Factors that impact early-life microbial colonization influence allergic multi-morbidity

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Background & Hypothesis

Aberrant microbial colonization, or dysbiosis, has been suggested as a driver of allergic disease. Factors implicated in early-life dysbiosis include birth by cesarean section (CS) rather than by vaginal delivery (VD), infant consumption of formula rather than breastmilk (BM), and early-life exposure to antibiotics or antiacids[1-5] (**Figure 1**). However, the extent to which these factors influence allergic multi-morbidity in children that develop atopic dermatitis (AD), IgE-mediated food allergy (FA), asthma, and/or allergic rhinitis (AR) has remained undefined. **Our main hypothesis was that birth by VD, BM consumption, and lack of early-life exposure to antibiotics and/or antiacids would associate with reduced allergic burden over time.**

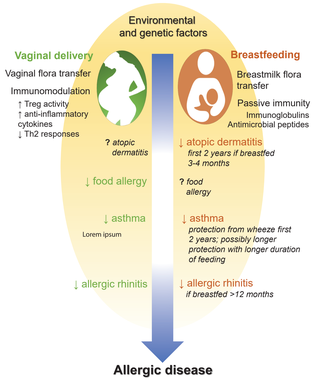
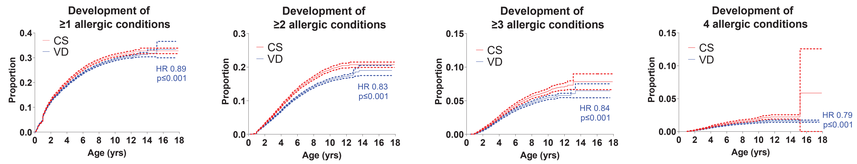


Figure 1. Schematic of documented and postulated effects of VD and BM consumption on predisposition to specific allergic diseases. Associations with reduced rates of AD, FA, asthma, and AR are indicated with down arrows, as informed by literature review (see Ref. 1-4). Question marks indicate poorly defined associations. Early-life antibiotic and antiacid exposure are also postulated to affect predisposition to allergic disease, in part through modulation of microflora (not shown; see Ref. 5).

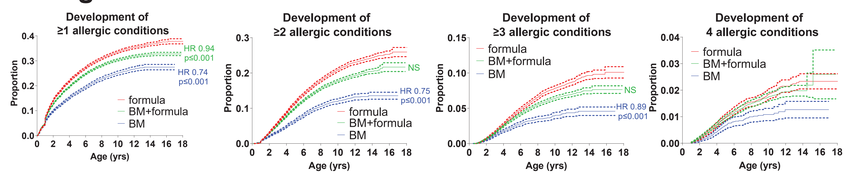
Results

Vaginal delivery, breastmilk consumption, and early-life avoidance of medications with microbiome-altering potential is associated with reduced cumulative burden of allergic disease

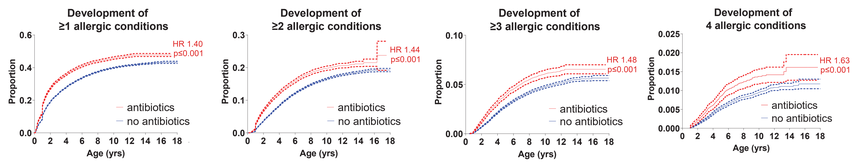
A. Delivery mode



B. Feeding mode



C. Antibiotics



D. Antiacids

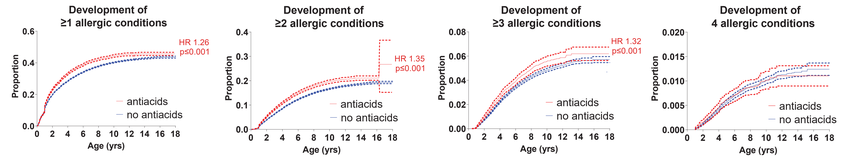


Figure 2. Kaplan-Meier curves demonstrating effects of (**A**) delivery mode, (**B**) feeding mode, (**C**) early-life antibiotic exposure, and (**D**) early-life antiacid exposure on the development of at least 1, 2, 3, or 4 allergic conditions. VD was associated with reduced rate of development of allergic conditions (**Figure 2A**). A protective association was observed for VD, regardless of degree of allergic burden (HR 0.89, 0.83, 0.84, 0.79 for development of 1, 2, 3, or 4 conditions respectively, p≤.001). Infant BM consumption was also associated with reduced occurrence of allergic disease (**Figure 2B**). Infant diets comprised of either exclusive BM (HR 0.74, 0.75, 0.89, for 1, 2, or 3 conditions respectively, p≤.001) or with formula-supplemented BM (HR 0.94 for 1 condition, p≤.001; no association with 2 or 3 conditions) were associated with reduced development of allergic conditions. Antibiotic exposure (**Figure 2C;** HR 1.40, 1.44, 1.48, 1.63 for at least 1, 2, 3, 4 conditions; p≤.001) and antiacid exposure (**Figure 2D;** HR 1.26, 1.35, 1.32 for at least 1, 2, 3 conditions; p≤.001; no association for 4 conditions) were each also associated with increased allergy development rate. Dashed lines indicate 95% confidence intervals. NS, not significant.

Methods

For our virtual birth cohort, we used a previously described dataset comprised of 158,422 children (**Table 1**) cared for at 31 different primary care sites across the Delaware River Valley.[6] Using R 3.3.2 software, we defined cohorts of patients with 0, ≥1, ≥2, ≥3, and/or 4 allergic conditions (AD, FA, asthma, and/or AR). We computed Cox hazard ratios (adjusted for race and gender) to measure effects of birth delivery mode (VD or CS), infant feeding mode (BM, formula, or both), or documented prescription of either antibiotics or antiacids during the first six months of life on subsequent allergy development. Observations were confirmed via chart review. The research was performed in accordance with CHOP Institutional Review Board regulations and was exempt from requiring ethics approval as it did not meet the definition of human subjects research.

Table 1. Demographic characteristics of full and specific allergic disease cohorts

	Full	AD	FA	Asthma	AR
Gender, % (n)					
Male	51 (81,266)	55 (10,210)	59 (3,819)	60 (17,512)	56 (15,200)
Female	49 (77,244)	45 (8,386)	41 (2,653)	40 (11,839)	44 (11,894)
Race, % (n)					
White	50 (78,691)	32 (5,964)	47 (3,034)	40 (11,688)	43 (11,698)
Black	32 (50,847)	51 (9,465)	34 (2,227)	46 (13,504)	44 (11,860)
Asian or Pacific Islander	4 (5,824)	5 (957)	7 (444)	3 (785)	3 (748)
Other	2 (3,158)	2 (312)	2 (140)	2 (548)	2 (416)
Unknown	13 (19,990)	10 (1,898)	10 (627)	10 (2,826)	9 (2,372)
Ethnicity, % (n)					
Hispanic or Latino	7 (10,495)	6 (1094)	4 (283)	7 (1,957)	6 (1,578)
Non-Hispanic or Latino	93 (148,015)	94 (17,502)	96 (6,189)	93 (27,394)	94 (25,516)
Birth year, % (n)					
2000 to 2004	8 (13,357)	14 (2,512)	9 (602)	13 (3,716)	15 (4,173)
2005 to 2009	38 (60,576)	42 (7,829)	45 (2,912)	47 (13,915)	53 (14,468)
2010 to 2014	39 (62,076)	32 (5,919)	38 (2,458)	35 (10,246)	29 (7,793)
2015 or later	14 (22,501)	13 (2,336)	8 (500)	5 (1,478)	2 (660)
Payer type, % (n)					
Medicaid	33 (52,289)	43 (7,994)	26 (1,678)	42 (12,364)	38 (10,175)
Non-Medicaid	67 (106,221)	57 (10,602)	74 (4,794)	58 (16,987)	62 (16,919)

AD, atopic dermatitis; FA, Ig-E mediated food allergy; AR, allergic rhinitis

Conclusions and Future Directions

We observed that birth by VD, BM consumption, and early-life avoidance of antibiotics and antiacids were associated with reduced cumulative development of allergic disease in children. Our findings suggest that BM or BM-supplemented diets and avoidance of early-life antibiotics and/or antacids might lessen allergic morbidity, in part through preventing dysbiosis, although protection through non-microbiome effects cannot be excluded. The absence of significant protective effects for individuals with 4 allergic conditions suggests a weaker role for environmental factors in pro-atopic genetic backgrounds. Admittedly, our study represents a retrospective case-control analysis examining associations, and our understanding of the complex interplay between environmental factors and allergic progression will benefit from future prospective longitudinal studies. We are actively investigating effects of additional factors (e.g. weight) and whether the trends described above are maintained in a geographically broader patient dataset.

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