

there are a few reports on glucocorticoid allergic patients having tolerated unconjugated nonesterified corticosteroids in challenge tests (1). Even in this paper, the three patients were challenged with different corticosteroids, and not with the same unesterified as we did for our two cases. There is one single report of a patient who had positive skin testing only to glucocorticoids with succinate ester but tolerance of derivatives without succinate ester. These findings suggest an independent immunologic potential of the esters (7). Again, the unesterified corticosteroid of the clinical reaction was not included in the one used for the challenges. Thus, our two cases make up the first direct proof of succinate allergy.

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References

1. Erdmann SM, Abuzahra F, Merk HF, Schroeder A, Baron JM. Anaphylaxis induced by glucocorticoids. *J Am Board Fam Pract* 2005;**18**:143–146.
2. Venturini M, Lobera T, Del Pozo MD, Gonzalez I, Blasco A. Immediate hypersensitivity to corticosteroids. *J Investig Allergol Clin Immunol* 2006;**16**: 51–56.
3. Kamm GL, Hagmeyer KO. Allergic type reactions to corticosteroids. *Ann Pharmacother* 1999;**33**:451–460.
4. Freedman MD, Schocket AL, Chapel N. Anaphylaxis after intravenous methylprednisolone administration. *JAMA* 1981;**245**:607–608.
5. Chapman SC, Loughnan BA, Somerfield SD. Immediate hypersensitivity skin testing in a case of hydrocortisone anaphylaxis: case report. *N Z Med J* 1979;**90**:380.
6. Moreno-Ancillo A, Martin-Munoz F, Martin-Barroso JA, Diaz-Pena JM, Ojeda JA. Anaphylaxis to 6-alpha-methylprednisolone in an eight-years-old child. *J Allergy Clin Immunol* 1996;**97**: 1169–1171.
7. Burgdorff T, Venemalm L, Vogt T, Landthaler M, Stolz W. IgE-mediated anaphylactic reaction induced by succinate ester of methylprednisolone. *Ann Allergy Asthma Immunol* 2002;**89**:425–428.
8. Sanz M, Gamboa PM, Antepara I. Flow cytometric basophil activation by detection of CD63 expression in patients with immediate-type hypersensitivity reactions to betalactam antibiotics. *Clin Exp Allergy* 2002;**32**:277–286.
9. Schuster C, Wüthrich B, Hartmann K, Kuhn M. Anaphylaxis to E-466. *Allergy* 2000;**55**:303–304.

Heterogeneity can impair the results of Cochrane meta-analyses despite accordance with statistical guidelines

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Key words: allergic rhinitis; Cochrane meta-analysis; heterogeneity; influence statistics; specific immunotherapy.

Results from Cochrane meta-analyses are regarded as 'golden standard' within evidence based medicine. Despite compliance with strict selection criteria for studies and specific statistical guidelines for a Cochrane meta-analysis (1), a significant limitation to the current methodology is the common lack of attention to the influence of heterogeneity on the overall outcome. The aim of this article is to illustrate how valuable information regarding the impact and size of heterogeneity can be obtained using influence statistics.

We recommend including influence plots and influence statistics in all meta-analyses impaired by significant heterogeneity.

A recently published meta-analysis evaluating the effect of specific immunotherapy (SIT) in patients with seasonal allergic rhinitis (AR) is used as an example (2). This meta-analysis confirms that SIT is effective in reducing symptoms and use of rescue medication; but, it is impaired by significant heterogeneity. The Cochrane statistical guideline recommends a test for the potential presence (χ^2 test) and size (I^2) of heterogeneity (1); but, no recommendations regarding the influence of heterogeneity on the final result of the meta-analysis are provided.

Here, we use the Cochrane AR meta-analysis (2) to illustrate how influence plots and statistics can be applied. An influence plot is easily interpretable and shows the overall result of the meta-analysis when leaving one study out at a time (3–5). Figure 1 is an influence plot of the symptom scores (Fig. 1A) and the medication scores (Fig. 1B) from the Cochrane AR meta-analysis (2). A large difference between the result obtained with fixed and random models indicates heterogeneity (3–5), which is confirmed by a small χ^2 test value and a large I^2 (Fig. 1).

For the symptom score, two outlier studies (6, 7) ($dfbetas < -0.5$) are identified as major contributors to the heterogeneity. The two studies performed by Ortolani et al. (6, 7) comprise 26 actively treated patients (and 24 placebo group patients) (2). After exclusion of these two studies comprising 4.7% of the patients, the overall standardized mean difference (SMD) changes from $-0.73 [-0.97; -0.50]$ to $-0.53 [-0.66; -0.39]$ [SMD (95% CI)] and the heterogeneity disappears (Fig. 1C).

For the medication score, a single study (8) comprising only 2.9% of all patients (18 actively treated and 10 placebo group patients) causes the heterogeneity and is an outlier (2) ($dfbetas < -1.3$). After exclusion of this study, the overall SMD for medication score changes from $-0.57 [-0.82; -0.32]$ to $-0.41 [-0.54; -0.27]$ (Fig. 1D).

Obvious reasons for the heterogeneity caused by outlier studies should be sought. In both studies by Ortolani et al. (6, 7) experimental extracts were used (2). The study by Dolz et al. (8) showing an impressive medication score, was performed with an established product (Alutard SQ, ALK-Abello, Denmark)

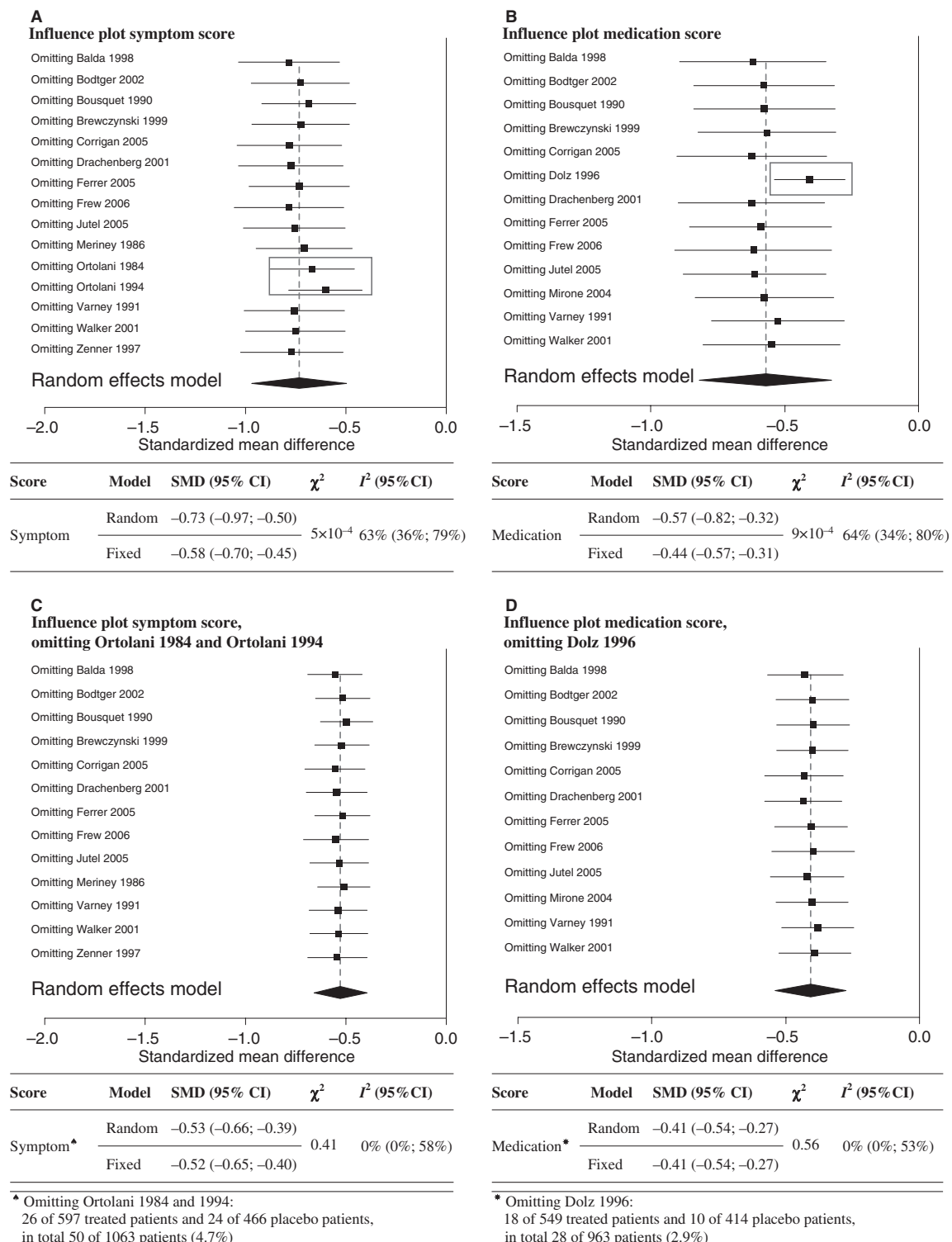


Figure 1. Figure 1 shows influence plots illustrating the symptom and medication scores, respectively, based on data from the AR meta-analysis (2). An influence plot shows the effect on the overall result after removing each of the single studies one by one. (A) Influence plot for the symptom scores based on data from the AR meta-analysis (2). The square frames the two outlier studies (Ortolani et al.). Significant heterogeneity is present (χ^2 test = 0.0005), [I^2 = 63% (36%; 79%)]. (B) Influence plot for the medication scores based on data from the AR meta-analysis (2). The square frames the outlier study (Dolz et al.). Significant heterogeneity is present (χ^2 test = 0.0009), [I^2 of 64% (34%; 80%)]. (C) Influence plot for symptom scores after omitting the two outlier studies by Ortolani et al. Significant heterogeneity is not present (χ^2 test = 0.41) [I^2 is approaching zero = 3.2% (0%; 58%)]. (D) Influence plot for medication scores after omitting the outlier study (Dolz et al.). Significant heterogeneity is not present (χ^2 test = 0.56) [I^2 = 0% (0%; 53%)].

given continuously for 3 years, whereas results following shorter treatment regimens were reported in most of the remaining studies (2). These factors may at least partly explain the extreme outcomes of the three influential studies, which were causing the heterogeneity of the original AR meta-analysis, and the lesson learned from this could be that characteristics of individual SIT products might also contribute to the different clinical outcomes.

Thus, excluding studies identified as extreme outliers from the AR meta-analysis (as generally advised within statistics) using influence statistics helped identify outliers and reasons for heterogeneity. Subsequently, the overall result of the AR meta-analysis was still clearly significant and without heterogeneity (Fig. 1C and D). However, there might be other cases where the outcome is less clear, and where very few patients can be pivotal for the final result.

In conclusion, caution should be exercised upon interpretation of results from meta-analyses with significant heterogeneity. We recommend including influence statistics and influence plots into the statistical guidelines of the Cochrane Library and in all meta-analyses impaired by significant heterogeneity.

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References

1. The Cochrane Collaboration[®]. Statistical Guideline. <http://www.cochrane.org>; accessed 1 October 2008.

2. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database of Systematic Reviews 2007; Issue 1: CD001936(DOI: 10.1002/14651858.CD001936.pub2).
3. Higgins JPT, Thomson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.
4. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–560.
5. Cook RD, Weisberg S. *Residuals and influence in regression*. New York: Chapman and Hall, 1982.
6. Ortolani C, Pastorello E, Moss RB, Hsu YP, Restuccia M, Joppolo G et al. Grass pollen immunotherapy: a single year double-blind, placebo-controlled study in patients with grass pollen-induced asthma and rhinitis. *J Allergy Clin Immunol* 1984;**73**:283–290.
7. Ortolani C, Pastorello EA, Incorvaia C, Ispuno M, Farioli L, Zara C et al. A double-blind, placebo-controlled study of immunotherapy with an alginate-conjugated extract of *Parietaria judaica* in patients with *Parietaria* hay fever. *Allergy* 1994;**49**:13–21.
8. Dolz I, Martinez-Cocera C, Bartolome JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. *Allergy* 1996;**51**:489–500.

Fruit proteins: another cause of food protein-induced enterocolitis syndrome

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Key words: enterocolitis syndrome; fruit proteins.

A female patient presented recurring vomiting and hypotonia. The patient was full-term, initially breast-fed. At 2 months, a hypoallergenic formula was used to supplement breast-feeding because of positive fam-

ily history for atopy. At 4 months, solid foods (apple, pear and banana, crisps and tapioca) were introduced in her diet without any evident problem. At the 5th month of age, cow's milk (CM)-based formula (Humana plus[®]; Humana Italia S.p.A., Milan, Italy) was introduced. Patient developed repeated episodes of vomiting, hypotonia and diarrhoea few hours after the meal. CM allergy was diagnosed and a soy-based formula was substituted to supplement breast-feeding. Soy formula was continued for 15 days without troubles, suspended because of exclusive breast-feeding for 2 weeks, and then introduced again. At this time, soy supplementation was associated with frequent vomiting, hypotonia and lethargy. Similar reactions after reintroduction of apple, pear and banana occurred. She was admitted to local hospital and treated with intravenous fluid. A fructose challenge performed at 10 months of age in a local hospital was negative. An amino acid formula (Neocate[®]; SHS International Ltd, Liverpool, UK) was introduced; this was well tolerated and it was the only food used up to 12 months of age when she was admitted to our department for further evaluation.

At admission, the child's physical examination was normal; weight was 1 SD below the median. Evaluation included urine, stool cultures, toxicology and metabolic screening that resulted negative. Serum tests for specific IgE (Unicap; Phadia, Uppsala, Sweden) were negative except for CM (1.71 kUA/l). Skin prick tests (prick by prick) with pear, apple, banana, soy and CM resulted negative.

We performed an oral food challenge to CM, which resulted negative, and consequently, CM was added to her diet. An oral food challenge to soy was considered unnecessary, but soy was not allowed. Some days later, an oral food challenge with 10 g of mixed fruits (apple, pear and banana) was performed. The dose was administered gradually over a period of 45 min. Two hours later, the patient developed repetitive vomiting, had a decrease in blood pressure, and became lethargic. A complete blood count performed before challenge (2228/mm³ PMNs; 25.7% PMNs) was compared with the one performed 6 h after the challenge

Proteins contained in fruits can be responsible of FPIES, which may have a prolonged course.