The atopic march and *Staphylococcus aureus* colonization are associated with fall birth

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Clinical Implications

- Observational studies on fall birth association with atopic dermatitis and food allergy have been performed. We demonstrate fall birth association with the entire atopic march and *Staphylococcus aureus* skin colonization, with the absent association for adult-onset allergic disease.

Individuals born in the fall (September through November) are known to be at increased risk of food allergy (FA) and atopic dermatitis (AD). This association has been seen in various demographic groups, and a recent meta-analysis examined this phenomenon.[1] The sequential progression of different allergic conditions is defined as the atopic march; in general, it begins with AD and progresses to FA, asthma, and allergic rhinitis (AR), suggesting that AD is an entry point for subsequent allergic diseases.[2] It is well described that AD peaks in early infancy. The presence of AD and skin barrier dysfunction promotes allergen sensitization and type 2 immune responses.[3,4] Previous studies that demonstrated a fall birth association with increased FAs have suggested that the seasonal variation in ultraviolet radiation exposure, and thus vitamin D levels, plays a role in FA pathogenesis.[1] Prior studies also implicated an association of *Staphylococcus aureus (S. aureus)* skin colonization with FA, independent of eczema severity.[5,6]

Although it is well described that fall birth is associated with a higher risk of FA and AD, the overall association between the season of birth and other aspects of the atopic march has not been studied. The aim of the current study was to examine the co-occurrence of AD, FA, asthma, and AR with fall births, thus, assessing the entire atopic march progression. In addition, the association of *S. aureus* colonization, which has been implicated in the pathogenesis of AD and FA,[5,6] with the season of birth was evaluated in this study. We hypothesized that children undergoing the atopic march would not only have a higher prevalence of fall births but also have skin cultures positive for *S. aureus*.

The National Jewish Health Research Database was queried to assess children under 6 years treated from February 2008 through August 2019. We received an institutional review board waiver to conduct this study. Common childhood FA diagnoses were obtained using International Classification of Diseases, Tenth Revision (ICD-10) codes and allergy history, including egg allergy (n = 1498), peanut allergy (n = 1870), and milk allergy (n = 735). These specific FAs were chosen as they are the predominant FAs in all children. In this same age group, we assessed the diagnoses of AD (n = 5378), AD without FA (n = 2651), AD with FA (n = 2727), AD with FA and asthma (n = 1010), AD and asthma without FA (n = 892), AD with FA, asthma, and AR (n = 594), AD with asthma and AR without FA (n = 376), AD with positive S. *aureus* skin cultures (n = 468), and AD with FA and positive S. *aureus* skin cultures (n = 339). These diagnoses were obtained using ICD-10 codes, and positive S. *aureus* skin cultures were extracted from the electronic medical record. As a control, we used adults 18 and older with shellfish allergy (n = 208), which is the most common adult-onset FA. Asthma without atopy (n = 16,995) was also assessed in adults 18 and older. These were used as control measures to capture adult-onset diseases, as they are less likely to have skin barrier disruption and undergo the atopic march. To control for seasonality of all births, a denominator for these analyses was determined by capturing all unique patients under 6 years seen at our institution during the study period. Detailed methods are described in this article's Online Repository at www.jaci-inpractice.org.

A conservative 1-sided 99% confidence interval was used to evaluate if there was a greater proportion of fall births (individuals born in September, October, and November) compared with the other 3 seasons in individuals with atopic diseases. We used the R programming language for all analyses.

During the study period, 14,877 unique patients under 6 years were seen in our clinics. There was no significant finding of season of birth, nor was there a significant difference in demographics based on race, gender, and age of the first visit (Table I; Table E2, available in this article's Online Repository at www.jaci-inpractice.org). We confirmed the association of fall birth with FA and AD (Table I; $P < .01$). In children 5 years old and younger, the common FAs of egg, peanut, and milk were more prevalent in those born in the fall. Interestingly, there was no fall birth association in AD without FA. The same pattern was observed when including asthma and AR, as there was a fall birth prevalence in AD + FA + asthma + AR, with the lack of fall predisposition in AD + no FA + asthma. In individuals 18 years and older, there was no seasonal predisposition in adults with asthma or adults with shellfish allergy (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Children 5 years old and younger with AD and skin cultures positive for *S. aureus* also had a higher prevalence of fall birth (Table II; $P < .01$). This observation was also seen when including those with FA (Table II; $P < .01$).

These data show the association of fall birth with the occurrence of the atopic march: patients with AD, FA, asthma, and AR. In our data set, there is a statistically significant incidence of fall birth in children with AD, FA, and *S. aureus* skin colonization. These data suggest that *S. aureus* skin colonization magnifies the fall birth association. Previous clinical studies have also emphasized the association of positive *S. aureus* skin cultures with atopic diseases. For example, Meylan et al[7] demonstrated in a prospective birth cohort study that there was higher *S. aureus* skin colonization in 3-month-old infants who later develop AD. In addition, it has previously been observed that *S. aureus* skin colonization is associated with the childhood FAs of peanut, egg white, and cow's milk.[5] Increased *S. aureus* and a defective skin barrier function were

TABLE I. Seasonal proportions for all births and in different atopic conditions

	N	Dec-Feb	Mar-May	June-Aug	Sept-Nov
All unique patients	14,877	0.247	0.239	0.256	0.259 [0.251,
Egg allergy	1,498	0.252	0.220	0.249	**0.279 [0.252,**
Peanut allergy*	1,870	0.250	0.233	0.232	**0.285 [0.261,**
Milk allergy*	735	0.248	0.201	0.249	**0.302 [0.264,**
AD*	5,378	0.252	0.225	0.251	**0.273 [0.259,**
AD + FA*†	2,727	0.255	0.217	0.241	**0.286 [0.267,**
AD + no FA	2,651	0.248	0.233	0.261	0.258 [0.238,
AD + FA + Asthma*†	1,010	0.263	0.200	0.236	**0.301 [0.269,**
AD + no FA + Asthma	892	0.257	0.214	0.294	0.235 [0.201,
AD + FA + Asthma + AR*†	594	0.258	0.200	0.239	**0.303 [0.261,**
AD + no FA + Asthma + AR	376	0.263	0.229	0.271	0.237 [0.184,

The table summarizes proportions of children born during different seasons and their concomitant atopic conditions. Values such as [0.251, (all births) are the conservative lower 1-sided 99% confidence bound for the proportion born in Sept-Nov. Bold values represent statistically different proportions with $P < .01$. n is the total number of births examined.

AR, Allergic rhinitis; *AD,* atopic dermatitis; *FA*, food allergy.

*The proportion of children born in Sept-Nov for all atopic conditions except egg allergy is greater than the proportion of all children (% years-of-age and younger) born in Sept-Nov seen at National Jewish during the same time period.

†The proportion of children born in Sept-Nov with FA is greater than the proportion of children without FA born in Sept-Nov seen at National Jewish during the same time period.

TABLE II. *S. aureus* and seasonal proportions

	n	Dec-Feb	Mar-May	June-Aug	Sept-Nov
AD + *S. aureus*	468	0.252	0.203	0.242	**0.303 [0.256,**
AD + FA + *S. aureus*	339	0.248	0.212	0.236	**0.304 [0.248,**
S. aureus	500	0.254	0.198	0.246	**0.302 [0.256,**

The table summarizes proportions of children born during different seasons, their concomitant atopic conditions, and the earliest recorded *S. aureus* skin culture results. Values such as [0.256, are the lower 1-sided 99% confidence bound for the proportion born in Sept-Nov. Bold values represent statistically different proportions with $P < .01$. n is the total number of births examined.

identified in lesional and even in nonlesional skin of children with AD and concomitant FA; these findings make them unique from AD patients without FA.[8] In animal models, oral administration of Staphylococcal enterotoxin B with food allergens was found to induce an immune response that disturbed oral tolerance and led to sensitization to food allergens.[9] In the Learning Early About Peanut Allergy study, participants with *S. aureus* skin colonization were more likely to have food sensitization, independent of AD severity.[6] Our observation of the increased prevalence of fall birth with *S. aureus* skin colonization supports the role of *S. aureus* in atopy and the progression along the atopic march.

As skin barrier dysfunction is important in the development of atopy, perinatal maternal and environmental factors also likely play a role in magnifying the allergic phenotype in fall births. The effect of environmental factors, namely air pollution, temperature, and humidity, may have *in utero* implications during winter conception, as well as postnatal implications with the fall birth. With climate change, overall warmer temperatures may enhance *S. aureus* skin growth in those progressing through the atopic march. Finally, it is interesting to note the absence of fall birth association in AD + no FA + asthma + AR (Table I). When FA is not included in a sequence of atopic manifestations, there is no seasonal birth predominance. This may emphasize that additional perinatal influences, such as environmental factors and *S. aureus* colonization, are required to be present for FA development. This also suggests that FA is most highly linked to the fall birth observation, with individuals at greater risk of atopic comorbidities.

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ONLINE REPOSITORY

METHODS

Cohorts were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes and the allergy history, which were entered by physicians or mid-level providers in the electronic medical records. For food allergy, specific foods were entered and captured by ICD-10 codes (ie, Z91.012 "allergy to eggs" and Z91.010 "allergy to peanuts"). For atopic dermatitis, the ICD-10 codes of L20.9 "atopic dermatitis, unspecified," L20.81 "atopic neurodermatitis," and L30.9 "dermatitis, unspecified" were used by providers, and these were the ICD-10 codes included in this analysis.

Staphylococcus aureus is obtained via superficial skin culture. With superficial skin cultures, the skin culture is plated and incubated for 24 hours. It is read over the course of 72 hours. S. aureus is recognized on the blood agar plate by beta hemolysis and color/size on the macro level. This is confirmed with the staph latex test, and then run on the Phoenix machine to confirm S. *aureus* via the coagulation test. The Phoenix machine also determines the minimum inhibitory concentration.

Research Informatics Services built the research database to handle both study data and patient data from our institution's electronic medical records. For this data, patient and build data are continually validated against the source. All loaded data are quality checked by comparing them with the output from an independent extraction process. Data analysts review new data brought into the database monthly and validate each data set released to researchers against source electronic medical records data.

TABLE E1. Adult controls and seasonal proportions

	n	Dec-Feb	Mar-May	June-Aug	Sept-Nov
Shellfish allergy	208	0.250	0.279	0.236	0.236 [0.164,
Asthma, no atopy	16,995	0.243	0.245	0.259	0.252 [0.244,

The table summarizes proportions of adults born during different seasons and their concomitant atopic conditions. Values such as [0.164, are the lower 1-sided 99% confidence bound for the proportion born in Sept-Nov. n is the total number of births examined.

TABLE E2. Demographic summary of the study population by season of birth

	Season of birth				
	Dec-Feb n = 3668	Mar-May n = 3549	June-Aug n = 3803	Sept-Nov n = 3868	*P* value
Race					
American Indian, n (%)	15 (0.4)	14 (0.4)	15 (0.4)	16 (0.4)	.21*
Asian, n (%)	58 (1.6)	38 (1.0)	35 (0.9)	39 (1.0)	
Black, n (%)	111 (3.0)	108 (3.0)	101 (2.6)	106 (2.7)	
Declined to report, n (%)	147 (4.0)	134 (3.8)	146 (3.8)	169 (4.4)	
More than 1 race, n (%)	56 (1.5)	47 (1.3)	46 (1.2)	42 (1.1)	
Hawaiian/Pacific Islander, n (%)	0 (0)	3 (0.1)	6 (0.2)	3 (0.1)	
Unknown, n (%)	664 (18.1)	594 (16.7)	693 (18.2)	673 (17.4)	
White, n (%)	1015 (27.7)	986 (27.8)	1084 (28.4)	1135 (29.4)	
No data collected, n (%)	1602 (43.7)	1625 (45.8)	1677 (44.0)	1674 (43.4)	
Gender					
Female, n (%)	1419 (38.7)	1441 (40.6)	1513 (39.8)	1483 (38.45)	.28*
Male, n (%)	2249 (61.3)	2100 (59.4)	2290 (60.2)	2373 (61.35)	
Unknown, n (%)	0 (0)	0 (0)	0 (0)	1 (0.03)	
Age at the time of first clinical visit, years (standard deviation)	2.40 ± (1.64)	2.47 ± (1.65)	2.39 ± (1.65)	2.38 ± (1.68)	.08†

*Pearson's χ^2 test.
†Kruskal-Wallis test.