

Correspondence

Reply

To the Editor:

We sincerely appreciate Winslow's comment¹ on our article.²

The hazard ratio (HR) for childhood food allergy in very preterm born infants (<32 weeks of gestation) in our study was 0.74 (95% CI, 0.56-0.98). In response to Winslow's query,¹ we examined the risk of food allergy in very preterm infants according to delivery mode. The combination of very preterm birth and vaginal delivery was associated with a 40% lower risk of food allergy (HR, 0.60; 95% CI, 0.38-0.95), whereas the risk was 13% lower in those born by means of cesarean delivery (HR, 0.87; 95% CI, 0.60-1.25). Hence, the decrease in risk was most apparent in very preterm infants delivered vaginally. The somewhat higher relative risk of food allergy in very preterm infants with cesarean delivery indicates a positive impact of this latter exposure on the risk of childhood food allergy,³ most likely through a delayed and altered gut microbiota composition,⁴ in line with the hygiene hypothesis.⁵

Regarding the second point made by Winslow, we attempted stratification of very preterm and moderately preterm born infants by age in gestational weeks completed at birth. This analysis showed that risk estimates for food allergy decreased by earlier preterm gestational ages. In particular, the HR for food allergy in infants born at less than 28 gestational weeks was 0.14 (95% CI, 0.04-0.56), strengthening the theory of a protective role of very preterm birth on the development of food allergy.⁶ Low-risk estimates remained until the end of the 33rd week of gestation (the only exception was observed in infants born at 28-29 weeks; HR, 0.82; 95% CI, 0.38-1.75), whereupon the HRs were no longer statistically significant (Table I). Indeed, in some of the subgroup analyses, statistical significance was not attained likely because of inadequate power (considering that the overall risk estimate was 0.74 for very preterm birth and 0.96 for moderately preterm, large numbers of participants are required to uncover minor excess risks).

It is well known that food allergy starts early in life. Recent studies have provided strong evidence that an opportunity window occurs during the first year of life within which to induce immunologic tolerance.⁷ The inverse association between very preterm birth and food allergy identified in our cohort is consistent with both the "hygiene"⁵ and the "dual-allergen exposure"⁷ hypotheses, suggesting that earlier exposure to pathogens and early ingestion of food proteins, respectively, might lead to clinical immune tolerance to food allergens in very preterm born infants. Future research should not only aim to identify perinatal exposures that predispose to food allergy but also immunologic mechanisms and early-life environmental factors that might

TABLE I. Preterm birth and risk of food allergy

Preterm birth (<37 wk of gestation)	Adjusted HR; 95% CI*
<28 wk	0.14; 0.04-0.56
28-29 wk	0.82; 0.38-1.75
30-31 wk	0.68; 0.50-0.93
32-33 wk	0.63; 0.52-0.76
34 wk	0.85; 0.73-1.00
35 wk	0.96; 0.85-1.07
36 wk	1.00; 0.92-1.09

Statistically significant findings are presented in boldface.

*Adjustment for sex, maternal age at delivery, country of birth, parity, body mass index, early pregnancy smoking, maternal asthma/pulmonary disease, cesarean delivery, and birth weight.

protect from atopic disease and potentially promote a tolerogenic response.

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REFERENCES

- Winslow A. The very preterm neonate's role in prevention of atopic disease. *J Allergy Clin Immunol* 2019;143:XXX-XXX.
- Mitselou N, Hallberg J, Stephansson O, Almquist 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;142:1510-1514.e2.
- Koplin J, Allen K, Gurrin L, Osborne N, Tang MLK, Dharmage S. Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: a systematic review. *Pediatr Allergy Immunol* 2008;19:682-7.
- van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. *J Allergy Clin Immunol* 2011;128:948-55, e1-3.
- Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
- Siltanen M, Kajosaari M, Pohjavuori M, Savilahti E. Prematurity at birth reduces the long-term risk of atopy. *J Allergy Clin Immunol* 2001;107:229-34.
- Du Toit G, Sampson HA, Plaut M, Burks AW, Akdis CA, Lack G. Food allergy: update on prevention and tolerance. *J Allergy Clin Immunol* 2018;141:30-40.

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