

Correspondence

The very preterm neonate's role in prevention of atopic disease

To the Editor:

I read with interest the November 2018 article titled "Cesarean delivery, preterm birth, and risk of food allergy: Nationwide Swedish cohort study of more than 1 million children."¹ This is an excellent start to our full-scope understanding of the variety of perinatal environmental factors that predispose our youngest infants to food allergy. These data bring support to a well-established association between cesarean delivery and increased risk of subsequent diagnosis of food allergy.² However, I am particularly interested in the data generated in this study demonstrating an inverse association between food allergy and very preterm gestation infants. As a general pediatrician excited by the direct impact Learning Early About Peanut allergy (LEAP) and LEAP-On have had on our practice in promoting immunologic tolerance to peanut,³ I have similar enthusiasm that these associations underscore the importance of identification of precise environmental and/or biologic mechanisms of immune tolerance unique to very preterm gestation infants.

Inherent differences in the physiology of the preterm dermatologic, gastrointestinal, and innate/adaptive immune systems as compared with those of term infants play an obvious role in this discussion, though the impact of these factors remain difficult to precisely characterize. Encouragingly, an established inverse association between eczema and very preterm gestation infants has been identified⁴; whether this inverse association is reflective simply of the immunologic immaturity unique to very preterm infants or is independently and causally related to downstream cutaneous sensitization remains to be seen. The importance of early emollient application in the prevention of eczema for high-risk term neonates has also been established,⁵ with clinical trials ongoing.⁶ Such trends are suggestive of the existence of additional modifiable environmental factors that may impact atopic disease development among infants. Although challenges certainly exist in the implementation of prospective randomized controlled trials in the neonatal population in the era of regimented, guideline-based care for pregnant women and preterm newborns, the identification of coexistent associations via a highly powered retrospective analysis is imperative. These very guidelines, importantly, may offer some degree of insight as to the gestational age-based environmental exposures unique to very preterm infants. Neonatal factors meriting further investigation include the impact of antenatal corticosteroids, the timing and volume of trophic enteral feed initiation, receipt of total parenteral nutrition, the presence of necrotizing enterocolitis, the usage of mother's breast milk and/or donor breast milk, the receipt of antimicrobial therapy, and the usage of H₂ blockers and/or proton pump inhibitors.

In the setting of 2 important and statistically significant associations emerging from this cohort, I would naturally query whether the authors had explored the subgroup of very preterm infants to analyze rates of food allergy when delivered via cesarean section as compared with vaginal delivery. Because a statistically significant association between food allergy and moderately preterm infants was not identified, one wonders the exact gestational age at which the association identified among very preterm infants no longer holds and whether any additional specificity can be achieved from the existent data that may help narrow the above environmental exposures. Have the authors attempted stratification of these very preterm and moderately preterm infants by number of weeks gestational age completed at birth in place of existent grouping?

Although the burden of care of pediatric patients with food allergy falls on general pediatricians and allergists alike, the time is now for a partnership with our academic neonatology colleagues to best characterize the early environmental measures linked to immunologic tolerance.

Andrew Winslow, MD

From Naval Medical Center Camp Lejeune, United States Navy, Lejeune, NC. E-mail: andrew.w.winslow2.mil@mail.mil.

The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the US government.

I am a military service member or employee of the US government. This work was prepared as part of my official duties. Title 17, USC, § 105 provides that "Copyright protection under this title is not available for any work of the U.S. Government." Title 17, USC § 101 defines a US government work as "a work prepared by a military service member of employee of the U.S. Government as part of that person's official duties."

Disclosure of potential conflict of interest: The author declares that he has no relevant conflicts of interest.

REFERENCES

1. Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. Cesarean delivery, preterm birth, and risk of food allergy: nationwide Swedish cohort study of more than 1 million children. *J Allergy Clin Immunol* 2018;142:1510-4.
2. Papathoma E, Triga M, Fouzas S, Dimitriou G. Cesarean section delivery and development of food allergy and atopic dermatitis in early childhood. *Pediatr Allergy Immunol* 2016;27:419-24.
3. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
4. Zhu T, Zhao J, Qu Y, Zhang L, Mu D. Association of very preterm birth with decreased risk of eczema: a systematic review and meta-analysis. *J Am Acad Dermatol* 2018;78:1142-8.
5. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WI, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;134:818-23.
6. Chalmers JR, Haines RH, Mitchell EJ, Thomas KS, Brown SJ, Ridd M, et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. *Trials* 2017;18:343.

<https://doi.org/10.1016/j.jaci.2019.01.035>