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Overcoming the Misinterpretation of a Measure in Observational Studies: What and When?

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Abstract: The measure of association in observational studies is often prone to misinterpretation, further necessitating a discussion of methodological challenges. Understanding the underlying causes and proposing proper steps may help prevent such issues in the literature. This article provides straightforward explanations of terminology and a decision tree to select appropriate measures and accurate interpretations.

Keywords: Measure of Effect; Bias; Statistical Analysis;

Introduction

Research on health-related outcomes has always been of particular interest. Access to real-world data (RWD) provides new avenues for medical research that are fuelling evidence generation (1). However, a considerable amount of this evidence comes from observational studies, and in addition to the lack of internal validity, their estimates are often associated with misinterpretation (2, 3). As a result, their impact remains limited as long as decision makers face issues in their reporting practice.

The odds ratio (OR) is arguably one of the most commonly used measures of association and is also frequently interpreted incorrectly, pretending to represent the risk of outcome (4). It can, however, approximate the risk ratio (RR), but only if certain conditions are met. Furthermore, the incidence rate ratio (IRR) or hazard ratio (HR) can and should also be calculated for specific case-control designs, although the OR is often reported instead. It is worth noting that there is nothing wrong with the OR, as long as it is interpreted appropriately. Previous surveys (5, 6) of over 200 observational studies published in leading medical journals revealed systematic issues in the methodology and interpretation of their findings, most of which inaccurately reported their measures, lacking sufficient discussion of their assumptions. Unfortunately, two decades after these findings were published, one can see that things are not going any better (7). Hence, discussing underlying issues and proposing appropriate steps might become key to preventing the recurrence of such issue.

Short-walk through ideas behind case-control and cohort studies.

A case-control study represents a family of different designs (hybrid retrospective, case-base, case-exposure, matched, nested, case-crossover, and case-cohort) to measure the distribution of exposure among the study population (8). Until certain assumptions are met, it is unclear whether the main parameter is the odds of exposure or the disease itself. Some of these designs are particularly efficient when the prevalence of the outcomes is low. Such circumstances allow for different estimates (e.g., RR and OR) to be used interchangeably. However, ignoring this assumption leads to an exaggeration of the effect size, further introducing both misinterpretation and magnitude error. As illustrated in Figure 1, when the outcome is less prevalent, the line becomes more diagonal, making RR and OR somewhat similar. However, as the outcome became more common, the difference between the two measures increases.

The RWD granted access to longitudinal data and provided detailed information on both the exposure and outcome. Unlike case-control studies, cohort studies (prospective, retrospective) can explicitly relate exposure to an outcome with an intuitive interpretation. The widespread use of logistic regression has made the OR a common measure, even for longitudinal data. However, it does not have a simple interpretation of RR. Furthermore, common outcomes may require incorporation of modified regression models. Nevertheless, this assumption only relates to studies that sample at the end of the follow-up period from a specific cohort, and current evidence suggests that this situation is rarely applicable in practice (5).

To properly define whether the main parameter of interest is OR, RR, IRR, or HR, one should understand the insights from the study design, sampling strategy, source of population, statistical analysis, and their interplay. This must be where the most confusion comes from, leading to some ignorance of these factors, which in turn causes errors in analysis and interpretation. Here, we aimed to simplify the terminologies, relate them to each other, and develop a straightforward decision tree for the selection of the appropriate measure with a focus on statistical techniques. To maintain simplicity, we set aside discussions of censoring, competing risks, and loss of follow-up.

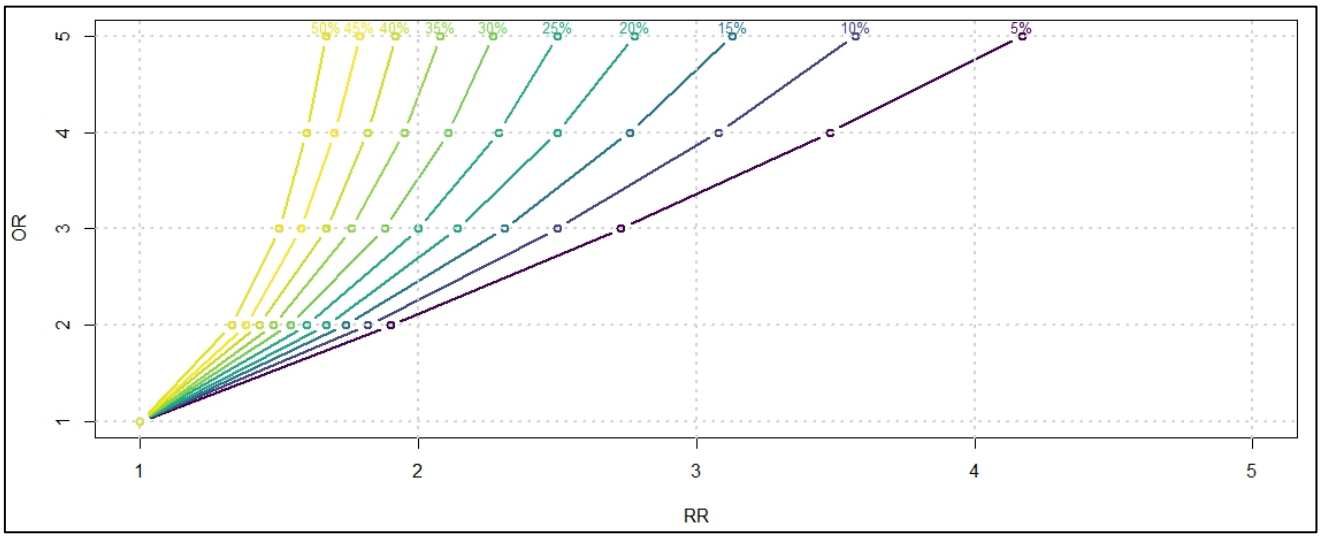

Figure 1. Comparison of odds ratios and risk ratios for different prevalence of outcome values.

The RR was approximated using formula: RR = OR / [(1−P0) + (P0 x OR). Where P0 represents the prevalence of the outcome in the non-exposed group.

Clearing confusion around the terminologies to define a measure of association

There are two population sources are available for observational studies: static and dynamic, also known as closed and open cohorts, respectively. The main difference lies in their structure over time. That is, in the closed cohort, participants are selected once, and no new entries are considered. For instance, a cohort of individuals diagnosed with pancreatic cancer in a particular year was further followed for over a year. However, open cohorts accept changes in size, follow-up, and multiple enrolments for the same participant. For example, a cohort of smokers can join if they are current smokers and leave if they quit smoking.

Both case-control and cohort studies require proper selection of the comparison group, and further interpretation of the OR differs depending on the nature of the denominator (person-time at risk, persons at risk, or survivors). The closed cohort has three commonly used sampling approaches. First, exclusive or cumulative incidence sampling that samples controls from those who remained free of outcome at the end of follow-up, where the denominator represents survivors. The measure for this sampling is OR of exposure. It can be interpreted as the RR of an outcome, assuming that the outcome is rare (<10%). Second, controls

selected from the total study population at the beginning of follow-up: inclusive sampling (case cohort). Its denominator represents the population at risk, and the measure of interest is also OR but should be interpreted as RR directly, regardless of the rare disease assumption (9). Third, controls can be sampled concurrently (longitudinally) with cases containing person-time at risk (sum of any time unit) in the denominator. The OR, in this instance will estimate the rate ratio, but it is more intuitive to use the IRR/HR right away for a clear interpretation of the estimand.

Within the open cohorts, controls are selected from the time unit at risk using incidence density sampling (nested case-control study). Another approach is to select controls at some point in time, either at the end, beginning, or during the period in which the cases are diagnosed. Such sampling allows the OR to better approximate the RR, compared to previous schemes, even assuming a rare disease (10). Although this instance allows the interpretation of OR as the rate ratio, it is more intuitive to use IRR/HR, given the information on the time unit for exposure (e.g., treatment onset, disease diagnosis date) and outcome. Finally, when it comes to recurrent diseases (e.g., acute conditions), cases return to the at-risk population after recovery (transient exposure) and represent their own controls (case-crossover). It allows the calculation of OR from conditional logistic regression, which ensures a proper account for such a dependency. The OR again approximates the RR if the outcome is rare and is not directly interchangeable.

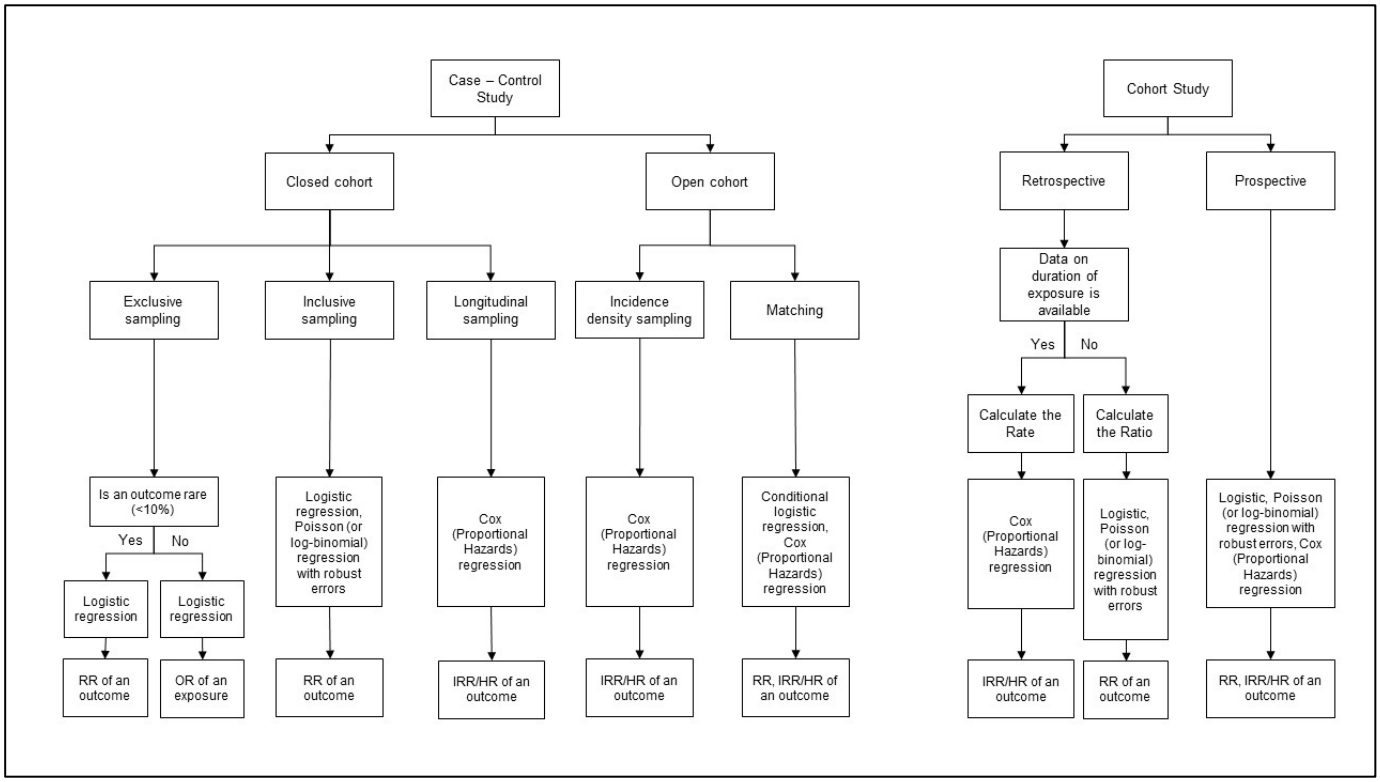

Figure 2. Decision tree for measure selection and interpretation.

In Figure 2, one can recognize that the only situation where the measure of association should be the OR, and interpreted as such, refers to a case-control study conducted within a closed cohort with exclusive sampling. Despite the fact that disease OR and exposure OR are identical, they should be interpreted as exposure OR, not a disease OR. When the study had a case-cohort design, the OR could not be interpreted as such but only as RR. The same is true for designs that use person-time rather than participant or survivor in the denominator. In these designs, the OR is not equal to the disease OR, although most studies that estimated the IRR/HR reported the OR instead. It is common to turn OR into RR, IRR, and HR immediately. However, the OR is questionable unless the assumptions are clarified.

Conclusion

Current literature suggests that a case-control study is nothing but a cohort study achieved by sampling a subset of controls to obtain a measure of exposure distribution among them. The discordance between the statistical interpretations of measures is likely driven by challenges in understanding methodological details in both epidemiology and statistics. To properly select and accurately interpret a measure, one should consider population, sampling, and statistical tests to avoid misinterpretation of the estimand.

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