7. Micol R, Kayal S, Mahlaoui N, Beauté J, Brosselin P, Dudoit Y, et al. Protective effect of IgM against colonization of the respiratory tract by nontypeable *Haemophilus influenzae* in patients with hypogammaglobulinemia. J Allergy Clin Immunol 2012;129:770-7.
8. Choi J, Nix EB, Gaultier GN, Cox AD, McCready W, Ulanova M. Naturally occurring bactericidal antibodies specific for *Haemophilus influenzae* lipooligosaccharide are present in healthy adult individuals. Vaccine 2015;33:1941-7.
9. Barra A, Dagan R, Preud'homme JL, Bajart A, Danve B, Fritzell B. Characterization of the serum antibody response induced by *Haemophilus influenzae* type b tetanus protein-conjugate vaccine in infants receiving a DTP-combined vaccine from 2 months of age. Vaccine 1993;11:1003-6.

Available online August 28, 2018.
https://doi.org/10.1016/j.jaci.2018.08.014

Breast-feeding and delivery mode modify the association between maternal atopy and childhood allergic outcomes

To the Editor:

A family history of allergy, especially maternal allergy, is associated with an increased likelihood of allergic sensitization and allergic diseases during childhood.[1,2] Furthermore, infancy and early childhood may be a critical period for environmental exposures to modulate allergic disease risk. Although breast-feeding and delivery mode appear to modify the risk of childhood allergic outcomes,[3-5] it is unclear whether they have the potential to attenuate or intensify the risk associated with vertical transmission of maternal atopy. In the Detroit area Wayne County Health, Environment, Allergy, and Asthma Longitudinal Study (WHEALS) birth cohort, we investigated whether the association between maternal atopy and childhood eczema and atopy depends on mode of delivery or breast-feeding.

Analyses were performed on data collected from protocols approved by the Henry Ford Health System Institutional Review Board. The WHEALS cohort included 1258 babies; 255 were dropped for reasons such as refusals and noncompliance. Of the remaining 1003 eligible, 673 were included in the analytic sample, as maternal atopy status was ascertained as described below and the child completed the 2-year clinic visit. Participants included in the analysis were more likely to be married, white, and breast-feed their children, among others (see Table E1 in this article's Online Repository at www.jacionline.org). The women were interviewed during their pregnancy to obtain demographic and environmental information. Postpartum questionnaires and home visits were targeted for ages 1 and 6 months. At the 1-month interview, women were asked about breast-feeding practices to determine whether they were exclusively breast-feeding (report of current breast-feeding and no formula). Delivery records were abstracted to obtain delivery type (vaginal or cesarean section [C-section]), as well as antimicrobial or antifungal use during pregnancy. Maternal atopy during pregnancy was defined as a serum IgE level of 0.35 IU/mL or greater for at least 1 of the 8 common allergens: dust mite, ragweed, *Alternaria alternata*, dog, cat, grass, cockroach, and egg. In cases in which a prenatal maternal serum sample was missing, a 1-month postnatal sample was substituted, as we have previously shown that sensitization status is relatively stable from the prenatal to the early postnatal period.[6] A clinic visit and interview was performed at age 2 to 4 years (mean age, 2.2 years) by Henry Ford Medical Group physicians and staff who were instructed in the study protocol. Physicians determined past or present eczema considering combined patient history and physical examination. Children's serum total and specific IgE levels were determined by ImmunoCAP, and atopy was defined as a serum IgE level of 0.35 IU/mL or greater for at least 1 of 10 common allergens (dust mite, ragweed, *Alternaria alternata*, dog, cat, grass, cockroach, egg, milk, and peanut). The association between maternal atopy and childhood outcomes was assessed using logistic regression ($P < .05$ considered significant), with effect modification by mode of delivery and breast-feeding evaluated ($P < .10$ considered significant).

Among the 673 children, 384 (57%) had atopic mothers (Table I). Atopic mothers were more likely to be black ($P < .001$) and have used antifungals during pregnancy ($P = .008$). Atopic mothers also received more antibiotics during pregnancy, but this trend did not reach statistical significance ($P = .056$).

After covariate adjustment, the odds of eczema by age 2 years did not significantly differ between children of atopic and nonatopic mothers (odds ratio [OR] comparing children of atopic vs nonatopic mothers = 1.15; 95% CI, 0.75-1.77; $P = .51$; see Table E2 in this article's Online Repository at www.jacionline.org). However, children of atopic mothers had approximately double the odds of being atopic (OR = 2.35; 95% CI, 1.56-3.53; $P < .001$), sensitized to foods (OR = 2.2; 95% CI, 1.46-3.31; $P < .001$), and sensitized to inhalants (OR = 2.04; 95% CI, 1.29-3.24; $P = .002$). Because women who delivered via C-section were less likely to exclusively breast-feed their child at age 1 month (11.3% vs 19.7%; $P = .006$), we assessed the effect of maternal atopy on child outcomes within each of 4 subgroups: vaginal/nonexclusively breast-fed (VN), vaginal/exclusively breast-fed (VB), C-section/nonexclusively breast-fed (CN), and C-section/exclusively breast-fed (CB) (Fig 1). The association between maternal atopy and childhood eczema was not significantly modified by mode of delivery nor exclusive breast-feeding (both interaction $P \geq .10$; Fig 1, *A*). However, exclusive breast-feeding significantly modified the association between maternal atopy and child atopy (interaction $P = .013$; Fig 1, *B*). Specifically, regardless of mode of delivery, maternal atopy was associated with higher odds of child atopy only if they were not exclusively breast-fed at age 1 month (OR [95% CI]$_{VN}$ = 2.34 [1.33-4.12]; OR_{VB} = 0.60 [0.23-1.59]; OR_{CN} = 4.61 [2.20-9.67]; OR_{CB} = 1.18 [0.36-3.87]). Similar results were observed for the association between maternal atopy and child inhalant sensitivity (breast-feeding interaction $P = .012$; C-section interaction $P = .49$; Fig 1, *D*). Furthermore, both exclusive breast-feeding and mode of delivery jointly modified the association between maternal atopy and child food sensitivity (interaction $P = .053$ and .042, respectively; Fig 1, *C*), where both exclusive breast-feeding and vaginal delivery appeared to mitigate the association between maternal atopy and child food sensitivity. Specifically, maternal atopy was highly associated with child food sensitivity among children who were born via C-section and were nonexclusively breast-fed (OR_{CN} = 4.64 [2.22-9.72]), whereas there was no association among children who were vaginally delivered and were exclusively breast-fed (OR_{VB} = 0.65 [0.25-1.70]).

While interpreting our results, we acknowledge certain limitations. We were able to obtain adequate information on maternal

TABLE I. Description of maternal, birth, and early-life characteristics and associations with maternal atopy

Covariate	Response	Overall (N = 673), n (%)	By maternal atopy status, n (%)		*P* value*
			Nonatopic (N = 289)	Atopic (N = 384)	
Maternal marital status	Not married	218 (32.4)	88 (30.4)	130 (33.9)	.35
	Married	455 (67.6)	201 (69.6)	254 (66.1)	
Household income	<$20K	76 (11.3)	36 (12.5)	40 (10.4)	.075
	20K-<$40K	140 (20.8)	67 (23.2)	73 (19)	
	40K-<$80K	179 (26.6)	83 (28.7)	96 (25)	
	$80K-<$100K	92 (13.7)	41 (14.2)	51 (13.3)	
	≥$100K	97 (14.4)	33 (11.4)	64 (16.7)	
	Refused to answer	89 (13.2)	29 (10)	60 (15.6)	
Maternal education	<HS Diploma	28 (4.2)	10 (3.5)	18 (4.7)	.84
	HS Diploma/equivalent	100 (14.9)	45 (15.6)	55 (14.3)	
	Some college	304 (45.2)	132 (45.7)	172 (44.8)	
	≥Bachelor's degree	241 (35.8)	102 (35.3)	139 (36.2)	
Maternal race	White	176 (26.2)	87 (30.1)	89 (23.2)	<.001
	Black	386 (57.4)	142 (49.1)	244 (63.5)	
	Mixed/Other	111 (16.5)	60 (20.8)	51 (13.3)	
Prenatal antibiotic use†	No	293 (45.4)	139 (49.6)	154 (42.1)	.056
	Yes	353 (54.6)	141 (50.4)	212 (57.9)	
Prenatal antifungal use†	No	526 (81.4)	241 (86.1)	285 (77.9)	.008
	Yes	120 (18.6)	39 (13.9)	81 (22.1)	
Indoor pets at predelivery	No	417 (62.0)	185 (64)	232 (60.4)	.34
	Yes	256 (38.0)	104 (36)	152 (39.6)	
Mode of delivery of offspring†	Vaginal	425 (63.2)	176 (61.1)	249 (64.8)	.32
	C-Section	247 (36.8)	112 (38.9)	135 (35.2)	
Current breast-feeding at 1 mo†	No	278 (42.8)	125 (45.3)	153 (40.9)	.26
	Yes	372 (57.2)	151 (54.7)	221 (59.1)	
Exclusive breast-feeding at 1 mo†	No	542 (83.4)	229 (83)	313 (83.7)	.81
	Yes	108 (16.6)	47 (17)	61 (16.3)	

HS, High school.
*Calculated by the χ^2 test.
†Some missing values in covariate: all rates of missingness <5%.

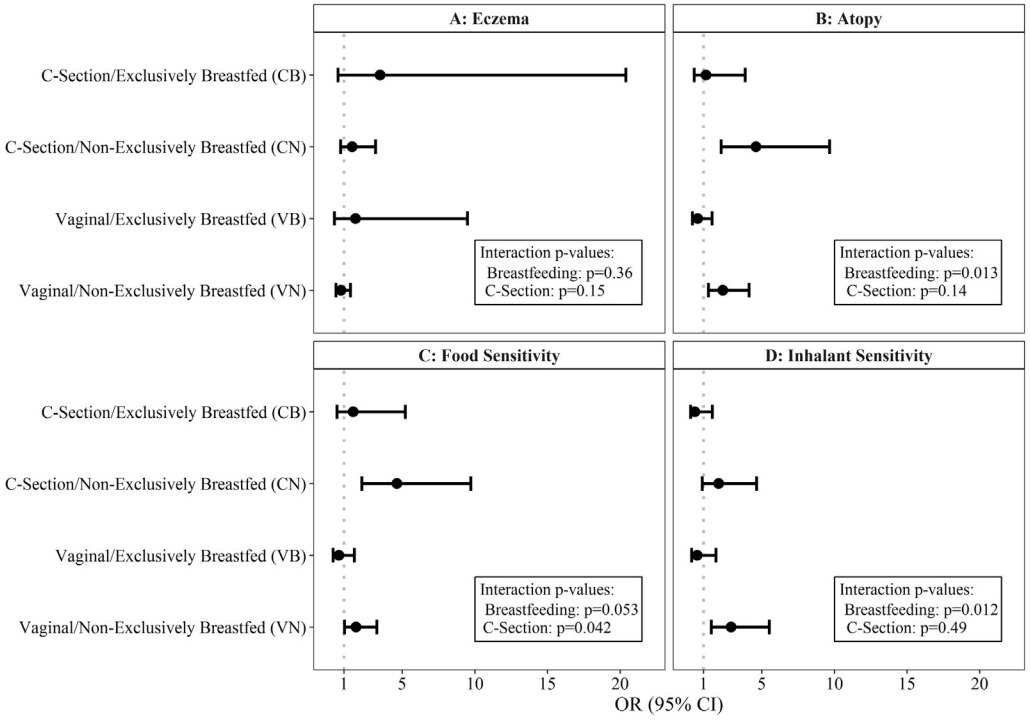

FIG 1. Association between maternal atopy and childhood allergic outcomes, by mode of delivery and exclusive breast-feeding at 1 month. Presented ORs and 95% CIs compare the odds of each outcome in children of atopic versus nonatopic mothers, within each of the 4 subgroups. Outcomes examined include eczema (adjusted for maternal race, **A**), atopy (adjusted for maternal race, **B**), food sensitivity (adjusted for maternal race, **C**), and inhalant sensitivity (adjusted for prenatal antibiotic use, **D**).

but not paternal atopy. Data were available only on a subset of the full cohort: this not only limits power to examine effect modification but also generalizability, because there was evidence of selection bias.

Our analyses suggest that vaginal delivery and exclusive breast-feeding in combination significantly modify the association between maternal atopy and atopic outcomes and suggest that the excess risk of allergy in offspring due to maternal atopy depends on these exposures. We found that maternal atopy is primarily a risk factor among children born via C-section and in nonexclusively breast-fed children, with early breast-feeding and vaginal delivery mitigating the transmission of atopy from mother to child. The biological mechanism explaining the effects of breast-feeding and delivery mode on allergy development is unknown. As we have previously shown in this cohort that these factors associate with an altered early-life gut microbiota,[7] we speculate that this pathway may play a role in early-life immune development. Studies have also directly linked C-section delivery to altered stress response, immune function, and epigenetic changes in offspring.[8] In addition, human milk contains various immunoactive components (eg, oligosaccharides, metabolites, and microbes) as well as vitamins and nutrients that may provide protection.[9] These results may be informative in regard to potential targeted prevention strategies in high-risk offspring of atopic mothers, though further studies will be necessary to determine the biological mechanisms behind these protective effects.

Alexandra Rene Sitarik, MS[a]
Nena Sabri Kasmikha, MD[b]
Haejin Kim, MD[b]
Ganesa Wegienka, PhD[a]
Suzanne Havstad, MA[a]
Dennis Ownby, MD[c]
Edward Zoratti, MD[b]
Christine Cole Johnson, PhD[a]

From [a]the Department of Public Health Sciences, Henry Ford Health System, Detroit, Mich; [b]the Department of Internal Medicine, Division of Allergy and Immunology, Henry Ford Health System, Detroit, Mich; and [c]the Department of Pediatrics, Augusta University, Augusta, Ga. E-mail: asitari1@hfhs.org.

This study was supported by the National Institutes of Health (grant nos. P01 AI089473 and R01AI051598) and the Fund for Henry Ford Hospital.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Bertelsen R, Rava M, Carsin A, Accordini S, Benediktsdóttir B, Dratva J, et al. Clinical markers of asthma and IgE assessed in parents before conception predict asthma and hayfever in the offspring. Clin Exp Allergy 2017;47:627-38.
2. Xu R, DeMauro SB, Feng R. The impact of parental history on children's risk of asthma: a study based on the National Health and Nutrition Examination Survey-III. J Asthma Allergy 2015;8:51.
3. Nwaru B, Craig L, Allan K, Prabhu N, Turner S, McNeill G, et al. Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. Clin Exp Allergy 2013;43:1263-73.
4. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy 2008;38:634-42.
5. 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. e3.
6. Perry LM, Ownby DR, Wegienka GR, Peterson EL, Woodcroft KJ, Joseph CL, et al. Differences in total and allergen specific IgE during pregnancy compared with 1 month and 1 year post partum. Ann Allergy Asthma Immunol 2009;103:342-7.
7. Levin AM, Sitarik AR, Havstad SL, Fujimura KE, Wegienka G, Cassidy-Bushrow AE, et al. Joint effects of pregnancy, sociocultural, and environmental factors on early life gut microbiome structure and diversity. Sci Rep 2016;6:31775.
8. Magne F, Puchi Silva A, Carvajal B, Gotteland M. The elevated rate of Cesarean section and its contribution to non-communicable chronic diseases in Latin America: the growing involvement of the microbiota. Front Pediatr 2017;5:192.
9. Munblit D, Peroni DG, Boix-Amorós A, Hsu PS, Land BVt, Gay MC, et al. Human milk and allergic diseases: an unsolved puzzle. Nutrients 2017;9:894.

Available online August 28, 2018.
https://doi.org/10.1016/j.jaci.2018.08.012

Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies

To the Editor:

This year, 2018, marks 50 years since the first allogeneic hematopoietic cell transplantations (HCTs) were performed for primary immune deficiencies (PIDs) in 1968 (severe combined immune deficiency [SCID] and Wiskott-Aldrich syndrome [WAS]).[1,2] Despite the passage of time and the expansion of allogeneic HCT to many PID diseases, data regarding recent changes in transplant practices and outcomes are lacking. There have been recent sizable studies for specific PIDs such as WAS and SCID.[3-5] Two older European studies described allogeneic HCT for very large groups of patients with and without SCID, but neither included data from the last 10 years.[6,7] In commemoration of this anniversary year, we examined the indications, practice changes, and survival of patients with PID treated with allogeneic HCT between 1974 and 2016 using data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

The CIBMTR is a voluntary network of more than 500 transplant centers worldwide (https://www.cibmtr.org/About/WhoWeAre/Centers/Pages/index.aspx). All allogeneic transplants in the United States are now reported to the CIBMTR in fulfillment of the Stem Cell Therapeutic and Research Act of 2005. We categorized transplantations by broad disease category (SCID and non-SCID) on the basis of reported diagnoses and by transplant periods: 1974 to 1989, 1990 to 1999, 2000 to 2009, and 2010 to 2016. Data were not collected from all centers during all time frames of this study; therefore, comparisons over time periods are limited to data reported to CIBMTR. Patients with SCID who underwent newborn screening were identified on the basis of their state of residence, date of implementation in their state, and birth date. The Institutional Review Board of the National Marrow Donor Program approved this study. For analysis of overall survival, death from any cause was considered an event and surviving patients were censored at last follow-up. The 3-year probabilities of overall survival were calculated using the Kaplan-Meier estimator.[8]

Nine hundred eighty-one patients with SCID and 1902 patients without SCID underwent allogeneic HCT between 1974 and 2016 (Tables I and II). The number of transplantations greatly increased over time. There were just over 100 transplants performed for PID from 1974 to 1989, whereas between 2010 and 2016, 352 and 816 transplants were performed for patients with and without SCID, respectively. SCID transplants were performed at a median age of 0.5 years. The median age for patients without SCID was 2 years, and the indication evolved over the decades. Approximately half the transplantations before 1990 were for WAS, whereas the most common recent indications were hemophagocytic

TABLE E1. Description of maternal-child pairs included and excluded from analyses

Covariate	Response	Included (N = 673)	Excluded (N = 585)	*P* value*
Maternal marital status	Not married	218 (32.4)	267 (45.6)	<.001
	Married	455 (67.6)	318 (54.4)	
Household income	<$20K	76 (11.3)	106 (18.1)	
	20-<$40K	140 (20.8)	155 (26.5)	
	40K-<$80K	179 (26.6)	168 (28.7)	
	$80K-<$100K	92 (13.7)	43 (7.4)	<.001
	≥$100K	97 (14.4)	51 (8.7)	
	Refused to answer	89 (13.2)	62 (10.6)	
Maternal education	<HS Diploma	28 (4.2)	46 (7.9)	
	HS Diploma	100 (14.9)	128 (21.9)	
	Some college	304 (45.2)	301 (51.5)	<.001
	≥Bachelor's degree	241 (35.8)	110 (18.8)	
Maternal race	White	176 (26.2)	114 (19.5)	
	Black	386 (57.4)	392 (67)	.002
	Mixed/Other	111 (16.5)	79 (13.5)	
Mother atopic†	No	289 (42.9)	248 (48.1)	.079
	Yes	384 (57.1)	268 (51.9)	
Prenatal antibiotic use†	No	293 (45.4)	43 (43.9)	.78
	Yes	353 (54.6)	55 (56.1)	
Prenatal antifungal use†	No	526 (81.4)	78 (79.6)	.67
	Yes	120 (18.6)	20 (20.4)	
Indoor pets at predelivery	No	417 (62)	403 (68.9)	.010
	Yes	256 (38)	182 (31.1)	
Mode of delivery of offspring†	Vaginal	425 (63.2)	359 (62.1)	.68
	C-Section	247 (36.8)	219 (37.9)	
Current breast-feeding at 1 mo†	No	278 (42.8)	223 (60.4)	<.001
	Yes	372 (57.2)	146 (39.6)	
Exclusive breast-feeding at 1 mo†	No	542 (83.4)	340 (92.1)	<.001
	Yes	108 (16.6)	29 (7.9)	

HS, High school.
*Calculated by the χ^2 test.
†Some missing values in covariate.

TABLE E2. Overall association between maternal atopy and childhood allergic outcomes

Outcome	Nonatopic mother: n (%)	Atopic mother: n (%)	OR (95% CI)*	*P* value
Eczema	55 (19.6)	91 (24.5)	1.15 (0.75-1.77)†	.51
Atopy	84 (42.6)	165 (59.1)	2.35 (1.56-3.53)†	<.001
Food sensitivity	69 (33.0)	139 (48.9)	2.20 (1.46-3.31)†	<.001
Inhalant sensitivity	34 (17.5)	82 (29.6)	2.04 (1.29-3.24)‡	.002

*Odds of outcome in children of atopic vs nonatopic mothers.
†Adjusted for maternal race.
‡Adjusted for prenatal antibiotic use.