

The Role of the Early-Life Environment in the Development of Allergic Disease



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KEYWORDS

• Asthma • Allergy • IgE • Prenatal • Eczema • Atopic dermatitis

KEY POINTS

- Brief summaries of several prenatal and early-life risk factors that have been analyzed for potential associations with the development of childhood allergy are presented.
- The results and conclusions from individual studies of a single risk factor are often conflicting and may be caused by considerable variability in the specific allergy-related outcomes evaluated as well as the methods used to measure an individual's exposure to the risk factor.
- Teams of scientists with diverse expertise are needed to work together to have the greatest impact on understanding risk factors for allergic diseases.

INTRODUCTION

The developmental origins of health and disease hypothesis suggests that a child's environment from conception to 1000 days greatly influences the child's risk for chronic disease. Although it is not well tested in association with immunologic diseases such as allergies and asthma, it is believed that this hypothesis is applicable to allergic diseases, and recent studies have focused on early-life risk factors and the development of allergic diseases later in life.^{1–3} In this review, studies of prenatal and early postpartum exposures and the subsequent development of allergy-related outcomes are summarized, with a focus on delivery mode, the gut microbiome, nutritional factors, and exposure to animals, medications, and airborne pollutants. Further, these early-life factors are reviewed in the context of disease incidence rather than disease exacerbation or management.

Disclosures: The authors receive research support from the National Institutes of Health (NIH) grants HL113010 and AI089473.

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Immunol Allergy Clin N Am 35 (2015) 1–17

<http://dx.doi.org/10.1016/j.iac.2014.09.002>

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DELIVERY MODE

Birth by cesarean section may increase the risk of allergic disease. The mechanism is not known, but recent research suggests that lack of exposure to beneficial microbes present in the birth canal may affect the colonization of the child's gut microbiome and subsequent immune development.

Comparisons of studies correlating delivery mode and allergy are affected by variability in both type of allergy assessed and outcome definitions (ie, clinical evaluation vs parental report). For eczema, most studies have shown no association between mode of delivery and diagnosis. No association between delivery mode and eczema diagnostic codes was found in the West Midlands General Practice Research Database ($n = 24,690$)⁴ or a Kaiser Permanente Northwestern birth registry cohort ($n = 7872$).⁵ In a Japanese birth cohort,⁶ no association was found between delivery mode and maternal report of physician-diagnosed eczema ($n = 213$). A meta-analysis conducted in 2008 resulted in a similar conclusion,⁷ as did the subsequent Finnish SKARP study ($n = 4799$).⁸ However, in the recent Netherlands KOALA study, children born via cesarean section were more likely to have parental-reported eczema.⁹

Stronger associations have been found between mode of delivery and allergic sensitization or food allergy. No association between delivery mode and skin prick test results at age 7 years was found in the English ALSPAC (Avon Longitudinal Study of Parents and Children) cohort.¹⁰ A meta-analysis concluded that children born by cesarean section were more likely to have food allergy/sensitization but not inhalant sensitivity.⁷ Similar associations with food allergy were reported in a systematic review¹¹ and in the KOALA birth cohort.⁹ Among offspring of nonallergic parents in the Dutch PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study ($n = 2917$), children born via cesarean section were more likely to have positive allergen-specific IgE testing.¹² Among Boston children, cesarean section was associated with positive skin prick tests or allergen-specific IgE at age 9 years,¹³ as it was among 8-year-old children whose parents were allergic in the Republic of Cyprus.¹⁴

A meta-analysis concluded that cesarean section is associated with increased asthma risk,⁷ although such an association was seen only among girls in the Kaiser Permanente study⁵ and restricted to children born by emergency cesarean section in a registry report from Sweden.¹⁵ In contrast, the West Midlands General Practice Research Database report found no association.⁴ Several studies using questionnaire data have reported associations between cesarean section and increased asthma frequency,^{12,14} whereas others failed to confirm this finding.^{8,10} Questionnaire data may not provide sufficient specificity for defining asthma as an outcome; hence, the emergence of conflicting results.

MICROBIOME

Intensive interest in the influence of the human microbiome, in particular the gut microbiome, on the developing immune system and allergy has been ignited with the recent development of culture-independent tools to more comprehensively measure bacterial community composition.^{16,17} However, even before these technologies, investigators^{18,19} postulated that mechanisms underlying the hygiene hypothesis were linked to alterations in patterns of normal infant intestinal microbial colonization. Small studies²⁰ using culture-dependent methods indicated differences in the prevalence of intestinal microorganisms between atopic and nonatopic infants, although subsequent studies²¹ did not find confirmed differences linked to food sensitization or atopic eczema using culture-dependent assessments. In 2001, Kalliomaki and colleagues²²

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