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Mischievous Odds Ratios

William Steinsmith

Pieter Reitsma and colleagues have explored—in a population of patients anticoagulated with coumarin congeners—the connection between the presence of mutant alleles of a single gene and the risk of haemorrhage [1].

Using as their denominator the odds for bleeding in a patient without mutant alleles, and using as their numerator the odds for patients with each of the two mutant alleles, the authors propose the resulting odds ratios as surrogates for the relative risk of haemorrhage.

It should be noted, however, that the conflation of an odds ratio with a relative risk is not generally justified [2,3]. The relative risk is the ratio of two probabilities (p2/p1), whereas the corresponding odds ratio is [p1/(1−p1)]/[p2/(1−p2)]. Equating these two ratios requires that p1 = p2, i.e., that the risk ratio be unity.

In Reitsma and colleagues' paper, none of the eight odds ratios presented in Table 2 turn out identical with the corresponding calculated risk ratio, and the most discordant pair of values diverge by a factor of about 1.4, i.e., the odds ratio of 2.6 corresponding to a relative risk of 1.9.

Mischievous conflation of odds ratios with probability ratios is widespread in the literature dealing with laboratory testing, with the odds ratio (confusingly termed the "likelihood ratio") typically presented as surrogate for the corresponding ratio of probabilities.

The power of a positive laboratory test to enhance the likelihood of disease presence in a given patient (properly termed the "positive probability-based likelihood ratio") is the ratio of two probabilities: the probability that the patient who tested positive is truly diseased (termed the "positive predictive value") divided by the probability of disease in the pre-test population (termed the "disease prevalence").

Expressed explicitly in terms of the subcategories of the test population, the positive predictive value is the ratio represented by (True Positives)/(True Positives + False Positives), and the prevalence is the ratio represented by (True Positives + False Negatives)/(True Positives + False Negatives + True Negatives + False Positives).

The calculus is easily adapted to compute the probability-based likelihood ratio for the absence of disease in a given patient. In this case, the post-negative-test probability of disease absence (termed the "negative predictive value") is the ratio represented by (True Negatives)/(True Negatives + False Negatives), and the pre-test probability is one minus the disease prevalence. The negative probability-based likelihood ratio is, then, the ratio represented by the post-test probability divided by the pre-test probability.

A more descriptive term for the probability-based likelihood ratio would be the "probability magnifying power," since it leads to the expanded probability of the presence (or absence) of disease yielded by a positive (or negative) test result. ■

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Authors' Reply

William Steinsmith is correct that the odds ratio (OR) is used to approximate the relative risk, but incorrect that in this instance, and most other ones, the two would differ by more than a trivial amount, since he has failed to appreciate the case-control design.

Indeed, if the cumulative risk of disease is p1 in the exposed and p0 in the nonexposed, the relative risk (p1/p0) only equates the OR, [p1/(1−p1)]/[p0/(1−p0)], when exposure confers no excess risk. However, in a case-control study, p1 and p0 cannot be directly estimated (nor, obviously, can their odds), and the OR is the only possible estimator (hence its frequent use).

We will illustrate the theory starting with a cohort study, and then moving from this to a case-control study. When risks are low, the OR will always be a good approximation of the relative risk because OR = (p1/p0)/[(1−p1)/(1−p0)], in which the second part of the term will be close to one. So, suppose a trait is present in 20% of a population, with a risk of disease of 1% in those without the trait, and 2.5%

in those with the trait, i.e., a relative risk of 2.5. These are likely to be close to the actual annual numbers for risk of haemorrhage under anticoagulant treatment with and without the *VKORC1* variant [1,2]. If we follow 10,000 people for one year—8,000 without the trait, of whom 80 will develop disease; 2,000 with the trait, of whom 50 will develop disease—RR = (50/2,000)/(80/8,000) = 2.5000, and OR = (50/1,950)/(80/7,920) = 2.5385.When the OR is written out in full to [(50/2,000)/(1,950/2,000)]/[(80/8,000)/(7920/8 000)], this can easily be reduced to the above.

In a case-control study, all cases are included, but there are only a fraction of all noncases (controls). With a sampling fraction of 1/10, the case-control study sampled from this cohort would look like the following: 80 cases without and 50 cases with the trait, 792 controls without and 195 controls with the trait (OR = [50/195]/[80/792] = 2.5385).

With a sampling fraction of 1/100, there would be 79.2 unexposed and 19.5 exposed controls, and the OR would still be 2.54. This demonstrates that the actual risk or odds of disease cannot be derived once only a sample of individuals without disease are included, but that the ratio of exposed over unexposed controls (195/792) remains valid whatever the sampling fraction. This has been called the "exposure odds", and many prefer to write the OR as the exposure odds ratio: OR = (50/80)/(195/792) = 2.54.

In a cohort study, the OR can be easily recalculated into a risk ratio (RR), since the actual risks (p0 and p1) are known [3]: RR = OR/[(1−p0) + p0*OR] [3]. In the example above, RR = 2.5385/(0.99 + 0.01*2.5385) = 2.5000.

In a case-control study, because the number of controls is only a fraction of the actual number of individuals without disease in the cohort, absolute risks cannot be calculated, and a recalculation from OR to RR is not possible (unless there is external information on the absolute risks).

This implies that it is not possible to calculate from our data how different the OR was from the RR, as Steinsmith tried. We can, however, in this particular case, make an estimate, since we know the risk of haemorrhage under anticoagulant treatment from previous studies to be around 1% per year. With a background risk of 1% per year, all the ORs mentioned in our paper are within 2% of the relative risk. The highest OR of 2.6 (2.5641) would relate to a relative risk of 2.5 (2.5246)—a trivial difference. Steinsmith's further suggestions for analyses, i.e., to use likelihood ratios, are relevant to studies of diagnostic tests in which the aim is to evaluate the presence or absence of disease. This is not the analysis one would use in aetiologic studies such as ours.

Generally, since most diseases are infrequent, ORs are good estimators of relative risks under this "rare disease assumption". For a disease with a frequency of 10%, which is high, the difference between OR and RR is still only 10%. On a higher theoretical level, one could argue that the parameter to estimate is not the relative risk, but the rate ratio, i.e., the ratio of two incidence rates. While a cumulative risk is a probability, an incidence has time −1 as its unit, and lies between zero and infinity. Since the incidence rate is the basic measure of disease occurrence, the rate ratio is the prime comparator, to be preferred over relative risks (which, over time, will converge to unity, because, to quote John Maynard Keynes, "in the long run we are all dead"). It can be shown that under certain sampling conditions, i.e., when controls are sampled from a dynamic population, there is no need for the "rare disease assumption", and the OR is the exact equivalent of an incidence rate ratio [4]. ■

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