

A confidence interval for the difference between two reaction indices

Oliver Kuss¹ and Heinrich Dickel²

¹Institute of Medical Epidemiology, Biostatistics, and Informatics, Medical Faculty, Martin-Luther-University of Halle-Wittenberg, Halle (Saale), Germany and

²Department of Dermatology, Venereology and Allergology, Ruhr University Bochum, Bochum, Germany

doi:10.1111/j.1600-0536.2010.01826.x

Key words: confidence interval; contact allergy; patch testing; reaction index.

Introduction

The reaction index (RI), introduced 1992 by Brasch and Henseler (1), is routinely used to evaluate the quality of patch test preparations. Only recently, we gave a simple formula for a confidence interval (CI) for the RI to assess the sampling variability of this index (2). Because the RI is also used to compare preparations of the same allergen in different and independent populations, we supplement our previous work here with a CI for the difference between two RIs. As an example, we use the recent comparison of RIs from a German (3) [Information Network of Departments of Dermatology (IVDK)] and a Danish (4, Odense) population on seven common allergens that is also discussed in Brasch and Geier (5).

Methods

We consider two groups (1 and 2) for which we would like to measure the difference between RIs. The RI in group 1

(henceforth denoted as 'RI₁') relates the number of allergic reactions to the number of non-negative reactions in group 1 by the formula

$$RI_1 = \frac{a_1 - q_1 - i_1}{a_1 + q_1 + i_1} \quad (1)$$

where a_1 is the number of allergic reactions, q_1 is the number of questionable reactions, and i_1 is the number of irritant reactions, all in group 1. The reaction index in group 2, RI₂, is defined analogously.

As already noted in our previous paper (2), RI₁ is not a true proportion with a range of values from 0 to 1, but we can perceive it as a difference of two true proportions, $p_1 = a_1/(a_1 + q_1 + i_1)$ and $p'_1 = (q_1 + i_1)/(a_1 + q_1 + i_1) = 1 - p_1$. Expanding the numerator of RI₁ by $(+a_1 - a_1)$ allows us (after some straightforward calculations) to write $RI_1 = 2p_1 - 1$. With the same approach for RI₂, the difference between RI₁ and RI₂ becomes $RI_1 - RI_2 = (2 \times p_1 - 1) - (2 \times p_2 - 1) = 2 \times (p_1 - p_2) = 2 \times RD$, where RD is the risk difference between p_1 and p_2 ($RD = p_1 - p_2$). That is, we can write the difference between two RIs as twice the difference between the true proportions p_1 and p_2 . This, however, immediately gives us a CI for the RI difference by use of the standard interval for a risk difference (6, p. 72)

Correspondence: Oliver Kuss, Institute of Medical Epidemiology, Biostatistics, and Informatics, Medical Faculty, Martin-Luther-University of Halle-Wittenberg, Magdeburger Str. 8, 06097 Halle (Saale), Germany.
Tel: +49-345-557-3582; Fax: +49-345-557-3580.
E-mail: oliver.kuss@medizin.uni-halle.de

Conflicts of interest: The authors have declared no conflicts.

and doubling its range. We find the 95% CI for the RI difference as

$$RI_1 - RI_2 \pm 1.96 \times 2 \times \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}} \quad (2)$$

where 1.96 equals the corresponding two-sided 5% quantile from the standard normal distribution. With use of the original terms, the 95% CI becomes

$$RI_1 - RI_2 \pm 1.96 \times 2 \times \sqrt{\frac{a_1(q_1 + i_1)}{(a_1 + q_1 + i_1)^3} + \frac{a_2(q_2 + i_2)}{(a_2 + q_2 + i_2)^3}} \quad (3)$$

In Table 1, we give RI differences and their 95% CIs for the comparison between the IVDK (3) and the Odense populations (4) for seven common allergens. In all but one case (formaldehyde), we find large RI differences with small CIs. As, in these cases, the value of 0 (indicating no RI difference) lies outside the CI, we find six allergens with significantly different RIs.

Discussion

For comparison of two RIs while correctly assessing sampling variability, we derived a CI for their difference. Like our previously proposed CI for a single RI (2), this is simple to calculate, and we encourage researchers to use it in their future work.

We issue two notes of caution. First, the CI proposed here was derived under the assumption of independent observations in both groups. This assumption is not necessarily fulfilled in all situations of interest; for example, when RIs for two different allergens in the same population are compared, one proband may contribute patch test results for both allergens, thus invalidating

Table 1. Comparison of reaction indexes (RIs) obtained from a German (3) [Information Network of Departments of Dermatology (IVDK)] and a Danish (4, Odense) population for seven common allergens

	RI _{IVDK}	RI _{Odense}	Difference between RIs (95% CIs)
Nickel sulfate	0.75	0.32	0.43 (0.39; 0.47)
p-Phenylenediamine	0.53	0.07	0.46 (0.34; 0.58)
Thiuram mix	0.59	0.10	0.49 (0.39; 0.60)
Fragrance mix I	0.52	-0.18	0.71 (0.64; 0.78)
Potassium dichromate	0.46	-0.42	0.88 (0.81; 0.96)
Myroxylon pereirae	0.46	-0.18	0.63 (0.51; 0.75)
Formaldehyde	0.27	0.22	0.05 (-0.08; 0.17)

CI, confidence interval.

It should be noted that Geier et al. (3) only reported a (number of positive reactions) and $q + i$ (number of doubtful or irritant reactions) in their population. However, our CI can be computed. Similarly, Andersen and Andersen (4) only reported the numerator ($a - q - i$) and the denominator ($a + q + i$) of the RIs. In this case, straightforward calculations yield the actual figures of a and $q + i$, and the CI for the RI difference can be computed.

the independence assumption. However, use of the CI proposed here necessarily gives a conservative result; that is, proper adjustment for dependent observations in both groups would always give a narrower interval. Moreover, with dependent observations and additional information on which observations come from which proband, one could view the problem of comparing RIs as a special case of a generalized linear mixed model (6, p. 492 ff.) with a binomial likelihood and an identity link, but we feel that a sound elaboration of this model is beyond the scope of this article.

Second, the CI proposed here is only valid asymptotically, that is, for large sample sizes. In accordance with our recommendation given for the CI of a single RI (2), we feel that sample sizes in both groups (n_1 and n_2) should be larger than 100, if p_1 and p_2 lie between 0.1 and 0.9, to give a valid CI for the difference between RIs.

References

- Brasch J, Henseler T. The reaction index: a parameter to assess the quality of patch test preparations. *Contact Dermatitis* 1992; **27**: 203–204.
- Kuss O, Dickel H. A confidence interval for the reaction index. *Contact Dermatitis* 2010; **62**: 252–253.
- Geier J, Uter W, Lessmann H, Schnuch A. The positivity ratio – another parameter to assess the diagnostic quality of a patch test preparation. *Contact Dermatitis* 2003; **48**: 280–282.
- Andersen K E, Andersen F. The reaction index and positivity ratio revisited. *Contact Dermatitis* 2008; **58**: 28–31.
- Brasch J, Geier J. How to use the reaction index and positivity ratio. *Contact Dermatitis* 2008; **59**: 63–65.
- Agresti A. Categorical data analysis. *Wiley Series in Probability and Statistics*, 2nd edition: Hoboken, John Wiley & Sons, Inc., 2002: pp. 1–710.