

Correspondence

No reason to change the current guidelines on allergy prevention

To the Editor:

Lowe et al¹ report on a single-blind randomized trial on the effects of soy or partially hydrolyzed whey formula (pHWF) compared with cow's milk protein formula (CMF) on allergy risk in 620 infants with a family history of allergy and found no group difference at age 2 years for cumulative incidence of any allergic manifestation (CMF, 48.7%; soy, 54.5%; pHWF, 53.4%), eczema, or food allergy. In contrast to the authors, we conclude that this study should not lead to changing current recommendations on allergy prevention because of its severe methodological limitations, including addition of a third intervention arm after study start, high randomization losses, lack of double blinding and information on allocation concealment, changing definitions of outcome parameters compared with previous publications on this cohort, unsatisfactory assessment thereof, and limited statistical power.

Lowe et al¹ reported a far higher prevalence for allergic outcomes than other high-quality trials, such as the German Infant Nutritional Intervention study,²⁻⁴ which appears to be due to weak outcome assessment. Moreover, different case definitions of eczema were used in the present publication¹ compared with previous publications on this study (see Table E1, the Methods section, and references in this article's Online Repository at www.jacionline.org).^{E1,E2} Even the single blinding must be questioned. In earlier publications an intervention was not reported, but it was considered an "epidemiologic study."^{E1,E2} A later publication reported randomization but no masking⁵ and stated that "parents of infants in any of the 3 randomly allocated formula groups could elect to give their child a non-randomly allocated soy formula or soy milk at any stage during the first 2 years of life." Children allocated to soy formula were more likely to consume parent-selected soy formulas or soy milk (35.9% vs 22.8% and 23.3% in the other groups).⁵ The preferential parental selection of soy milk in infants allocated to soy study formula questions whether the study's blinding was effective.

The current publication does not report any data on non-adherence but only numbers of children who did not receive allocated formula. The results are uninterpretable without disclosing the number of infants exposed to a formula other than the allocated formula during the intervention. The authors do not reveal the number of study formula-fed infants compliant with the allocated feeding regimens in the first 4 months of life. The data suggest that 32% (61/193) of subjects receiving CMF and 23.6% (45/191) of subjects receiving pHWF were noncompliant. Only 80 to 82 children per group consumed the allocated formula for 2 or more weeks during the first 4 months. The calculated statistical power based on such a small group number is only 12% with the reported 6% difference in prevalence.

It is unexplained why this report on primary study outcome assessed at age 2 years was only published some 17 years after the end of recruitment, whereas several publications on secondary questions have been previously published.^{5,E1-E5} The authors postulate a publication bias of the Cochrane review supporting the preventive use of pHWF in infants with a family risk of allergy.⁶ They fail to cite 2 further meta-analyses on the subject^{E6,E7} and

that the Cochrane review excluded their study because of excessive randomization losses (38%), which are not reported in the present publication.

The reported study results and the authors' conclusions do not provide a sufficient basis to change the evidence-based recommendations for infant feeding strategies to reduce allergy risk.

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Disclosure of potential conflict of interest: B. Koletzko receives research support from the European Commission, Bundesministerium für Bildung und Forschung, and the Child Health Foundation. A. von Berg receives honoraria from Nestlé. The rest of the authors declare that they have no relevant conflicts of interest.

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Available online October 27, 2011.
doi:10.1016/j.jaci.2011.08.038

Reply

To the Editor:

We agree with Koletzko et al¹ that our study,² like all studies, has some limitations. However, these limitations are by no means as severe as they suggest.¹ We address their criticisms of the scientific merit of the study here, while dealing with this group's other statements, including the delay in publication, within this article's Online Repository at www.jacionline.org.

In our study 92.7% of children completed follow-up until 2 years of age compared with 79.8% for the German Infant Nutritional Intervention (GINI) study.³ The Cochrane review on this topic⁴ excluded studies with less than 80% follow-up.

ADDITIONAL COMMENTS

According to the retrospective trial registration of the Melbourne Allergy Cohort Study (ACTRN12609000734268, registered on 25.08.2009, <http://www.anzctr.org.au>), the primary outcome of the study (allergic manifestations, such as eczema, food reactions, and urticaria) was assessed by means of telephone interviews with parents. The present publication reported that a case definition was based on doctor-diagnosed eczema or any rash that was treated with a topical steroid preparation, excluding a rash that only affected the scalp or nappy region.¹ In contrast, the authors reported using different case definitions for eczema in previous publications on this cohort, such as at least 8 days¹ or at least 10 days² of steroid treatment. Many parents could not recall whether their doctor had mentioned the word "eczema."¹ Different numbers are reported in the different publications. For example, in the 2007 publication, it was stated that "50 had insufficient data to determine whether they had eczema during the first year of life,"^{E3} whereas the recent article states that 45 children (620-575 children) had insufficient data and therefore did not enter final analysis.¹ Similarly, the definition on food reaction was based on parental reporting of development of a skin rash, a flare of pre-existing eczema, signs of anaphylaxis, or vomiting. It is well known that parental reporting leads to a marked overestimation of food allergy prevalence.^{E8} In contrast, in the German Infant Nutritional Intervention study all outcome items were fixed in a study manual before recruitment. The children were seen 6 times within the first 2 years of life, with extra visits in case of suspected allergic manifestation.^{2,3} If eczema was identified by the study physician, a specialist in allergy who was blinded to any information on that child assessed the morphology of the skin lesions and the location/spreading, severity, subjective symptoms,

and duration with a SCORAD score.^{E9} The persistence of skin lesions was documented in parental diaries on a weekly basis for the first 6 months of life and monthly thereafter. Diagnosis of atopic dermatitis was based on an algorithm with the requirement that 2 physicians confirmed skin lesions plus itching or use of steroid/antihistamines in addition to a documented persistence of dermatitis for more than 14 days or recurrent lesions. Case definitions for urticaria and food allergy were based on a meaningful allergen elimination and challenge procedure.²

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TABLE E1. Comparison between the GINI study² and MACS¹ regarding recruitment, study characteristics, and definitions of outcome parameters

	GINI (n = 2252)	MACS (n = 620)
Recruitment years	1995-1998	1990-1994
At-risk children	Yes	Yes
Control formula	CMF	CMF
Intervention	pHWF, eHWF, eHCF	pHWF, soy formula
Intervention period	6 mo	12 mo
Randomization at birth	Yes	Yes but later addition of pHWF arm
Blinding	Double blind, 4 letters for each of the 4 formulas, which were packed in identical tins	Single blind, no information given whether size and shape of tins were identical
Allocation concealment	Yes	No
Exclusive breast-feeding until 4 mo	42% to 44%	~50%
Assessment at follow-up	Weekly diaries, 0-6 mo; monthly diaries, 7-12 mo; interviews at visits and per telephone	Telephone interview monthly until 64 wk and at 78 and 104 wk
Physical examination	≥6 times within 2 y	
Definition of outcome parameters	Defined in study manual before recruitment, strict algorithm for case definition	Case definition changed over the years and between different publications on the same cohort
Eczema	Skin inspection by 2 independent study physicians and SCORAD score, ^{E7} symptoms, and medication	Parental reporting by telephone
Urticaria	Two times by the same food, elimination/challenge procedure	Parental reporting by telephone
Food allergy	Elimination/challenge procedure	Parental reporting by telephone
Specific IgE	Specific IgE in serum at 4, 12, and 36 mo	Skin prick tests at 6, 12, and 24 mo
Eczema in ITT at 2 y in CMF	16.2%	43.0%
Eczema in ITT at 2 y in pHWF	14.9%	48.7%
Sensitization to milk at 12 mo	4.4%	5.8%

The cumulative prevalence of eczema at 2 years of age was 2.7 to 3.3 times higher in MACS compared with that seen in the GINI study, with similar rates for milk sensitization. *eHCF*, Extensively hydrolyzed casein formula; *eHWF*, extensively hydrolyzed whey formula; *GINI*, German Infant Nutritional Intervention; *ITT*, intention-to-treat population; *MACS*, Melbourne Allergy Cohort Study.