

Early Introduction of Egg and Development of Egg Allergy

Bandar Al-Saud^{a, b} Sigurveig T. Sigurdardóttir^{c, d}

^aSection of Pediatric Allergy/Immunology, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; ^bCollege of Medicine, Alfaisal University, Riyadh, Saudi Arabia; ^cDepartment of Immunology, Landspítali University Hospital, Reykjavik, Iceland; ^dFaculty of Medicine, University of Iceland, Reykjavik, Iceland

Dear Editor,

Di Mario and Cattaneo [1] wrote a letter with several critiques on our recent published systematic review and meta-analysis on early introduction of egg and the development of egg allergy in children [2]. The points addressed are extremely important. The population was identified to include a wide definition because we expected a limited number of published randomized clinical trials. However, all the studies included patients who were considered high-risk infants, as >50% of the patients in any study had a positive family history for a first-degree relative with atopic diseases. Moreover, we clearly pointed this out in our paper, whereas heterogeneity of the populations was one of the limitations. The study by Natsume et al. [3] included infants at age of 4–5 months and randomized them at the age of 6 months, this is still within our inclusion window of 3–6 months of age. In our meta-analysis, we did as well point out that the trial by Natsume et al. [3] showed unequivocal benefit from feeding high-risk infants with egg in a step-up dose manner until 12 months of age. That study raises the question if such a low

dose induces tolerance via hyposensitization or via primary prevention. The primary outcome in the study by Tan et al. [4] was egg sensitization by allergy skin tests; however, they also had oral food challenge at 12 months, which was reported as a secondary outcome data that we and others [5] extracted for the meta-analysis. The first trial by Palmer et al. [6] included only patients with eczema; however, all the other trials had patients with eczema as well (range 9–100%) [2]. Di Mario and Cattaneo suggested to exclude these three trials [3, 4, 6] from the analysis because of clinical heterogeneity. However, all three studies included in the forest plot by Di Mario et al. [7–9] also had issues in clinical heterogeneity. The population in Perkin et al [7] is healthy babies, while in Palmer et al. [8] it is infants with a first-degree relative with atopic disease. The dose and the nature of the egg are different in these studies as well. Therefore, clinical heterogeneity is unavoidable, as studies brought together in a systematic review will differ, and the variability among studies will lead to heterogeneity. There are multiple strategies for ad-

ressing heterogeneity other than to exclude studies [10]. Two strategies were used in our meta-analysis, namely performing a random-effects meta-analysis and conducting subgroup analyses to explore the variable egg dose used in the trials. Moreover, as long as the statistical heterogeneity is acceptable ($I^2 < 50\%$), the pooled effect can be reported in a meta-analysis [10]. Heterogeneity should be discussed and considered when it comes to applying the results in clinical practice and policy making. We also acknowledge that caution should be taken when discussing early feeding of allergenic food to children. As we pointed out in our paper, the evidence for early introduction to egg (as early as 3 months of age) to the diet of infants is of low-to-moderate quality.

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