

Correspondence

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.

The slight delay in the introduction of the final formula did not materially influence the study results because the baseline risk factors remained balanced between the groups. Exclusion of the 97 children recruited before the third formula became available did not substantially alter the study outcome (odds ratio of 1.23 [95% CI, 0.80-1.89] when comparing partially hydrolyzed whey formula [pHWF] with cow's milk formula for the primary end point).

It was intended that the research staff and participants be blinded in this study, but because of events beyond our control (late supply of pHWF), blinding of research staff could potentially have been broken. For this reason, we have limited the description of this study as being single (participant) blind. Despite the claims of Koletzko et al,¹ there was no evidence that participants were unblinded. We asked parents to breast-feed or only use the allocated formula up to the child's first birthday.² Although we encouraged parents to adhere to these recommendations, parents could choose to break with this feeding protocol. As we clearly stated, most (69.1% to 76.4% across the 3 study arms) were fully compliant with these guidelines. At the conclusion of the 12-month dietary guidelines, children in our soy arm were slightly more likely to receive nonallocated soy formula.⁵

Since 2006, we have published 8 articles from this study related to eczema, and all have defined eczema in the same manner as reported in the current article.^{5,E11-E18} The prior definitions mentioned¹ were used in 2 articles published before 2004.

In contrast, the definitions used by GINI have changed between publications from clinically diagnosed disease^{6,7} to parent-reported outcomes.³ The reason provided by the GINI group to justify this change was that the "[p]reventive effects for AD and AM were *more often significant* when the diagnosis was based on parent-reported physician's diagnosis,"³ suggesting the possibility of selective outcome reporting from this study.

To allow direct comparison of the results of both the GINI study^{3,6,7} and the Melbourne Allergy Cohort Study,² the 2 largest studies on this topic, we have provided a table with the reported results (see Table E1 in this article's Online Repository at www.jacionline.org). Both studies failed to demonstrate a beneficial effect of pHWF for allergic manifestations, eczema, asthma or allergic rhinitis with intention-to-treat analysis. The only area in which the results of these studies diverge is on the per-protocol analysis within the first year of life. Per-protocol analyses are not protected (from bias) by the randomization process.

Furthermore, a per-protocol analysis of our data² does not confirm the findings of the GINI analysis.^{3,6,7}

It is necessary to integrate data across studies to obtain an overview of the effectiveness of a treatment. To this end, we have informed the authors of the Cochrane review on this topic,⁴ the most reliable and independent meta-analysis on this subject to date, that the results of our study have now been published. We have requested that these review authors consider this study when they next update their review. We look forward to the proper integration of the current study² into the literature before any decisions are made to change (or retain) the current infant-feeding guidelines.

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ADDITIONAL RESPONSES TO KOLETZKO ET AL

Koletzko et al^{E1} comment extensively on the high prevalence of eczema reported within this study^{E2} when compared with results of their own.^{E3-E5} First, the difference in the rate of eczema observed between these studies is related to differences in baseline prevalence. Australia leads the world in rates of eczema and other allergic diseases. For example, from the International Study of Asthma and Allergies in Childhood Phase Three study, the estimated prevalence of eczema in 6-year-old Melbourne children was 17.1% compared with 7.9% in Germany,^{E6} where the GINI study was conducted.^{E3-E5} Furthermore, most eczema commences in very early life and then commonly goes into remission.^{E7} In a community setting 40.6% of unselected 1-year-old Victorian children were found to have current eczema when examined by a dermatologist.^{E8} In the GINI study, a modified version of Hanifin and Rajka's^{E9} definition of eczema was used, which has not previously been validated in children less than 2 years of age. In our recent validation study, although the definition used within the GINI study was highly specific (100%; 95% CI, 86.8% to 100%), it missed approximately 50% of cases of current eczema (sensitivity, 48.0; 95% CI, 27.8% to 68.7%) in the first year of life.^{E10} We suspect the GINI group might have underestimated eczema in their cohort.

At the end of 1996, a report from our study was submitted to the funding body, indicating that we were unable to identify any protective effect of pHWF in this at-risk population. Nonetheless, we elected to continue following this population, and the final collection of 7-year-old data was completed in 2001. Recognizing the value of these data for understanding the natural history of allergic diseases in childhood and for the risk factors related to them, we elected to use the data to examine a range of important questions in work that has resulted in multiple publications.^{E11-E23} Given the lack of effect of the allocated formula within this study, results from the different groups were pooled. The use of data arising from randomized controlled trials to address research questions that were not the primary intention of the original study is common, and the GINI group have done this repeatedly with their own data (eg, Filipiak et al^{E24}).

Since the reporting of the GINI study data from 2003 onward^{E3-E5} suggesting a beneficial effect of pHWF feeding on the incidence of allergic manifestations in high risk children, the support for this strategy has increased to such a point that guideline documents are now promoting its use. Hence we re-examined our data by extending our analysis for the 1996 report to include asthma and other allergic outcomes in childhood, but we did not find any benefit associated with use of pHWF. We believe that it is important to add our sobering experience with this intervention to the literature, particularly given the current level of enthusiasm for pHWF.

The systematic reviews and meta-analyses^{E25,E26} cited by Koletzko et al^{E1} were both published after we submitted our article.^{E2} As stated by the US Food and Drug Administration in May 2011 (<http://www.fda.gov/Food/LabelingNutrition/LabelClaims/QualifiedHealthClaims/ucm256731.htm>), which considered the meta-analyses cited by Koletzko et al,^{E1} "the relationship between feeding a 100 percent whey-protein partially hydrolyzed infant formula for the first 4 months of life and a reduced risk of atopic dermatitis throughout the first year of life and up to 3 years of age is uncertain."

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TABLE E1. Comparison of results between the MACS and GINI trials for the comparison of pHWF versus conventional cow's milk formula for allergic disease prevention

	MACS ^{E2}	GINI, 1 y ^{E3}	GINI, 3 y ^{E4}	GINI, 6 y ^{E5}
Compliance				
0-4 mo	91.5% (526/575)	93% (1834/1972)	91% (1877/2061)	91% (1877/2061)
0-6 mo	88.5% (509/575)	Not reported	Not reported	Not reported
0-12 mo	73.7% (424/575)	Not applicable	Not applicable	Not applicable
Intention-to-treat analysis				
Infancy (0-1 y)	n = 193 and 191	Not reported	Not reported	n = 434 and 449
AM	1.02 (0.67-1.54)	Not reported	0.90 (0.64-1.27)	0.82 (0.61-1.10)
AD	1.14 (0.75-1.75)*	Not reported	0.88 (0.61-1.26)	0.84 (0.60-1.18)
Cumulative to 3 y				
AM	Not reported	Not applicable	0.94 (0.73-1.20)	0.78 (0.64-0.95)
AD	Not reported	Not applicable	0.90 (0.67-1.22)	0.77 (0.61-0.98)
6/7-y period prevalence				
Asthma	0.91 (0.57-1.45)	Not applicable	Not applicable	1.60 (0.74-3.45)
Allergic rhinitis	0.94 (0.56-1.58)	Not applicable	Not applicable	0.87 (0.57-1.33)
Eczema	1.08 (0.69-1.68)	Not applicable	Not applicable	0.83 (0.61-1.12)
Per-protocol analysis†				
Infancy (0-1 y)	n = 94 and 86	n = 256 and 241	n = 245 and 229	n = 240 and 218
AM	1.09 (0.60-2.01)*	0.65 (0.38-1.1)	0.57 (0.33-0.99)	0.56 (0.37-0.86)
AD	1.03 (0.55-1.93)*	0.56 (0.32-0.99)	0.49 (0.27-0.88)	0.54 (0.34-0.87)
Cumulative to 3 y			n = 245 and 229	n = 224 and 208
AM	Not reported	Not applicable	0.81 (0.51-1.28)	0.67 (0.51-0.89)
AD	Not reported	Not applicable	0.60 (0.37-0.97)	0.58 (0.41-0.82)
6/7-y period prevalence	n = 82 and 77			n = 217 and 201
Asthma	0.73 (0.37-1.45)*	Not applicable	Not applicable	1.64 (0.59-4.53)
Allergic rhinitis	0.80 (0.39-1.64)*	Not applicable	Not applicable	0.95 (0.55-1.63)
Eczema	0.82 (0.44-1.53)*	Not applicable	Not applicable	0.53 (0.34-0.84)

AD, Atopic dermatitis; AM, allergic manifestations; GINI, German Infant Nutritional Intervention Study; MACS, Melbourne Allergy Cohort Study.

*We have performed these additional analysis to allow direct comparison between the 2 studies.

†Per-protocol analysis was performed per the definitions used by the GINI study. Specifically, these analyses excluded those children who were either not exposed to the allocated formula or who were noncompliant (exposed to another formula) by 4 months of age.