



What can we learn about predictors of atopy from birth cohorts and cord blood biomarkers?



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Key Messages

Birth cohorts can simultaneously assess many factors involved in atopy development, and will hopefully provide clinicians with information to prevent asthma and allergies.

- Family history contributes to atopic risk of a child.
- Several potential biomarkers have been evaluated in cord blood; however, there is no conclusive evidence suggesting one single predictive biomarker.
- Maternal exposures during pregnancy can contribute to the child's atopic outcomes.
- Numerous early life environmental exposures have been identified to either promote or prevent allergies and asthma, such as cigarette smoke exposure or the timing of food introduction.
- Birth cohort study designs have proven to be effective in evaluating several early life exposures at different time points prospectively; however, they have difficulty in reproducing data and often report conflicting findings.

INSTRUCTIONS

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- Review the target audience, learning objectives and all disclosures.
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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the use of birth cohorts to study the developmental origins of asthma and allergic disorders.
- Discuss the various risk factors and exposures that contribute to or limit atopic disease development in children.

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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All identified conflicts of interest have been resolved. Any unapproved/investigative uses of therapeutic agents/devices discussed are appropriately noted.

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Introduction

Atopic disorders such as allergy and asthma are affecting children at an increasing rate.¹ The reason for this increase and the precise mechanisms behind the development of allergic disorders in children are unclear. Factors such as family history, prenatal exposures, and early childhood exposures are each known to be involved in atopy development in children. The use of large-scale birth cohorts has presented a useful opportunity to study the relations among risk factors, potential biomarkers in cord blood, early life exposures, and their associations with atopy. This review focuses on several different risk factors that contribute to allergic disease development, how birth cohorts evaluate these factors, and what clinicians can learn from these studies to help prevent, decrease, and/or revert the development of atopic disorders.

Importance of Family History

The influence of genetics and family history on allergy and asthma development has been well documented. It is clear maternal and

paternal atopic statuses contribute to overall atopic risk of the child; however, many studies have indicated their influence is not equal.^{2–4} Some studies have suggested maternal atopic status has a stronger bearing on childhood atopy; and maternal asthma, allergic rhinitis, and atopic dermatitis have each been positively correlated with offspring disease development of the same type.^{2–4} In comparison, only paternal asthma has been associated with asthma development in offspring.³ Differences between maternal and paternal effects can be a result of maternal exposures during pregnancy or the complex maternal-fetal interactions that occur in utero. Recent findings from the Isle of Wight Birth Cohort have suggested child sex-specific patterns, with paternal asthma associated with increased asthma in boys but not in girls (prevalence ratio [PR] 1.99, 95% confidence interval [CI] 1.42–2.79, $P < .001$) and maternal asthma associated with asthma in girls but not in boys (prevalence ratio 1.91, 95% CI 1.34–2.72, $P = .003$).³ This sex-specific inheritance pattern observation could be due to epigenetic imprinting, in which parental alleles are preferentially expressed in somatic cells of the offspring or to transgenerational genetic effects.⁴ Furthermore, inheritance patterns of allergy have been established in that at-risk

children are more likely to develop the same atopic disorder as their parents rather than different allergic diseases.⁵ This is potentially suggestive of unique modes of inheritance for asthma, allergic rhinitis, and other atopic disorders.

Considering the sex of the child and family history with respect to atopy is valuable to discern disease risk, because not all children born to parents with atopy develop allergic disorders and not all children with atopy are born from parents with allergy. Clinicians need to consider the role of additional influences that contribute to atopy when predicting disease.

Potential Cord Blood Biomarkers

The analysis of cord blood for potential biomarkers of atopic disease has been an area of interest, because it has been hypothesized that many non-communicable diseases such as asthma and allergy develop in utero or in early life.⁶ The goal of most biomarker research is to determine differences in many of the cellular and genetic components of cord blood in children who are at risk of atopy or proceed to develop allergic disorders, and to eventually develop methods to predict future atopic status. These studies have identified several potential cord blood biomarkers of atopic risk (Table 1).

Because of the widely accepted role for immunoglobulin E (IgE) in allergic conditions,¹⁴ it has been thoroughly investigated in cord blood as a potential predictor for atopic disease; however, findings are conflicting. Results from a Danish birth cohort reported an association between increased cord blood IgE levels and allergic disease development; however, the positive and negative predictive values of future atopic status were low and were useful in predicting disease development in children but not in adolescents and adults.⁷ Furthermore, differences in cord blood IgE levels between mothers with and without atopy have been detected, but

not in children with and without atopy.¹⁵ These 2 studies highlight the limitation of cord blood IgE as a predictor of atopy.

Although IgE has a crucial role in many allergic disorders, additional components contribute to the pathogenesis of these diseases. Individuals with atopic disorders have a decrease in the ratio of T-helper cell type 1 (T_H1) to type 2 (T_H2), known as the “T_H2 shift.”¹⁶ This shift has been well documented in allergic diseases, and the study of the same in cord blood could offer potentially important biomarkers. One investigation of T_H1:T_H2 cell ratios in cord blood found that individuals with atopic dermatitis had a decreased T_H1:T_H2 ratio at birth compared with those without atopic dermatitis (with T_H1:T_H2, 0.37, 95% CI 0.24–0.83; without T_H1:T_H2, 1.89, 95% CI 0.91–3.92, *P* = .001).⁸ This shift at birth also has been reported by means of T_H1- and T_H2-related cytokines, in which increased T_H2 cytokines and decreased T_H1 cytokines have been correlated with wheeze, allergic sensitization, and atopic dermatitis in the first 2 to 5 years of life.¹⁷ It should be noted a T_H2-dominating environment is expected in most pregnancies; however, it is hypothesized that children who develop atopic disorders have an exaggerated response at birth that continues into early life.^{17,18} Therefore, understanding how the T_H1:T_H2 balance is restored, and whether there are any differences in this process between children with and without atopy, could be important for atopic disease pathogenesis mechanisms.

Part of the regulation of the T_H1:T_H2 ratio is controlled by regulatory T cells (Tregs), a subset of T lymphocytes marked by the transcription factor forkhead box P3 (FOXP3).⁹ In a study of Treg numbers and stable FOXP3 expression in cord blood samples from participants with high and low risk of atopy, findings suggested children with fewer Tregs in cord blood were at increased risk of developing atopic dermatitis and food allergy sensitization (odds ratio [OR] 1.55, 95% CI 1.00–2.41; OR 1.55, 95% CI 1.06–2.25

Table 1
Summary of Potential Biomarkers and Role in Atopy

Biomarker	Role	Finding	Result	<i>P</i> value
Cord blood IgE levels <0.5 kU/L	IgE binds to mast cells and causes degranulation and histamine release	Associated with allergic symptoms at 1½ and 5 y but not at 10, 15, or 26 y ⁷	1½ y (OR 1.9, 95% CI 1.2–2.9) 5 y (OR 2.1, 95% CI 1.0–4.02) 10 y (OR 1.2, 95% CI 0.3–2.0) 15 y (OR 1.1, 95% CI 0.7–1.9) 26 y (OR 1.4, 95% CI 0.9–2.3)	.008 .047 .424 .619 .144
T _H 1:T _H 2 ratio	Altered balance in individuals with atopy and increased T _H 2 cell numbers and response	Lower T _H 1:T _H 2 cell numbers associated with atopic dermatitis ⁸	Atopic dermatitis (T _H 1:T _H 2 0.37, 95% CI 0.16–0.89), no atopic dermatitis (T _H 1:T _H 2 1.89, 95% CI 0.91–3.92)	.001
Treg number	Cells responsible for maintaining and regulating balance of T _H 1 and T _H 2 cells	Lower Treg numbers in cord blood associated with increased risk of atopic dermatitis and food allergy sensitization ⁹	Atopic dermatitis (median 0.91, IQR 0.54–1.39), no atopic dermatitis (median 1.22, IQR 0.75–1.72) Food allergy (median 0.97, IQR 0.76–1.76), no food allergy (median 1.21, IQR 0.76–1.76)	.046 .032
Eosinophil and basophil progenitor cells	Eosinophilic inflammation involved in asthma	Higher numbers of cord blood IL-5–stimulated CFU results in increased risk of wheeze ever and recurrent wheeze within first 2 y ¹⁰	Wheeze ever (aOR 1.57, IQR 1.02–2.42) Recurrent wheeze (aOR 1.65, IQR 1.06–2.70)	.042 .048
IL-12	Involved in T _H 1 cell function	Nonspecifically stimulated CBMCs secreted lower levels in children with vs without allergy ¹¹	Allergic (mean 0.71 pg/mL); nonallergic (mean 2.34 pg/mL)	.026
IL-15	Involved in T-helper cell function	Nonspecifically stimulated CBMCs secreted lower levels in children with vs without allergy ¹¹	Allergic (mean 3.74 pg/mL), nonallergic (mean 21.87 pg/mL)	.021
CCL22	T _H 2-related chemokine, ligand is enhanced on T cells in T _H 2 responses	Cord blood levels positively correlated with total IgE levels at 6 mo, 18 mo, 4 y, 6 y ¹²	All ORs 1.54 (95% CI 1.25–1.89)	<.0001
IL-10	T _H 1-related cytokine	Decreased IL-10 response to lipopolysaccharide in cord blood associated with recurrent wheeze ¹³	OR 0.50 (95% CI 0.27–0.92)	.02
IL-4	T _H 2-related cytokine	Increased IL-4 response to cockroach and house dust mite in peripheral blood associated with atopy ¹³	Cockroach (OR 1.52, 95% CI 1.09–2.27) Dust mite (OR 1.52, 95% CI 0.99–2.32)	.016 .055

Abbreviations: aOR, adjusted odds ratio; CBMC, cord blood mononuclear cell; CCL22, C-C motif chemokine ligand 22; CFU, colony-forming unit; CI, confidence interval; IgE, immunoglobulin E; IL, interleukin; IQR, interquartile range; OR, odds ratio; T_H, T-helper cell type; Treg, regulatory T cell.

respectively).⁹ Studies on human newborn Treg function have found a correlation between decreased function at birth and increased allergic outcomes.⁴ In addition, children with food allergy by 2 years of age have been shown to have fewer Tregs expressing *FOXP3* in cord blood samples than children who did not develop food allergy (geometric mean ratio 0.17, 95% CI 0.05–0.29).¹⁹ These results suggest the frequency and function of Tregs are imperative for atopy development, and analyzing these 2 components at birth could serve as an important predictive biomarker.

Eosinophils are important for allergy and asthma pathogenesis, and eosinophil and basophil progenitor cells (Eo/B) have been investigated as predictors of respiratory illness. The Lifestyle and Environmental Factors and Their Influence on Newborn's Allergy Risk (LINA) cohort investigated the predictive nature of Eo/B by analyzing colony-forming units of interleukin (IL) 5-stimulated cord blood Eo/B.¹⁰ They reported children with wheezing symptoms and physician-diagnosed bronchitis had more cord blood Eo/B colony-forming units in response to IL-5 stimulation compared with children without wheeze and bronchitis ($P = .033$ and $P = .44$).¹⁰ In addition, adults with atopic disorders have been found to have Eo/B with upregulated responses to IL-5 in peripheral blood samples.²⁰ These findings could be useful as a biomarker at birth; colony-forming units could be measured in response to IL-5 and, depending on the production of eosinophils, asthma risk could be hypothesized.

Cytokine and chemokine production could be a valuable tool to predict atopy development, because these mediators are important in many pathways in the key cells involved in allergy. One evaluation of cord blood cytokine profiles and allergic disorders suggested that children with IgE-mediated allergies secrete lower levels of IL-12 and IL-15 compared with children without allergy ($P = .026$ and $P = .021$ respectively).¹¹ Cord blood levels of the T_H2 -related chemokine C-C motif chemokine ligand 22 were positively correlated with total IgE levels at 6 months, 18 months, 4 years, and 6 years, suggesting the presence of intrauterine T_H2 skewing at birth in children who develop increased IgE levels (combined time points, OR 1.54, 95% CI 1.25–1.89, $P < .0001$).¹² Furthermore, atopic dermatitis by 2 years of age was associated with increased IL-4 and decreased interferon- γ at birth.¹⁷ In the Urban Environment and Childhood Asthma (URECA) birth cohort, low IL-10 cytokine secretion in response to lipopolysaccharide in cord blood was associated with recurrent wheeze (OR 0.50, 95% CI 0.27–0.92, $P = .02$), and increased IL-4 secretion peripheral blood at 1 year in response to cockroach and house dust mite stimuli was associated with atopy (OR 1.52, 95% CI 1.09–2.27, $P = .016$; and OR 1.52, 95% CI 0.99–2.32, $P = .055$).¹³ These findings each suggest functional differences present at birth and in early life between children who develop atopic disorders and those who do not, and further investigation in cytokine production and profile is warranted.

No consensus has arisen for a single most effective biomarker in cord blood for the prediction of disease. It might be more realistic to use a panel of biomarkers to determine atopic risk or even a systematic algorithm of the same, because multiple factors are correlated with disease development and contribute to the overall atopic risk of the child (Table 1). Clinicians should understand that the inability to conclusively link these biomarkers to atopic disease development lies in part with potential differences in environmental exposures during the prenatal and postnatal periods.

Effect of Prenatal Exposures

Developmental origins of health and disease studies have suggested that exposures during critical periods of development affect chronic disease development.⁶ Emerging research has indicated that these exposures affect disease through epigenetic changes and alterations of DNA configuration through histone modification (methylation, acetylation, etc), which in response influence gene

expression.²¹ These modifications affect expression through induction or silencing of genes that can manifest into clinical symptoms.² Environmental exposures can induce these changes and contribute to or protect against disease and have been studied with respect to atopic disorders.^{2,22–24}

Maternal smoking during pregnancy is a risk factor for allergic diseases and has been correlated with multiple epigenetic changes and DNA methylation patterns in cord blood.²⁵ Recent findings from the Taiwan Birth Panel Cohort indicated differences in DNA methylation patterns on the thymic stromal lymphopoietin gene (*TSLP*), a gene involved in the maturation of T cells, in mothers who smoked during pregnancy compared with mothers who did not ($P = .018$).²⁶ In addition, methylation patterns and maternal smoking were positively associated with an increased risk of atopic dermatitis (OR 3.23, 95% CI 1.06–5.11).²⁶ The LINA cohort demonstrated that prenatal smoking was associated with a decrease in cord blood Treg numbers and an increase in atopic dermatitis risk (OR 2.012, 95% CI 1.12–3.67).²⁷ In a pooled analysis of 8 European birth cohorts, prenatal smoking was associated with wheeze and asthma from 4 to 6 years of age (OR 1.39, 95% CI 1.08–1.77; and OR 1.65, 95% CI 1.18–2.31, respectively).²⁸ In addition, direct prenatal smoking was associated with an increased risk of wheeze (OR 1.41 95% CI 0.99–2.01) and “chestiness” (OR 1.46, 95% CI 1.03–2.01), whereas secondhand smoke exposure in pregnancy of nonsmoking mothers was associated with cough (OR 1.62, 95% CI 1.05–2.51).²⁹ Furthermore, findings from the Kingston Allergy Birth Cohort (KABC) suggested prenatal smoking was associated with parental report of cough or wheeze without a cold by 2 years of age (hazard ratio 2.68, 95% CI 1.48–4.84, $P = .001$).³⁰ These findings emphasize the influence smoking has on the risk of developing atopic disease. Therefore, it is paramount mothers avoid smoking and secondhand smoke exposure during pregnancy, particularly if their offspring have a higher allergic or asthmatic risk from a family history of atopy.

Vitamin D has immuno-inflammatory modulating properties and its potential role in asthma and allergy was discussed in a recent review.³¹ To avoid overlap with that review, vitamin D is not discussed in depth here; however, the conflicting evidence on its role in atopy development should be highlighted because vitamin D status was associated with increased, decreased, or no risk of atopy.³¹

Air pollution and particulate matter create oxidative stress and airway inflammation, worsen respiratory symptoms, and decrease lung function.³² Prenatal exposures to volatile organic compounds and/or particulate matter can increase childhood risk of atopic dermatitis (incidence rate 1.55, 95% CI 0.99–2.44).³³ Exposure to nitrogen dioxide during pregnancy has been associated with DNA methylation patterns and alterations in expression of genes involved in antioxidant defense pathways.³⁴ In addition, increased exposure to particulate matter during mid-gestation (16–25 weeks) has been associated with an increased OR for asthma at 6 years in boys compared with girls ($P = .01$).³⁵ This observation could be attributable to sex differences that occur in utero, because fetal breathing and surfactant production occur later in boys compared with girls.³⁵ Recent findings from the EDEN study cohort (pre- and postnatal determinants of the child's development and health) suggested for every 10- $\mu\text{g}/\text{m}^3$ increase in particulate matter 3 months before and during the first, second, and third trimesters of pregnancy, percentages of cord blood Tregs decrease by 0.82% ($P = .01$), 0.71% ($P = .04$), 0.88% ($P = .02$), and 0.59% ($P = .04$) respectively.³⁶ In addition, early pregnancy exposure to air pollution has been associated with lower cord blood IgE levels, whereas later exposures have been shown to result in higher IgE levels.³² The presence of critical windows of exposure to air pollution could be important to determine disease risk.

Understanding the implications of the different prenatal exposures that influence atopic risk is important because some exposures can drive low atopic risk in children to a higher atopic risk. Having

a detailed picture of maternal exposures during pregnancy is crucial in determining an accurate disease risk at birth and therefore key for suggesting and implementing preventative measures in early life.

Effect of Postnatal Exposures

As with prenatal exposures, postnatal exposures influence allergic disease development. These exposures have been evaluated in many birth cohorts.

The health benefits of breastfeeding on a developing baby is widely accepted by clinicians and scientists; however, its implications for atopy development remain controversial.³⁷ Similar to what has been seen with vitamin D, multiple studies have investigated breastfeeding and allergic disease development, with some studies showing a protective effect, some showing a damaging effect, and others showing no effect.^{37–43} For example, a lower risk of atopic dermatitis was observed for children who were exclusively breastfed for 3 months (OR 0.58, 95% CI 0.41–0.20) but only in children who were classified as having a high atopic risk.³⁸ Similar findings were observed for asthma, in which asthma risk was lower at 4 or 5 years in children with high atopic risk who were breastfed for more than 3 months (relative risk 0.69, 95% CI 0.52–0.93).³⁹ Each month of exclusive breastfeeding was correlated with a lower asthma prevalence in 2- to 6-year-old children and a decrease in risk of asthma of 17% at 2 years, 12% at 3 years, 11% at 4 years, 12% at 5 years, and 9% at 6 years.⁴⁰ Children who were never breastfed were reported to have an increased risk of wheeze (OR 1.44, 95% CI 1.24–1.66), shortness of breath (OR 1.26, 95% CI 1.07–1.48), dry cough (OR 1.25, 95% CI 1.08–1.44), and phlegm in lungs (OR 1.57, 95% CI 1.29–1.91) for the first 4 years of life.⁴¹ These studies each highlight the potentially preventative properties breastfeeding can have on allergy; however, these were strongest in at-risk children and did not necessarily show a preventative effect in children with lower or no atopic risk.^{38–40} It is important to note that although there are protective effects observed with a decrease in asthma and atopic dermatitis risk, these results can be confounded by disease-related exposure modification through the decrease of early life infections, which individually contribute to disease development.³⁷ Moreover, potential adverse effects have been reported with respect to food allergy.^{37,39,42} Children who were breastfed were reported to have an increased relative risk of food allergy to cow's milk, peanut, and egg (relative risk 1.81, 95% CI 1.18–2.76).³⁹ One study suggested breastfeeding was associated with an increased risk of food sensitization (adjusted OR 2.43, 95% CI 1.03–5.74) but not food allergy (adjusted OR 0.365, 95% CI 0.23–1.83).⁴² The increase in food sensitization risk could be due to exclusive breastfeeding leading to the delay of solid food introduction, including highly allergenic food, which independently has been shown to play a role in food allergy development.⁴⁴ Questions of whether maternal dietary avoidance during lactation is useful to prevent atopic disease have arisen; however, little to no evidence suggests this is particularly effective.^{45,46} Therefore, it is important for mothers to breastfeed if capable and eat a balanced diet for their offspring's health and their own health.

The introduction of food into a child's diet and its timing have been extensively studied given recent increases in food allergy prevalence.⁴⁷ Preventing the introduction of potentially antigenic foods was previously advised as a means of preventing sensitization; however, several studies have suggested reconsidering this notion.^{44,47–51} Although not a birth cohort study per se, the Learning Early About Peanut Allergy (LEAP) study reported that in low- and high-risk children, peanut consumption groups had a lower percentage of prevalence of peanut allergy compared with the peanut avoidance group ($P < .001$ in low-risk group and $P = .004$ in high-risk group).⁵⁰ In high-risk children, the consumption of peanut products was associated with a 70% relative decrease in peanut

allergy prevalence, stressing the importance of food introduction, specifically peanuts, early in life as a preventative measure.⁵⁰ In addition, early egg introduction has been associated with a decrease in risk of egg allergy (relative risk 0.56, 95% CI 0.36–0.87, $P = .009$).⁴⁴ Importantly, a diet lacking diversity has been associated with an increased risk of atopic eczema at 6 months (OR 1.38, 95% CI 0.96–1.81, $P = .03$), wheeze at 12 months (OR 2.76, 95% CI 1.68–4.55, $P = .004$), and allergic rhinitis at 12 months (OR 3.52, 95% CI 2.03–6.11, $P < .001$).⁴⁸ These studies and similar ones have generated newfound knowledge of the preventative effects of early food introduction, rather than avoidance, with respect to food allergy development. This has recently influenced clinical guidelines.⁵² In 2015 an expert panel of 26 members gathered to develop an addendum to the “Guidelines for the Diagnosis and Management of Food Allergy in the United States” published by the National Institute of Allergy and Infectious Diseases (NIAID), based on recent evidence regarding food introduction and subsequent food allergy.⁵² It was published in 2017 and recommended specific IgE testing, skin prick testing, oral food challenge (if necessary), and the introduction of peanuts at 4 to 6 months in high-risk children (severe eczema and/or egg allergy), peanut introduction at 6 months in moderate-risk children (mild to moderate eczema), and peanut introduction at family preference in low-risk children (no eczema or food allergy).⁵²

Indoor and outdoor air pollution has been linked to an increased risk in childhood asthma and wheeze.^{53–55} In a recent systematic review of birth cohorts, maternal smoking was associated with childhood wheeze at 2 years (OR 1.70, 95% CI 1.24–2.35), 3 to 4 years (OR 1.65, 95% CI 1.20–2.68), and 5 to 18 years (OR 1.18, 95% CI 0.99–1.4).⁵⁴ Furthermore, secondhand smoke exposure in early life was associated with an increased risk of asthma (OR 1.23 95% CI 1.01–1.51), rhinitis (OR 1.18, 95% CI 1.01–1.39), and eczema (OR 1.26, 95% CI 1.09–1.45).⁵³ An increasing dose and response has been observed for outdoor air pollution exposure in early life and *FOXP3* methylation in Tregs, with *FOXP3* methylation associated with persistent childhood wheeze (OR 3.05, 95% CI 1.54–6.05), early transient wheeze (OR 1.57, 95% CI 1.01–2.41), and asthma (OR 2.12, 95% CI 1.14–3.85).⁵⁶ More recently described is that the regular use of air fresheners has been associated with parental report of childhood wheeze by 2 years of age ($P = .04$).³⁰ This could be a result of phthalate exposure, because many scented products contain these chemicals.^{30,57} Phthalates are proposed to play a role in atopy development, and recent findings from a birth cohort of 483 mother-child pairs reported correlations among urine phthalate levels, serum IgE levels, and development of atopic dermatitis at 2 years.⁵⁸ Although these findings do not indicate causality, they suggest early life exposure to phthalates can increase a child's risk of allergy and asthma.

Understanding the potentially protective or harmful postnatal exposures that influence childhood atopy development is important for clinicians. Continued research on these exposures will build the knowledge for clinical policy makers to make informed decisions based on strong evidence to develop guidelines, similarly to the NIAID guidelines discussed earlier.

Current Birth Cohorts

The exposures and risk factors discussed in this review are only some of the many factors investigated in atopy-based birth cohorts. These cohorts gather information on exposures throughout early life, often in large scale with a diverse population. This model type is superior to previous epidemiologic study designs (ie, retrospective cohorts), limiting reverse causation by studying early exposures at several different time points prospectively.⁵⁹ However, there are limitations because birth cohorts take time to establish and recruit participants, and are expensive. Following participants is crucial to

Table 2
Current Allergy and Asthma-based Birth Cohort Studies

Birth cohort	Name of cohort	Country	Children, N
ACROSSOLAR	Atopic Childhood Disease Risk Factors in the Second Generation of the SOLAR Participants ⁶¹	Germany	800 expected (currently in recruitment)
CHILD	Canadian Healthy Infant Longitudinal Development ⁶²	Canada	3,542
COPSAC	Copenhagen Prospective Studies on Asthma in Childhood ⁶³	Denmark	700
LINA	Lifestyle and Environmental Factors and Their Influence on Newborns Allergy Risk Cohort ¹⁰	Germany	629
KABC	Kingston Allergy Birth Cohort ³⁰	Canada	560
URECA	Urban Environment and Childhood Asthma ⁶⁴	USA	560

gather data, and low retention rates can challenge several researcher groups. Furthermore, classifying exposures that occur during prenatal and postnatal periods is difficult because some exposures often occur in these 2 periods, such as air pollution. It also is important to be aware of bias, because people who participate in cohort studies might be different than the general population. In addition, when data are self-reported, researchers need to be cautious of over- and under-reporting of exposures and outcomes in their studies. Confounding variables can be present in these studies and need to be accounted for, although they can be easily missed.⁵⁸ Conflicting data and difficulty of reproducing findings between cohorts are common and can be due to a combination of the limitations identified earlier. One way of potentially limiting this issue is using exposome-based analysis, a technique that models the influence and interconnectedness of several exposures and outcomes and measures correlations.⁶⁰ This type of modeling can control for several confounding variables to study their influence on disease development and has been used recently in a birth cohort in Canada.³⁰

Conclusion

This review article has discussed the use of birth cohorts and biomarkers as a means to study allergic disease development. Clinicians should understand the multiple factors that contribute to atopic disease development prenatally, at birth, and in early life and use this knowledge to create a “risk profile” when determining disease risk and suggesting preventative measures. With many birth cohorts currently underway, we can expect only a deeper pool of knowledge on the relations and interplay among these exposures, risk factors, and disease development in children. Clinicians can learn much from staying up to date with recent findings from these cohorts^{10,30,61–64} (Table 2), because these results could provide valuable information to develop guidelines aimed to prevent, reverse, or slow the onset of atopic disorders.

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