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Relative Excess Risk: An Alternative Measure of Comparative Risk

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The proverbial relative risk may not always be the most suitable measure to compare the risk of two exposures, since it inherently includes a background effect. An alternative comparative measure, the *relative excess risk*, is introduced. It applies to situations in which an "unexposed" reference group is included in addition to the two exposures under evaluation. This comparative measure is based solely on the component of risk due to the exposures, since it removes the background risk. Estimators of the relative excess risk are presented, along with formulas for the confidence intervals under cohort and case-control designs, using both crude and adjusted rate ratios. This new measure is illustrated with data from epidemiologic studies of the risks of oral contraceptives and antidiabetic drugs. *Am J Epidemiol* 1999;150:279–82.

case-control studies; cohort studies; relative risk; statistics

In assessing the risk of a drug or other exposures, a variety of comparative measures are often used. The risk of a condition subsequent to drug exposure may be estimated relative to the risk of the condition in subjects unexposed to the drug. Alternatively, the risk may be compared with that of a competing drug. For example, recent studies of the risk of venous thromboembolism (VTE) associated with the use of various oral contraceptives assessed the risk in contrast to nonuse of oral contraceptives as well as between second- and third-generation pills. In one of those studies (1), the crude rate ratio of VTE for third-generation pills compared with noncurrent use was 7.6, while that of second-generation pills was 4.2. Naturally, the resulting rate ratio that directly compares the risks of third- with second-generation pills is the ratio of the two rate ratios, namely 1.8. This rate ratio is the traditional measure used in the direct comparison of the risk of two drugs. It may not be the most suitable measure for such head-to-head comparisons.

In this paper, I propose an alternative comparative measure of risk, the relative excess risk (RER). I also provide estimates of this measure along with formulas for the confidence intervals applicable to cohort and case-control designs.

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Abbreviations: CI, confidence interval; ER, excess rate; RER, relative excess rate; RR, rate ratio; VTE, venous thromboembolism.

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BACKGROUND

Consider a cohort or case-control study designed to assess the risk of two drugs. Assume that, in addition to the two drug exposures under evaluation, the study includes an "unexposed" reference group of subjects who do not use either of the two drugs. Table 1 displays the usual contents of the frequency table resulting from such a cohort study, with r_1, r_2, and r_0 as estimates of R_1, R_2, and R_0 representing the unit rates of the event under study for drug 1, drug 2, and the unexposed group, respectively. Typically, three rate ratios (RR) will be estimated to assess the risk of these two drugs: $RR_1 = R_1/R_0$ and $RR_2 = R_2/R_0$ compare the risk of drugs 1 and 2, respectively, with the baseline unexposed risk, while $RR_{12} = R_1/R_2$, also equal to RR_1/RR_2, compares the risk of drug 1 with that of drug 2. To distinguish between the two types of rate ratios, RR_1 and RR_2 are called measures of *baseline relative risk*, and RR_{12} is called a measure of *comparative relative risk*.

While the meaning of the baseline relative risk measured by RR_1 or RR_2 is indisputable—it provides the multiplicative increase in risk over the background risk of the event- –the relevance of the comparative relative risk measured by RR_{12} is debatable. Indeed, the fact that the risk of drug 1 is RR_{12} times higher (or lower) than the risk of drug 2 may be useful as a direct comparison of risks, but conceals an important element, namely that the risks R_1 and R_2 are each inherently inflated by the background risk R_0. In fact, R_1 and R_2 are better expressed as $R_1 = R_0 + ER_1$ and $R_2 = R_0 + ER_2$, respectively, where ER_1 and ER_2 are the excess risks due to drugs 1 and 2. Expressing RR_{12} as $(R_0 + ER_1)/(R_0 + ER_2)$ reveals the role of the background risk

TABLE 1. Typical display and notation for a cohort study with two exposure groups and an unexposed group

Exposure	Cases	Person-time	Rate
Drug 1	a_1	N_1	$r_1 = a_1/N_1$
Drug 2	a_2	N_2	$r_2 = a_2/N_2$
No exposure	a_0	N_0	$r_0 = a_0/N_0$

on this comparative relative risk measure. In contrast, the comparative excess risk $ER_{12} = R_1 - R_2 = ER_1 - ER_2$ is not affected by the background risk R_0, since it is eliminated by subtraction, which is not the case for the comparative relative risk.

As an example, consider a study of the risk of motor vehicle crash among elderly drivers associated with the use of two drugs. Consider that the baseline rate is 10 motor vehicle crashes per 1,000 elderly drivers per year. If drug 1 causes an additional eight motor vehicle crashes per 1,000 elderly drivers per year, while drug 2 causes an additional four motor vehicle crashes per 1,000 per year, R_1 and R_2 would be 18 and 14 per 1,000, respectively. The comparative excess risk would be $ER_{12} = 18 - 14 =$ four motor vehicle crashes per 1,000 per year, which is unaffected by the background rate of 10 per 1,000. On the other hand, the comparative relative risk is $(10 + 8)/(10 + 4) = 1.3$, which does not express adequately the comparative nature of the two risks because it inherently includes the background effect.

METHODS

I submit that a more appropriate and telling measure of the comparison between the two drug risks is the RER, measured by the ratio of the excess rates, given by

$$\text{RER} = (R_1 - R_0)/(R_2 - R_0).$$

This measure is based solely on the component of the risk due to drug exposure, since it removes the background risk. I present estimators of the RER under a cohort or a case-control design for both crude rates and regression-adjusted rate ratios. In all cases, the confidence intervals are estimated both directly and by using the logarithmic transformed RER using the Taylor's series approach.

Crude rates

For the crude rates given in table 1, based on a cohort design, assume that the numbers of events a_i are distributed as Poisson(R_iN_i), $i = 0, 1, 2$, respectively, where R_i represents the unknown unit rate estimated by $r_i = a_i/N_i$. Thus, the estimator of RER (denoted by rer) is given by

$$\text{rer} = (r_1 - r_0)/(r_2 - r_0),$$

with 95 percent confidence interval given by

$$\text{rer} \pm 1.96\{[(r_0(\text{rer} - 1)^2/N_0) + (r_1/N_1) + (r_2\text{rer}^2/N_2)]/(r_2 - r_0)^2\}^{1/2},$$

and, on the log scale, by

$$\text{rer}\exp\{\pm 1.96[((r_0(\text{rer} - 1)^2/N_0) + (r_1/N_1) + (r_2\text{rer}^2/N_2))/(r_1 - r_0)^2]^{1/2}\},$$

where exp refers to the exponential function.

Case-control designs

Typical data from a case-control design are displayed in table 2. Since the absolute rates are not estimable from case-control studies, we note that the RER can be rewritten as a function of the two baseline rate ratios

$$\text{RER} = (\text{RR}_1 - 1)/(\text{RR}_2 - 1),$$

where RR_i are estimated by the odds ratios $\text{rr}_i = (a_id)/(b_ic)$, $i = 1, 2$. Assuming trinomial distributions for exposure among cases and controls, the estimator of RER is given by

$$\text{rer} = (\text{rr}_1 - 1)/(\text{rr}_2 - 1),$$

with the 95 percent confidence interval given by

$$\text{rer} \pm 1.96\,\text{rer}\,V^{1/2},$$

where

$$V = d((a_1(a_1 + b_1 + c + d)/D_1^2)$$

TABLE 2. Typical display and notation for a case-control study with two exposure groups and an unexposed group

Exposure	Cases	Controls	Baseline rate ratio
Drug 1	a_1	b_1	$\text{rr}_1 = (a_1d)/(b_1c)$
Drug 2	a_2	b_2	$\text{rr}_2 = (a_2d)/(b_2c)$
No exposure	c	d	1 (reference)

$$+ (a_2(a_2 + b_2 + c + d)/D_2^2)$$

$$+ a_1/(b_1D_1) + a_2/(b_2D_2)$$

$$- (a_1b_2 + a_2b_1 + 2a_1a_2)/(D_1D_2)),$$

$$D_1 = a_1d - b_1c \text{ and } D_2 = a_2d - b_2c.$$

On the log scale, the confidence interval is

$$\text{rer} \exp\{\pm 1.96V^{1/2}\}.$$

Adjusted baseline rate ratios

In the situation in which the baseline rate ratios, estimated from either cohort or case-control designs, are adjusted using logistic or Poisson regression models, the formula for confidence intervals must be modified. Here, the estimated logarithms of the baseline rate ratios along with their corresponding variances and covariances must first be obtained from the regression model. Let β_1 and β_2 represent the estimated coefficients of the logarithm of the two baseline rate ratios RR_1 and RR_2, respectively, v_1 and v_2 represent the variance estimates of β_1 and β_2, respectively, and v_{12} represent the covariance between the two. Therefore, the estimator of RER is given by

$$\text{rer} = (e^{\beta_1} - 1)/(e^{\beta_2} - 1)$$

and the 95 percent confidence interval by

$$\text{rer} \pm 1.96[(e^{2\beta_1}v_1 - 2e^{\beta_1+\beta_2}\text{rer}\, v_{12} + e^{2\beta_2}\text{rer}^2v_2)/$$

$$(e^{\beta_2} - 1)^2]^{1/2}$$

or, on the log scale, by

$$\text{rer} \exp\{\pm 1.96[(e^{2\beta_1}v_1 - 2e^{\beta_1+\beta_2}\text{rer}\, v_{12} + e^{2\beta_2}\text{rer}^2v_2)/$$

$$(e^{\beta_1} - 1)^2]^{1/2}\}.$$

TABLE 3. Data from a cohort study of the risk of venous thromboembolism (VTE) associated with the use of oral contraceptives*

Oral contraceptive	VTE cases	Person-years	Rate/ 100,000/year	Baseline rate ratio
Third generation	52	180,633	28.8	7.6
Second generation	23	143,255	16.1	4.2
No current use	5	130,590	3.8	1 (reference)

* Data are from Jick et al. (1). Comparison is for second- and third-generation oral contraceptives, including a currently unexposed reference group.

ILLUSTRATION

To illustrate this comparative measure, we consider two studies of drug risk assessment. First is the cohort study of VTE risk associated with the use of oral contraceptives, with data presented in table 3 (1) . The background (unexposed) rate of VTE is 3.8 per 100,000 per year, while the rates for third- and second-generation pills are, respectively, 28.8 and 16.1 per 100,000 per year. The baseline rate ratios of third- and second-generation pills are $rr_1 = 28.8/3.8 = 7.6$ and $rr_2 = 16.1/3.8 = 4.2$. The comparative rate ratio for third-generation pills relative to second generation is $rr_{12} = 28.8/16.1 = 1.8$ (95 percent confidence interval (CI): 1.1, 2.9). On the other hand, the RER is estimated as rer = (28.8 – 3.8)/(16.1 – 3.8) = 2.0 (95 percent CI: 0.7, 3.3 or, on the log scale, 1.1, 3.8).

The second illustration is a case-control study of the risk of motor vehicle crash associated with the use of antidiabetic drugs among elderly people, with data displayed in table 4 (2) (B. Hemmelgarn et al., submitted for publication). To assess the comparison of risk between the oral hypoglycemic metformin and insulin, the population-based study classified cases and controls as exposed to insulin, exposed to metformin, or unexposed to any antidiabetic drug in the year prior to the index date. The baseline rate ratios of insulin and metformin are $rr_1 = (79 \times 51{,}522)/(562 \times 5{,}082) = 1.43$ and $rr_2 = (37 \times 51{,}522)/(334 \times 5{,}082) = 1.12$, while the comparative rate ratio for insulin relative to metformin is $rr_{12} = (79 \times 334)/(37 \times 562) = 1.27$ (95 percent CI: 0.8, 1.9). The RER is estimated as rer = (1.43 – 1)/(1.12 – 1) = 3.4, with 95 percent CI: 0.1 – 84.9 or – 7.6 to 14.5 using the logarithmic transform. The adjusted comparative rate ratio is 1.38/1.14 = 1.21 (95 percent CI: 0.7, 1.8), while the corresponding RER is 2.8 (95 percent CI: 0.1, 55.3) or from the log scale (95 percent CI: –5.5 to 10.9).

CONCLUSION

The common relative risk may not be the most suitable measure for head-to-head comparisons of the

TABLE 4. Data from a case-control study of the risk of motor vehicle crash associated with the use of antidiabetic drugs*

Antidiabetic drug	Cases	Controls	Baseline rate ratio†	
			Crude	Adjusted‡
Insulin	79	562	1.43	1.38
Metformin	37	334	1.12	1.14
No exposure	5,082	51,522	1	1

* Data are from B. Hemmelgarn et al. (manuscript submitted for publication). Comparison is for insulin and metformin, an oral hypoglycemic agent, including an unexposed reference group.
† Rate ratio estimated from odds ratio.
‡ Adjusted for age, sex, and comorbidity.

risks of two exposures, since it conceals the background risk. The RER may be more appropriate, since it is based solely on the risk due to exposure, beyond the background risk. This approach applies in situations in which, in addition to the two exposures under evaluation, an unexposed reference group is included. Since the RER can have negative values, further research is needed on the appropriateness of the logarithmic transform to estimate confidence intervals.

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REFERENCES

1. Jick H, Jick SS, Gurewich V, et al. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995;346:1589–93.
2. Hemmelgarn B, Suissa S, Huang A, et al. Benzodiazepine use and the risk of motor vehicle crashes in the elderly. JAMA 1997;278:27–31.