

CORRESPONDENCE

Is it the true incidence of IgE-cow's milk allergy (CMA) or CMA or IgE-CMA in some countries and CMA in others

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We were pleased to read the manuscript by Schoemaker et al. (Allergy 2015, doi: 10.1111/all.12630), which analyzes the prevalence of cow's milk allergy (CMA) in a large prospective cohort representing various geographical and ethnic regions of origin of the European population. The most interesting and meaningful finding was that the prevalence of IgE-associated CMA was 0.44–0.59%, similar to data from a population-based prospective study that included a comparable number of newborns born in the same period (2004–2006) from Israel (1). This prevalence is much lower than the perceived allergy to cow's milk and lower than the most widely cited figures for IgE-mediated food allergy (2).

The authors included in the report both IgE-CMA and non-IgE-mediated CMA. These conditions differ in their prevalence, inheritance, diagnostic criteria, prognosis, morbidity, and even mortality. The inclusion criteria were defined as symptoms within 2 h, to ensure the capture of cases of IgE-CMA allergy. As all of the infants whose parents refused an oral food challenge (OFC) had negative skin prick tests (SPTs), it is reasonable to assume that not even a single case of IgE-CMA was missed.

The 2-h observation interval should have eliminated the non-IgE reactions or non-allergic reactions. However, this time limitation might have excluded some Food Protein Induced Enterocolitis Syndrome (FPIES) patients while including others. It is also possible that parents of an infant with a recent FPIES reaction would have chosen to defer the challenge.

Furthermore, the criterion of a reaction manifested by repetitive vomiting ($\pm$ lethargy, $\pm$ diarrhea) is missing both in the inclusion criteria and in the report of OFC outcome. Is it possible that there was not a single case of FPIES? This seems unlikely, considering that in the Israeli birth cohort, cow's milk FPIES was diagnosed in

0.34% of the infants under the age of 12 months (3). Or perhaps were they included under the non-IgE-sensitized patients? It seems that at least some if not all non-IgE-sensitized CMA in the report had FPIES. Is it possible that FPIES cases were reported from the UK and the Netherlands only, two centers with the highest rates of non-IgE-CMA?

Many authors include food protein-induced allergic proctocolitis (FPIAP) under CMA. As there were no cases of bloody stools in the report, there are two options: either these cases were not included or there was not a single case of FPIAP in the study population. While the estimates of FPIAP prevalence vary widely, ranging from 0.16% in a prospective cohort study (4) to 64% of the infants with isolated rectal bleeding (5, 6), it seems unlikely that no cases of rectal bleeding have occurred.

Considering the limitations of the study methodology and potential selection bias, we are concerned that the study underestimated the prevalence of non-IgE-mediated infantile CMA, in particular cow's milk FPIES and FPIAP, and as such cannot be considered an accurate estimate of an overall CMA prevalence.

Conflicts of interest

No conflict of interest.

Y. Katz¹, A. Nowak-Węgrzyn²

¹Allergy and Immunology Institute, Assaf Harofeh Medical Center, Zerifin, Israel,

²Icahn School of Medicine, New York, NY, USA

E-mail: ykatz49@gmail.com

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Reply

We thank our colleagues for their comments on our manuscript 'Incidence and natural history of challenge-proven cow's milk allergy in European children – EuroPrevall birth cohort' (1) and contributing to the debate concerning the prevalence of non-IgE-associated cow's milk allergy.

Katz and Nowak-Węgrzyn as well as Koletzko and Heine suggest that we may have underestimated the incidence of non-IgE cow's milk allergy in our population-based study as our stringent double-blind placebo-controlled food challenge design was more likely to identify children with IgE- rather than non-IgE-associated cow's milk allergy. As we stated in our manuscript, the definition of confirmed cow's milk allergy used in the present analysis was strict [i.e., only predefined objective signs of an allergic reaction within 2 h of the food challenge test and/or an increase in eczema (i.e., SCORAD score ≥ 10)]. This was to eliminate potential study center and physician differences which may occur when cases are defined using subjective and delayed (mostly gastrointestinal) symptoms. By doing this, we aimed to ensure that the cases across all nine study centers were similarly defined, allowing a better comparison to be made between the countries involved in the multicenter cohort, which was a major objective of the EuroPrevall birth cohort study. As a trade-off, this meant that some possible cases of cow's milk allergy with a different symptomatology may not have been identified in this multinational European cohort while possibly being considered as being cow's milk allergic by the local center physicians. This point was made in the limitations section of our manuscript (1) and explains the difference in the number of cases in the Netherlands cohort between our manuscript and that published by Petrus et al. (2) who also included children who did not meet our strict EuroPrevall definition but developed (parent-reported) delayed reactions. These children could have had symptoms (i) later than 2 h of the challenge finishing, (ii) after a prolonged double-blind food challenge test over 10 days, or (iii) after an open challenge to cow's milk.

Katz and Nowak-Węgrzyn and Koletzko and Heine also raised concern that cases of food protein-induced enterocolitis syndrome (FPIES) and/or food protein-induced allergic proctocolitis (FPIAP) may have been missed by our diagnostic approach. Although we cannot completely rule this out, we do not believe that many such cases were missed due to the close and sustained follow-up of the cohort participants throughout the duration of the study.

During the preparation of the manuscript, the authors debated whether only IgE-associated cow's milk allergy should be included in the results (for clarity), but most considered it important to highlight that not all cow's milk allergy is associated with IgE antibodies. Therefore, we decided to also report the number of children who met the stringently defined diagnostic criteria although they had no measurable IgE antibodies. Such cases have not often been reported in previous epidemiological research papers, and this practice may perpetuate the clinical situation of some children with cow's milk allergy being misdiagnosed due to the absence of measurable IgE antibodies or positive skin prick test.

However, we would like to join with the authors of these letters in the call for well-designed epidemiological studies to determine the true prevalence of non-IgE-associated food allergy. Our experience demonstrates that such a clinically diverse population as is seen in food allergy requires careful methodological design to ensure all cases are identified, regardless of their immunological mechanism. Within the iF-AAM project, which follows up children of the EuroPrevall birth cohort, we aim to achieve this using symptom grading, a predefined decision algorithm which accounts for a harmonized set of questionnaire items and multiple outcomes along the subjective/objective continuum.

K. E. Grimshaw¹, K. Beyer², L. Grabenhenrich³, T. Keil³,
A. B. Sprickelman⁴ and G. Roberts¹

¹*Clinical Experimental Science Academic Unit, University of Southampton Faculty of Medicine, Southampton, UK,*

²*Department of Paediatric Pneumology and Immunology, Charité University Medical Centre,*

³*Charité University Medical Centre, Epidemiology and Health Economics, Charité University Medical Centre, Berlin, Germany,*

⁴*Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands*

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