

Do rapid infant growth and childhood asthma have common developmental origins?

Diane R. Gold, MD, MPH *Boston, Mass*

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Rapid body mass index gain in the first 2 years of life was associated with increased incidence of asthma up to 6 years of age in a study published in this issue of the *Journal*.¹ Investigators analyzed combined data on 12,050 children from 8 European birth cohorts participating in the the Global Allergy and Asthma European Network (GA²LEN) Initiative. How strongly do their study results support the Developmental Origins of Health and Disease (DOHAD; www.dohad.org) hypothesis that common environmental influences in fetal and early life can reprogram the genome and simultaneously influence growth and the risk of a chronic disease like asthma?

As a birth cohort, victims of the Dutch famine, or Hunger Winter (November 1944 through May 1945), provide stark evidence supporting this hypothesis. Persons whose mothers were exposed to famine during gestation were smaller for gestational age and more prone to glucose intolerance, obesity, and obstructive airways disease.² Follow-up studies of the grandchildren of the women exposed to the famine suggest transgenerational inheritance of some of these characteristics.³ Diabetes and overweight status in adulthood have also been described as a legacy of the Biafrin famine (1968-1970).⁴

The relation of fetal and postnatal growth to asthma risk has also been studied in cross-sectional and longitudinal studies of populations without stark or historically obvious gestational exposures, such as famine. Anderson et al⁵ reviewed the small body of literature evaluating associations of postnatal growth trajectories with asthma and found it to be inconclusive and contradictory. Our Project Viva Boston birth cohort study reported that infants with higher weight-for-length *z* scores at 6 months had a greater risk of recurrent wheezing at 6 months of age.⁶ Although recurrent wheezing predicts increased risk of asthma in later childhood,⁷ it is well documented that many infants and toddlers are transient wheezers whose viral infection-induced symptoms resolve as their airways grow and might not have an atopic (allergic) phenotype.⁸

In the recent Promotion of Breastfeeding Intervention Trial (PROBIT) study of 12,171 term infants from the republic of Belarus, all weight gain variables except birth weight were positively associated with ever wheezing, but no growth trajectory measurement between 0 and 60 months was linked to asthma or allergic sensitization at 6.5 years of age. Whereas PROBIT used age 6.5 years as its end point, GA²LEN used incident asthma from early childhood up through age 6 years. It is possible that a significant portion of the incident asthma in GA²LEN represented wheeze that, like the symptoms in the Belarusian children from PROBIT, had resolved by age 6 years. The analytic approach in GA²LEN leaves us unable to judge whether early-life growth trajectories predicted atopic asthma that lasted beyond earlier childhood.

PROBIT used child-specific growth trajectories to predict the time-specific end point of asthma, whereas GA²LEN grouped children into discrete classes of trajectories (“normative,” “early rapid growth only up to 2 years of age,” and “persistent rapid growth up to 6 years of age”). The creation of the growth trajectory classes, which complicates investigation of within-person analyses of predictors and modifiers of asthma risk, might have been dictated in part by the necessity of blending different study designs with different timing of measurements.

As with children of the hunger famine, the children from GA²LEN with “early rapid growth only up to 2 years” are described as having low birth weight followed by catch-up growth with an “overshoot” of weight gain. The authors argue that despite the relation of early catch-up growth to being overweight at the time of asthma diagnosis, their analyses suggest that both early rapid growth and current overweight status are independently associated with asthma risk. The observations of the GA²LEN study, along with the observations of other longitudinal birth cohort studies on growth trajectories and asthma, provide important starting points for understanding the developmental origins of chronic diseases. But what genetic, genomic, inflammatory, or structural mechanisms can account for these associations? What is the role of the environment in determining early-life growth trajectories, and how plastic and mutable are the trajectories after early life?

A new generation of birth cohort studies with repeated measures of environmental exposures and intermediate epigenetic and inflammatory outcomes in multiple compartments might help us decipher mechanistic links among exposures during gestation and early life, early-life growth trajectories, and the development of obesity and asthma. For example, the relation of gestational and early childhood polycyclic aromatic hydrocarbons to child growth, obesity, and asthma risk is being disentangled by the Mothers and Children Study in Northern Manhattan and the South Bronx birth cohort from Columbia University.⁹ Polycyclic aromatic hydrocarbons, components of air pollution that belong to a family of chemical carcinogens

From the Channing Laboratory, Harvard Medical School, Brigham and Women's Hospital.

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Corresponding author: Diane R. Gold, MD, MPH, Channing Laboratory, Harvard Medical School, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115-5804. E-mail: diane.gold@channing.harvard.edu.

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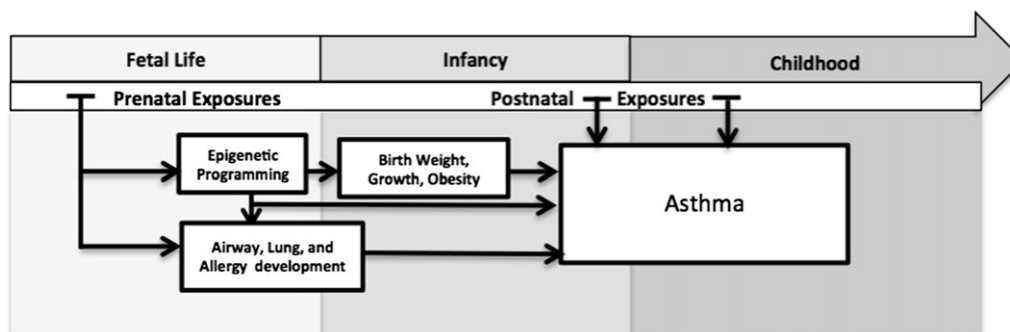


FIG 1. Hypothesized pathways through which early-life environmental exposures can influence growth trajectories and asthma risk.

created during incomplete combustion, are structurally similar to estrogen, have estrogenic effects in murine models, and are now being considered one of many families of chemical endocrine disruptors¹⁰ that might play a role in the development of early-life and later childhood obesity by mimicking or interfering with the function of hormones in the body. In addition to being found in air pollution, “endocrine disruptors can be found in many everyday products, including some plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides” (www.nih.niehs.gov).¹⁰ In the Columbia birth cohort study, higher prenatal polycyclic aromatic hydrocarbon exposures were associated with 5' CpG hypomethylation of IFN- γ in cord blood white cells¹¹ and childhood obesity.¹² At age 5 to 6 years, repeated exposure (prenatal plus childhood exposure) to the polycyclic aromatic hydrocarbon pyrene was associated with increased risk of asthma, including asthma without indoor allergic sensitization.⁹ Could endocrine-disrupting chemicals increase both obesity and asthma risk through developmental reprogramming of the epigenome, increasing chronic systemic adipokine or innate inflammation or endogenous steroid production?^{3,13} Could gestational exposures to environmental chemicals have structural effects on airway growth or lung structure? Pathways for the influences of early-life environmental exposures could involve multiple direct effects of *in utero* or early-life exposures on epigenetic reprogramming, influencing somatic growth and lung development separately (Fig 1). Alternatively, formation of adipocytes, obesity and inflammation, and physiologic restriction related to obesity could mediate the relation of gestational environmental exposures with asthma. Longitudinal pre-birth cohort studies are now taking advantage of emerging technologies to measure multiple exposures (including chemicals), intermediate genomic and proteomic responses, and physiologic and symptom end points to further delineate pathways linking somatic growth to asthma. These new initiatives might provide guidance for regulatory decisions related to

environmental exposures that jointly influence early-life growth trajectories and asthma.

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