

CORRESPONDENCE

The accuracy of allergometric test for diagnosis of food allergy

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We thank Soares-Weiser et al. (1) for their interesting article and we would like to discuss some points.

By reading the article, we do not clearly understand whether a distinction has been made between IgE-mediated and non-IgE-mediated food allergy (FA). We assume that the authors agree that assessing sIgE in a non-IgE-mediated disease such as food-protein-induced enterocolitis syndrome does not add to the diagnostic accuracy. If reported data merely refer to the IgE-mediated FA, then the results are pretty disheartening. There are more than 10% expected failed diagnosis in IgE-mediated cow milk allergy (CMA).

As it is difficult to compare food allergen extracts produced by different manufacturers, prick by prick (PbP) with fresh food is widely considered a reliable diagnostic tool. Authors seem to overlook the PbP technique. Onesimo et al. (2) report PbP with fresh cow milk to have a 100% sensitivity in IgE-mediated CMA. In their study, they actually utilize open oral food challenge (OFC) instead of double-blind placebo-controlled food challenge (DBPCFC). Nevertheless, OFC may be considered reliable in case of negative challenges or for those positive challenges that elicit objective signs correlated with the clinical history and laboratory data (3). Soares-Weiser et al. (1) included only 24 studies in which 50% or more of diagnosis had been reached by DBPCFC. Including studies in which open OFC had been utilized might have broaden the search strategy.

On the other hand, it can be argued that 50% of DBPCFC is not that much, anyway. As it is impossible to separate the patients who have been submitted to the DBPCFC from the patients who have not, the diagnostic accuracy of the test may lose much of its reliability.

However, the authors include in their review the Sampson's study (4) where we read: '...in the present study only 33% of the diagnoses of egg or milk allergy, 2% of the diagnoses for peanut allergy, and none of the diagnoses of fish allergy were based on DBPCFC results. Because the previously established diagnostic predictability for soy- and

wheat-specific IgE values were poor, most children underwent DBPCFCs to establish the diagnosis of wheat or soy'. Considering the above-mentioned inclusion criteria, one should expect the Sampson's data to be considered only for what concerns wheat and soy, but in the table this is not clearly shown. It seems, on the contrary, that all foods have been considered.

Could the authors better clarify the reasons for such an apparent contradiction?

The authors searched seven databases, they write. This is pretty good, but it would be appreciable to know the key words they have utilized for their research. We would also like to ask authors to better clarify the exclusion criteria of the studies. For example, we wonder why the Ott et al. study (5) has not been considered eligible for the review. In this study, diagnosis was obtained by the DBPCFC in 71% of cases (6), and moreover, it could have been one of the few studies in which data of component-resolved diagnosis (CRD) were available.

Finally, the authors claim that 'due to the limited number of studies available for each meta-analysis, we were unable to use meta-regression to explore potential sources of heterogeneity in test performance as planned'. But, if so, would not have been it better to avoid the meta-analysis at all and perform instead a qualitative systematic review?

Conflicts of interest

None declared.

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REPLY

We thank Sopo and Scala for their letter in response to our systematic review (1). Our focus in this work was on IgE-mediated food allergy and this is clearly documented in our published systematic review protocol (2). Our search strategy is also detailed in this protocol (2).

We undertook searches for the time period 2000–2012, focusing on the major bibliographic databases and the tests that are most commonly employed in clinical practice across Europe. Based on our experiences of undertaking numerous systematic reviews, we think it is probably unlikely that extending our searches to additional databases would have uncovered much of an additional literature. We do however agree that future work should seek to extend this work to include prick-by-prick tests.

We took the a priori decision to consider the double-blind placebo controlled food challenge (DBPCFC) as the reference standard (2), and therefore excluded studies predominantly employing open food challenges [OFC] because of the high risk of bias associated with such procedures (2). In relation to the Sampson 2001 study (3), this was included because it had DBPCFC for more than 50% for some allergies, but because this was not consistently the case data from this study were not incorporated into any of the meta-analyses. The authors are we think confusing this study with two other studies by the same author i.e. Sampson 1984 (4) and Sampson 1997 (5). The Ott 2008 study was excluded because we at the time of undertaking the review only had access to a conference proceeding which noted 'controlled oral food challenge', but without giving additional details (6).

In relation to the point about heterogeneity, this is expected in meta-analysis of diagnostic test accuracy studies (7, 8). As such, meta-analyses tend to focus on computing average rather than common accuracy, hierarchical random effects models are recommended to provide an estimate of the average accuracy and to describe the variability across studies. In test accuracy reviews, large differences (some of which may be due to chance because test accuracy studies are often small) are often observed between studies indicating that diagnostic test accuracy does vary between the studies and/or that there is heterogeneity in test accuracy. We made a judgment that it was appropriate to pool the data after considering the similarity of the patient populations and tests, the methodological quality of the included studies and whether the results were likely to mislead. One of the sources

of heterogeneity here was the different test thresholds used to make a diagnosis. In our meta-analyses, in order to obtain pooled estimates of sensitivity and specificity from the bivariate model we therefore restricted meta-analyses to studies that reported a common threshold. The uncertainty around the point estimates was reflected in the size of the confidence region around each summary point on the SROC plots and prediction regions (not shown on the plots) provided an indication of the between study heterogeneity. Meta-regression models allow investigation of the relationship between test accuracy and potential sources of heterogeneity in an attempt to explain some of the observed variation in accuracy between studies. In summary, we believe we have not overstated our conclusions which take into account the uncertainty, quality and paucity of the evidence.

Conflicts of interest

Karla Soares-Weiser has no conflict of interest in relation to this document. Antonella Muraro has provided scientific advice for Meda. Karin Hoffmann-Sommergruber has received honoraria from ThermoFisher and Milupa. Aziz Sheikh has provided scientific advice to ALK-Abelló, Meda, Lincoln Medical, ThermoFisher, Pfizer, and Stallergenes; he is on the Anaphylaxis Campaign UK's Scientific Committee, World Allergy Organization's Anaphylaxis Special Committee, UK Resuscitation Council's Anaphylaxis Committee, and the BSACI's Standard of Care Committee.

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Primary prevention of food allergy in children and adults

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de Silva et al. (1) summarized the literature on primary prevention of food allergy, concluding that:

there was evidence to recommend avoiding cow's milk and substituting with extensively or partially hydrolyzed whey or casein formulas for infants at high risk for the first 4 months

We believe this conclusion is premature and does not appropriately reflect the level of evidence currently available (2) for the following reasons.

Firstly, the authors based these comments on studies that had imprecise measures of food allergy. These studies used either aggregate outcomes (including all atopic disease in one outcome variable) or heterogeneous outcomes varying from self-report (well known to overestimate food allergy) to the gold standard of challenge-proven food allergy. Of the six original RCTs included in this review which both had a food allergy outcome and compared either extensively or partially hydrolyzed formula with cow's milk formula, five studies comprising 1145 children showed no significant difference and only one study comprising 58 children showed reduced cow's milk sensitivity associated with hydrolyzed formula at 6 months of age. Furthermore, inclusion of studies using parent report and other non-gold standard measures severely limits the robustness of the findings when these studies are summarized in systematic reviews (3). Neither of the two systematic reviews (4, 5) cited in support of extensively hydrolyzed formula had a specific food allergy or food sensitization outcome; the outcomes instead were measured as 'atopic disease'.

Secondly, conclusions drawn from the two systematic reviews cited to support the use of partially hydrolyzed

formula for food allergy prevention are questionable. One of the systematic reviews does not advocate the use of partially hydrolyzed formulas for food allergy prevention. Rather, after noting the poor quality and heterogeneity of the studies within the review, the authors recommend that further trials of a larger and better quality are required before firm conclusions can be drawn (6). Although the second review (7) concluded that the use of partially hydrolyzed formula instead of standard formula was effective in allergy prevention, when the results were broken down by type of allergy, this was only true for atopic dermatitis/eczema. In this review, evidence to support the use of partially hydrolyzed formula for the prevention of food allergy came from a single RCT that included only 67 exclusively formula-fed infants. In this study, differences in atopic symptoms were found only for the first 6 months of a 5-year follow-up. In contrast, neither of the two largest RCTs investigating this question, the Melbourne Atopy Cohort Study and the German Infant Nutritional Intervention, have shown a reduction in food allergy associated with the use of hydrolyzed formulas.

Finally, the majority of these studies are underpowered. The number of participants for individual studies varied from 58 to 2252; however, these were then divided into three or more groups for different formula arms, and positive outcomes within these groups were rare. To have 80% power to detect a reduction of at least 30% in food allergy between different formula groups, assuming a food allergy prevalence of 10%, you would require 1422 participants in each formula group.

As any recommendation for the prevention of allergic disease, including food allergy, has the potential to affect