J Bras Pneumol. 2016;42(4):240-240
http://dx.doi.org/10.1590/S1806-37562016000000225

Test for trend: evaluating dose-response effects in association studies

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PRACTICAL SCENARIO

In a prospective cohort study, the association between maternal stress and asthma in children was evaluated. The authors were interested in determining the effect that increasing levels of maternal stress has on the prevalence of asthma in offspring by 6 years of age. Maternal stress was measured using a questionnaire and categorized as 0, 1-2, 3-4, or ≥ 5 negative pre- and post-natal life events; asthma was diagnosed by physicians. The authors reported that increasing levels of maternal stress, compared with zero negative events, were associated with increasing odds of offspring having asthma during childhood: for 1-2 events, OR = 1.30 (95% CI: 0.72-2.37); for 3-4 events, OR = 1.92 (95% CI: 1.03-3.57); and for ≥ 5 events, OR = 3.52 (95% CI: 1.79-6.93). The p for trend (ptrend) was < 0.01 (Figure 1).

BACKGROUND

When conducting studies that evaluate the association between a risk factor with more than two categories and with a natural ordering—in our example, maternal stress is an ordinal variable with four levels—we can choose to evaluate the association between each category of the risk factor and the outcome by comparing it with a reference level or determining whether increasing or decreasing levels of the risk factor are associated with increasing or decreasing levels of the outcome.[1,2] This analysis is called *testing for dose-response* or *testing for trend* of the effect of the risk factor on the outcome.[3]

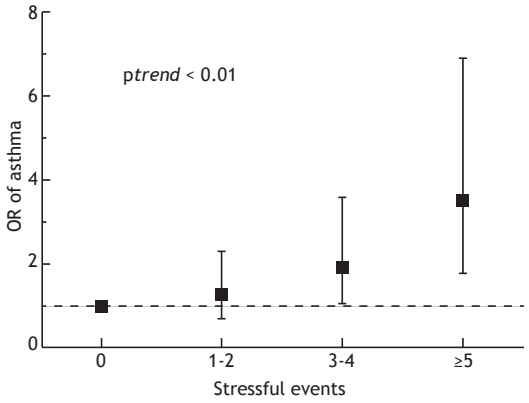

Figure 1. Association between the number of maternal pre- and post-natal stressful events and the odds of childhood asthma in offspring. Black squares represent ORs, and error bars are the 95% confidence intervals. A dose-response effect is confirmed with the test for trend (p*trend*)[2].

In our example, the authors were interested in determining whether an increasing number of maternal stressful life events was associated with increased odds of offspring being diagnosed with asthma. They first reported the effects that each level of maternal stress had on the diagnosis of asthma in offspring by reporting the OR and 95% CI compared with the lowest level of such stress; then, they reported the dose-response effect or trend of the effect of maternal stress on asthma in offspring by calculating and reporting the p*trend,* which was statistically significant. If we consider the OR for each level of stress, compared with zero negative events, we see that all levels of exposure to maternal stress increased the risk of asthma in offspring (all ORs > 1.0), although only 3-4 events and ≥ 5 events were statistically significant, indicated by the fact that the corresponding 95% CI did not include 1.0. However, the p*trend* indicates that increasing maternal stress across *all* levels increases the odds of physician-diagnosed asthma in offspring.

Regression methods are commonly used to test for trend.[3] When reporting a test for trend, we usually list each category of the risk factor and the strength of the effect (i.e., odds ratio) of each category on the outcome compared with the reference level, the p value at each level, and additionally the p*trend.* The p*trend* is the unique information we need in order to determine whether there is a dose-response effect.

WHY TEST FOR TREND?

As shown in our example, a test for trend can demonstrate a dose-response association between the risk factor and the outcome even if the association is not statistically significant for any particular level of exposure. Translated to clinical decision-making, knowledge of a dose-response association can help clinicians and patients understand that any increase in the level of exposure to a modifiable risk factor (e.g., maternal stress, cigarette smoking, and air pollution) increases the effect of that risk factor on a particular outcome.

RECOMMENDED READING

1. Lee A, Mathilda Chiu YH, Rosa MJ, Jara C, Wright RO, Coull BA, et al. Prenatal and postnatal stress and asthma in children: Temporal- and sex-specific associations. J Allergy Clin Immunol. Mar 4. pii: S0091-6749(16)00191-3. [Epub ahead of print] http://dx.doi.org/10.1016/j.jaci.2016.01.014
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ISSN 1806-3713