

CORRESPONDENCE

# Filaggrin gene loss-of-function variants modify the effect of breast-feeding on eczema risk in early childhood

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With great interest, we read the article by Turati et al. (1) demonstrating that early weaning (reduced duration of exclusive breastfeeding) may diminish the risk of eczema. The authors presented data collected between 2011 and 2014 using a matched case-control study by enrolling children from 10 Italian hospitals. They have carefully analyzed their data by including several confounders. We are similarly interested in the effect of early infant diet on eczema. However, we conducted studies in the context of filaggrin gene (*FLG*) variants, extending our findings on eczema and *FLG* loss-of-function (LOF) variants (2–4) by addressing whether *FLG* variants modulate the association between duration of breastfeeding and eczema risk in early childhood.

Apart from immunological mechanisms, eczema is a disease characterized by epidermal barrier dysfunction with a strong genetic component. Filaggrin is a crucial component of the outermost cornified epidermis and maintains epidermal barrier function (2). The *FLG* variants constitute a strong risk for eczema development (2–4). We have previously

reported that a combination of *FLG* variants and allergic sensitization increased the risk of eczema in early life and also jointly increased the risk of allergic comorbidities, including asthma and rhinitis in later childhood (2, 4). Hence, we were curious to understand the role of breastfeeding.

To assess whether the association between breastfeeding duration and eczema at age 1 or 2 years is modified by *FLG* variants, we evaluated data from the Isle of Wight birth cohort, UK established in 1989, using Poisson regression with robust error variance. Of the 1536 eligible mother-child pairs, 1456 children were enrolled and followed up at 1, 2, 4, 10, and 18 years of age with detailed interviews and examinations at each follow-up (2). Eczema was defined as chronic or chronically relapsing, itchy dermatitis lasting more than 6 weeks with characteristic morphology and distribution. Focusing on eczema at 1 and 2 years of age, collected in a narrow time window, we combined assessments from both years. Information regarding breastfeeding duration (in weeks), formula feeding, maternal smoking, age of gestation,

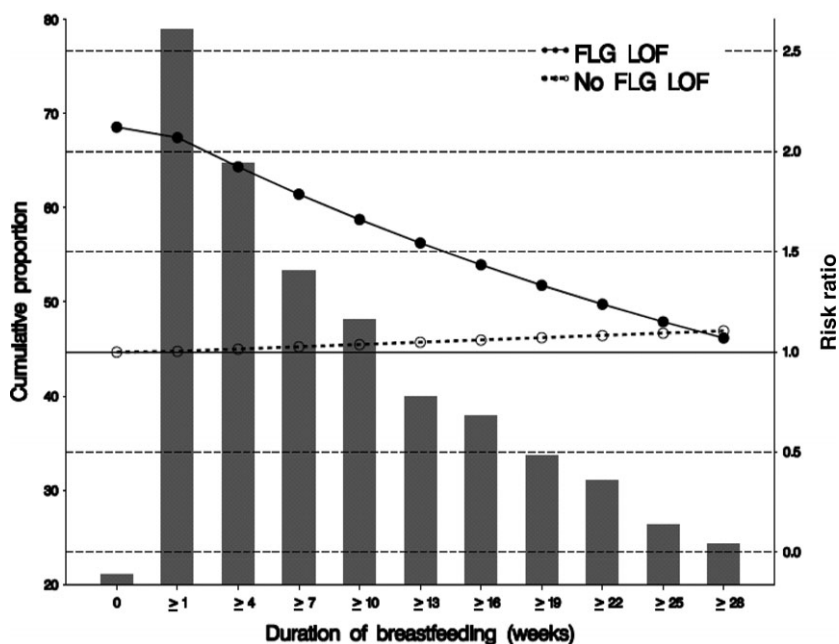


**Figure 1** Comparison of association of breastfeeding duration and eczema at age 1 and 2 in children with and without *FLG* LOF. The horizontal axis represents duration of breastfeeding in weeks, and the grey bars represent the cumulative proportion of breastfed children in specific intervals; for example, 78% of the children were breastfed for at least 1 week; 65% for at least 4 weeks. The black dots and white circles represent the risk of eczema in children with and without *FLG* LOF, respectively.

birth order, maternal and paternal eczema, and age of the mother at birth was obtained using questionnaires. *FLG* variants R501X, 2282del, and S3247X were genotyped, and children carrying the minor allele for at least one of the *FLG* variants were classified as having *FLG* haploinsufficiency (2). There were 885 participants with information of *FLG* variants, eczema at 1 or 2 years, duration of breastfeeding and all the confounders. Statistical analysis was carried out using Statistical Analysis software (SAS 9.4, Cary, NC, USA).

*FLG* variants modified the association between breastfeeding duration and eczema. In children with *FLG* LOF variants ( $n = 94$ ), the median breastfeeding duration was lower in those with eczema (median = 7 weeks) compared to those without eczema (median = 9 weeks). Among children with *FLG* LOF variants, prolonged breastfeeding duration was associated with reduced risk of eczema at age 1 or 2 years (Fig. 1,  $P = 0.02$ ). In contrast, in children without *FLG* LOF variants, breastfeeding duration was not associated with eczema risk 1 or 2 years ( $P = 0.64$ ). Interestingly, *FLG* LOF variants are rare in Italian population (1.4%) (5). Such findings encourage caution in making conclusions and when generalizing to other populations.

*FLG* variants may not be the only genetic factor that modifies the role of breastfeeding on eczema. In addition, as we have previously shown (6), consumption of breastmilk may be in the form of direct breastfeeding and/or indirect breastfeeding (bottled breastmilk); and pumped milk may pose a

different exposure to the child. Hence, more refined information on the mode of breastfeeding is needed to ascertain the impact of infant diet and feeding practices on health outcomes.

### Conflicts of interest

All authors declare no conflicts of interest.

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### Reply

We thank Dr. A.H. Ziyab et al. for their commentary on our manuscript. As highlighted by the results of their study, atopic dermatitis (AD) is a heterogeneous disease in which genetic subtypes contribute to different patterns of risk and penetrance across populations.

We take this opportunity to clarify an important aspect of our study. We were in fact interested in two separate but linked issues. The first was the impact of breast-feeding on AD occurrence and, secondly, the additional effect of introduction of solid foods. Thus, our analysis focused only on breast-fed children. Our results showed a beneficial role of early introduction of solid foods, even though

such introduction may have started without stopping breast-feeding.

Interestingly, when we considered the global sample of breast-fed children, no major differences emerged between cases and controls in breast-feeding duration, with a median duration of 22 weeks for cases and 20 weeks for controls (Table 1). These values are higher than those registered in the Isle of Wight birth cohort study described by Ziyab et al., suggesting that, as mentioned by those authors, not only genetic factors but also breast-feeding habits, which are heterogeneous across populations, may jointly impact on AD progression.

**Table 1.** Breast-feeding duration (in weeks), in 329 cases of atopic dermatitis diagnosed within 24 months of age and 329 controls of same age. Italy, 2011–2014

|          | N   | Median | Lower<br>quartiles | Upper<br>quartiles | Mean | Standard<br>deviation |
|----------|-----|--------|--------------------|--------------------|------|-----------------------|
| Cases    | 329 | 22     | 16                 | 31                 | 24.7 | 15.1                  |
| Controls | 329 | 20     | 12                 | 28                 | 21.8 | 14.8                  |

Hence, it is important to complement epidemiological studies with genetic analysis as those presented by Ziyab et al., and Giardina et al. (1), in order to dissect at best the wide spectrum of subsets of patients with AD.

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