarding the neurosurgical management of epilepsy often focus on risk factors for epilepsy and the efficacy and safety of surgical options including vagus nerve stimulation and responsive neurostimulation.[42,43] Nevertheless, these studies are limited by the low prevalence of epilepsy in the general population, heterogeneity of epilepsy, small proportion of individuals with epilepsy who undergo epilepsy surgery, and the cost of conducting studies. Case-control studies may again provide a helpful alternative.

UTILITY OF CASE-CONTROL STUDY DESIGNS IN NEUROSURGERY

Hospital-based case-control studies and exposure odds ratios may be utilized to characterize potential factors associated with favorable or unfavorable clinical, radiographic, or electroencephalographic or patient-reported outcomes of treatment for neurosurgical conditions.

Our advice for the future of research in neurosurgery is the development of international, multicenter databases of patients harboring various diseases. These databases should contain previously established relevant baseline variables. These databases will ensure that efficient, large case-control studies can be carried out in a cost-effective manner. Observational multicenter cohorts should also be established for certain diseases such as SAH or refractory epilepsy. Within these cohorts, nested case-control designs can be implemented, offering quick responses to research questions identified as important by the research community. While the ideal order of magnitude of centers working together to produce the desired nested case-control studies depends on the research question, this design nonetheless provides a means to engage a large sample size of cases and controls. Additionally, incidence density—sampled case control studies comprise the recommended unbiased method for sampling controls and allow for a snapshot of the outcome of interest at any specified time period.

Undoubtedly, the limitations of case-control studies are important to consider. A proper control group must be selected to augment the ability of the study to reveal valid associations between exposures and disease states.[4] Case-control studies are prone to recall bias, meaning those with an outcome are more likely to remember exposures than those without an outcome. This is particularly problematic for nongenetic lifestyle exposures.[4] Appropriate documentation of exposures at the time they occur, if possible, will minimize this possibility. Lastly, case-control studies must identify and appropriately measure confounding factors to mitigate their impact. Restriction or matching during the design phase or conditional logistical regression or stratification during the analysis phase represents common approaches to address confounding.[4]

CONCLUSIONS

Although the odds ratio is often cited as the singular effect measure in case-control studies, many case-control studies, if well conducted, calculate risk ratios or incidence ratios rather than odds ratios. Neurosurgeons must understand the types of case-control studies and their associated effect measures to properly conduct research and incorporate research findings into clinical practice.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Nathan A. Shlobin: Writing — original draft, Investigation, Formal analysis, Methodology, Project administration. **Victor Volovici:** Writing — review & editing, Investigation, Supervision, Validation. **M. Kamran Ikram:** Writing — review & editing, Supervision, Validation, Visualization.

REFERENCES

1. Nesvick CL, Thompson CJ, Boop FA, Klimo P. Case-control studies in neurosurgery: a review. *J Neurosurg*. 2014;121:285-296.
2. Dupépé EB, Kicielinski KP, Gordon AS, Walters BC. What is a case-control study? *Neurosurgery*. 2019;84:819-826.
3. Esene IN, Mbuagbaw L, Dechambenoit G, Reda W, Kalangu KK. Misclassification of case-control studies in neurosurgery and proposed solutions. *World Neurosurg*. 2018;112:233-242.
4. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet*. 2002;359:431-434.
5. Newman TB, Browner WS, Cummings SR, Hulley SB. Designing case control studies. *Designing Clin Res*. 2013;97.
6. Lewallen S, Courtright P. Epidemiology in practice: case-control studies. *Community Eye Health*. 1998;11:57.
7. Schlesselman JJ. *Case-control studies: design, conduct, analysis*. vol 2. England: Oxford University Press; 1982.
8. Knol MJ, Vandenbroucke JP, Scott P, Egger M. What do case-control studies estimate? Survey of methods and assumptions in published case-control research. *Am J Epidemiol*. 2008;168:1073-1081.
9. Labrecque JA, Hunink MM, Ikram MA, Ikram MK. Do case-control studies always estimate odds ratios? *Am J Epidemiol*. 2021;190:318-321.
10. Vandenbroucke JP, Pearce N. Case—control studies: basic concepts. *Int J Epidemiol*. 2012;41:1480-1489.
11. Miettinen O. Estimability and estimation in case-referent studies. *Am J Epidemiol*. 1976;103:226-235.
12. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011—2015. *Neuro Oncol*. 2018;20(suppl_4):iv1-iv86.
13. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: State of the art and future directions. *CA Cancer J Clin*. 2020;70:299-312.
14. Keime-Guibert F, Chinot O, Taillandier L, et al. Radiotherapy for glioblastoma in the elderly. *New Engl J Med*. 2007;356:1527-1535.
15. Hegi ME, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *New Engl J Med*. 2005;352:997-1003.

16. Vanderbeek AM, Rahman R, Fell G, et al. The clinical trials landscape for glioblastoma: is it adequate to develop new treatments? *Neuro Oncol*. 2018;20:1034-1043.

17. Mansouri A, Beyn ME, Pancholi A, et al. Evolution of the Neurosurgeon's role in clinical trials for glioblastoma: a systematic overview of the Clinicaltrials.Gov Database. *Neurosurg*. 2021;89:196-203.

18. Bagley SJ, Kothari S, Rahman R, et al. Glioblastoma clinical trials: Current landscape and Opportunities for Improvement. *Clin Cancer Res*. 2021;28:594-602.

19. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10:626-636.

20. Investigators ISoUIA. Unruptured intracranial aneurysms—risk of rupture and risks of surgical intervention. *New Engl J Med*. 1998;339:1725-1733.

21. Kassell NF, Torner JC, Jane JA, Haley EC, Adams HP. The International cooperative study on the timing of aneurysm surgery: Part 2: surgical results. *J Neurosurg*. 1990;73:37-47.

22. Huang J, Van Gelder JM. The probability of sudden death from rupture of intracranial aneurysms: a meta-analysis. *Neurosurgery*. 2002;51:1101-1107.

23. Bederson JB, Awad IA, Wiebers DO, et al. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Circulation*. 2000;102:2300-2308.

24. Chan V, Lindsay P, McQuiggan J, Zagorski B, Hill MD, O'Kelly C. Declining admission and mortality rates for subarachnoid hemorrhage in Canada between 2004 and 2015. *Stroke*. 2019;50:181-184.

25. Wiebers DO, Whisnant JP, Sundt TM, O'Fallon WM. The significance of unruptured intracranial saccular aneurysms. *J Neurosurg*. 1987;66:23-29.

26. Wiebers DO, Whisnant JP, O'Fallon WM. The natural history of unruptured intracranial aneurysms. *New Engl J Med*. 1981;304:696-698.

27. Hasan DM, Mahaney KB, Brown RD Jr, et al. Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture. *Stroke*. 2011;42:3156-3162.

28. Brown RD Jr, Broderick JP. Unruptured intracranial aneurysms: epidemiology, natural history, management options, and familial screening. *Lancet Neurol*. 2014;13:393-404.

29. Rinkel GJ, Djibuti M, Algra A, Van Gijn J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke*. 1998;29:251-256.

30. Lee EJ, Lee HJ, Hyun MK, et al. Rupture rate for patients with untreated unruptured intracranial aneurysms in South Korea during 2006—2009. *J Neurosurg*. 2012;117:53-59.

31. Juvela S. Growth and rupture of unruptured intracranial aneurysms. *J Neurosurg*. 2018;131:843-851.

32. Sonobe M, Yamazaki T, Yonekura M, Kikuchi H. Small unruptured intracranial aneurysm verification study: SUAVe study. *JPN Stroke*. 2010;41:1969-1977.

33. Pierot L, Barbe C, Herbreteau D, et al. Rebleeding and bleeding in the year following intracranial aneurysm coiling: analysis of a large prospective multicenter cohort of 1140 patients—analysis of Recanalization after Endovascular Treatment of Intracranial Aneurysm (ARETA) Study. *J neurointerventional Surg*. 2020;12:1219-1225.

34. Pierot L, Barbe C, Ferré J-C, et al. Patient and aneurysm factors associated with aneurysm rupture in the population of the ARETA study. *J Neuroradiol*. 2020;47:292-300.

35. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurg*. 2000;93:379-387.

36. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: a systematic review and meta-analysis of international studies. *Neurology*. 2017;88:296-303.

37. Lhatoo SD, Sander JW. Cause-specific mortality in epilepsy. *Epilepsia*. 2005;46:36-39.

38. Hitiris N, Mohanraj R, Norrie J, Brodie MJ. Mortality in epilepsy. *Epilepsy Behav*. 2007;10:363-376.

39. Cockerell OC, Hart Y, Sander JW, Goodridge D, Shorvon S, Johnson A. Mortality from epilepsy: results from a prospective population-based study. *Lancet*. 1994;344:918-921.

40. Cloppenborg T, May TW, Blümcke I, et al. Trends in epilepsy surgery: stable surgical numbers despite increasing presurgical volumes. *J Neurol Neurosurg Psychiatr*. 2016;87:1322-1329.

41. Okubo Y, Fallah A, Hayakawa I, Handa A, Nariai H. Trends in hospitalization and readmission for pediatric epilepsy and underutilization of epilepsy surgery in the United States. *Seizure*. 2020;80:263-269.

42. Geller EB. Responsive neurostimulation: review of clinical trials and insights into focal epilepsy. *Epilepsy Behav*. 2018;88:11-20.

43. Fan JJ, Shan W, Wu JP, Wang Q. Research progress of vagus nerve stimulation in the treatment of epilepsy. *CNS Neurosci Ther*. 2019;25:1222-1228.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 2 March 2022; accepted 21 March 2022

Citation: World Neurosurg. (2022) 163:e187-e191.
https://doi.org/10.1016/j.wneu.2022.03.097

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***