Staphylococcus aureus colonization is associated with wheeze and asthma among US children and young adults

To the Editor:

Asthma prevalence has been on the rise in the past decades, although its drivers are incompletely understood.[1,2] While exposure to allergens and gram-negative endotoxin is associated with asthma and wheeze,[3] the link between other microbial exposures, which stimulate the human immune system in myriad ways, and the risk of asthma remains unclear. One microbe, the gram-positive bacterium *Staphylococcus aureus*, exacerbates atopic eczema and contributes to development of chronic rhinosinusitis with nasal polyposis via a T_H2-biased immune response to bacterial superantigen proteins such as staphylococcal enterotoxins (SE),[4] suggesting that *S aureus* could also affect T_H2-driven airway disease.

Interestingly, although 1 study found no significant associations between *S aureus* nasal colonization in neonates and subsequent asthma outcomes,[5] 2 other studies found evidence for a diagnosis of asthma being a risk factor for *S aureus* colonization, including 1 study using data from the National Health and Nutrition Examination Survey (NHANES) 2001-2002.[6,7] Building on these findings, we evaluated *S aureus* nasal colonization as a risk factor for a range of asthma-associated outcomes, including diagnosis, symptoms, and exacerbations, among the US population using data from NHANES 2001-2004. We also examined the effect of age on relationships between *S aureus* colonization and asthma- and wheeze-related outcomes.

NHANES, a nationally representative survey, includes data on demographic characteristics, health status, and nutrition of noninstitutionalized US residents ages 1 to 85 years old. Details on the conduct of NHANES surveys are available online at http://www.cdc.gov/nchs/nhanes.htm. This analysis includes respiratory outcomes related to self-reported symptoms of wheeze and asthma in the past year. Population-standardized prevalence rates were calculated, and unadjusted and adjusted associations between *S aureus* nasal colonization and asthma and wheeze outcomes were examined using logistic regression modeling to estimate odds ratios (OR) using Stata 13.1 (Stata, College Station, Tex). Details on these methods are available in this article's Online Repository at www.jacionline.org.

In NHANES 2001-2004, an estimated 28.4% (95% CI: 27.3%, 29.6%) of the population was nasally colonized with *S aureus*. Table I provides prevalence rates of asthma and wheeze outcomes in the NHANES 2001-2004 cohort among the 16,234 participants 6 to 85 years old, as described in this article's Online Repository at www.jacionline.org. In the analysis of associations between *S aureus* and outcomes related to wheeze and asthma, age appeared to modify the effects of exposure, with positive associations observed among younger individuals (~6-30-year-olds) and negative associations observed among older individuals (~31-85-year-olds) (Fig E1). *S aureus* colonization in the younger group was associated with increased population prevalence rates for respiratory outcomes (Fig E2).

Table II displays models adjusted for *a priori* covariates and demonstrates that, for most outcomes, statistically significant interactions between *S aureus* colonization and age category were observed. For example, *S aureus* colonized individuals had a significant 1.52-fold (95% CI: 1.15, 2.00) increase in odds of nocturnal wheeze compared with noncolonized individuals among 6- to 30-year-olds, but *S aureus*–colonized individuals had a nonsignificant decrease in odds (OR 0.79, 95% CI: 0.53, 1.18) among 31- to 85-year-olds, with interactive effects present between *S aureus* colonization and age category ($P = .01$). Results were similar between unadjusted and adjusted models (Table E1).

In this analysis of NHANES data, representative of the US population, *S aureus* nasal colonization was associated with increased risk of asthma prevalence, symptoms, and exacerbations in children and young adults. No associations were seen for most asthma-related outcomes among adults aged 31 to 85. Together, these findings implicate *S aureus* colonization in the pathogenesis of asthma prevalence and morbidity in children and young adults. While 2 prior epidemiologic studies evaluating risk factors for *S aureus* colonization identified asthma as 1 factor among many,[6,7] no previous studies have evaluated whether *S aureus* colonization is a risk factor for asthma-related symptoms and exacerbations and whether these relationships are modified by age. Our hypothesized causal direction from *S aureus* colonization to asthma diagnosis and morbidity is biologically plausible. Numerous human and animal studies suggest that exposure to intrinsic or secreted components of *S aureus* (eg, peptidoglycan, SE) may exacerbate upper respiratory disease via local or systemic T_H2-driven host immune responses,[4,8] which could contribute to exacerbation or progression to lower airway disease.

This is the first study to note differences in associations between *S aureus* colonization and asthma outcomes among younger versus older participants, which we discuss further in this article's Online Repository at www.jacionline.org. Because host responses, including atopic status, may mediate the relationships between *S aureus* colonization and asthma and wheeze, children and young adults, who typically are more atopic, could be more susceptible to the respiratory effects of *S aureus* than older adults. However, atopic status was not measured in NHANES 2001-2004, precluding our ability to explore this host factor as a potential mediator of the observed relationships. It is also possible that the associations between *S aureus* colonization and asthma outcomes were only observed in younger individuals because of misclassification of asthma in older adults. For example, adults are more likely to have comorbidities that can be mistaken for asthma, such as chronic obstructive pulmonary disease and congestive heart failure. However, removing individuals with heart disease, chronic bronchitis, and emphysema did not affect the findings (data not shown).

Like other NHANES analyses, this study is limited by its cross-sectional study design, precluding testing the causal direction for observed associations. Incomplete and biased measurement of staphylococcal enterotoxins in NHANES 2001-2004 limited our ability to analyze whether the relationship between *S aureus* and asthma outcomes differed according to the SE status of the colonizing isolate. Another potential limitation of this work is the assessment of only nasal colonization, because *S aureus* also may colonize skin, pharyngeal,

TABLE I. Participant characteristics and prevalence rates for *S aureus* colonization among 6- to 85-year-old NHANES participants, 2001-2004

		Sample	*S aureus* colonized	Not *S aureus* colonized	X^2
	Demographic characteristics				
Row	**Characteristic**	**n (%)**	**Population % [95% CI]**	**Population % [95% CI]**	***P* value**
I	Total	16,234	28.4% [27.3%, 29.6%]	71.6% [70.4%, 72.7%]	
II	Sex				<.001
	Female	8,337 (51.4%)	47.6% [45.1%, 50.1%]	54.1% [52.9%, 55.3%]	
	Male	7,897 (48.6%)	52.4% [50.0%, 54.9%]	45.9% [44.7%, 47.1%]	
III	Ethnicity category				<.001
	NH white	6,980 (43.0%)	75.8% [71.7%, 79.3%]	71.4% [66.5%, 75.8%]	
	NH black	4,190 (25.8%)	8.5% [6.4%, 11.1%]	12.2% [9.7%, 15.2%]	
	Mex Am	3,985 (24.6%)	6.8% [5.2%, 8.7%]	7.7% [5.6%, 10.4%]	
	Other/multi	476 (2.9%)	3.9% [3.0%, 5.0%]	4.2% [3.2%, 5.5%]	
	Hispanic	603 (3.7%)	5.1% [3.2%, 8.2%]	4.5% [2.9%, 7.1%]	
IV	BMI category				.11
	Underweight	325 (2.0%)	1.7% [1.1%, 2.6%]	1.9% [1.5%, 2.3%]	
	Normal	6,665 (41.1%)	29.5% [26.7%, 32.4%]	31.4% [29.9%, 32.9%]	
	Overweight	4,452 (27.4%)	32.6% [30.2%, 35.0%]	34.0% [32.3%, 35.8%]	
	Obese	4,792 (29.5%)	36.2% [33.4%, 39.1%]	32.8% [31.1%, 34.6%]	
V	Smoking in the home*				.01
	Yes	3,371 (21.0%)	18.4% [16.1%, 20.9%]	22.5% [19.9%, 25.3%]	
	No	12,689 (79.0%)	81.6% [79.1%, 83.9%]	77.5% [74.7%, 80.1%]	
VI	Flu, pneumonia or ear infection‡				.98
	Yes	772 (5.1%)	4.9% [3.8%, 6.3%]	4.5% [3.9%, 5.3%]	
	No	14,398 (94.9%)	95.1% [93.7%, 96.2%]	95.5% [94.7%, 96.1%]	
		Mean (SD)	**Mean [95% CI]**	**Mean [95% CI]**	***P* value**
VII	Age in years	34.6 (23.3)	46.0 [45.7, 46.3]	46.3 [46.0, 46.6]	.12
VIII	Number of health care visits in past year*	1.97 (1.36)	2.06 [1.98, 2.14]	2.08 [2.04, 2.13]	.47
IX	Family PIR (income)‡	2.39 (1.60)	3.05 [2.92, 3.19]	2.96 [2.86, 3.05]	.04
X	Average household size	3.73 (1.75)	3.06 [2.96, 3.15]	3.01 [2.93, 3.09]	.25
	Respiratory outcomes				
Row	**Outcome**	**n (%)**	**Population % [95% CI]**	**Population % [95% CI]**	***P* value**
	Wheeze outcomes:				
XI	Wheeze in the past year*	2,091 (12.9%)	14.9% [12.9%, 17.2%]	15.2% [14.0%, 16.5%]	.57
XII	Wheeze during exercise*	1,011 (6.2%)	6.3% [5.3%, 7.4%]	7.0% [6.2%, 7.9%]	.92
XIII	Nocturnal wheeze‡	922 (6.1%)	6.6% [5.4%, 8.2%]	6.5% [5.7%, 7.3%]	.21
XIV	Emergency room visit for wheezing†	785 (4.9%)	5.8% [4.6%, 7.4%]	5.0% [4.3%, 5.9%]	.05
XV	Wheeze limits activities†	779 (4.9%)	5.6% [4.4%, 7.1%]	5.5% [4.6%, 6.4%]	.48
XVI	Medication for wheezing‡	562 (3.7%)	3.2% [2.4%, 4.2%]	4.2% [3.4%, 5.2%]	.23
XVII	Miss work or school due to wheeze†	408 (2.6%)	1.7% [1.1%, 2.7%]	1.9% [1.5%, 2.4%]	.15
	Asthma outcomes:				
XVIII	Asthma diagnosis ever*	2,169 (13.4%)	12.9% [11.4%, 14.6%]	11.8% [10.7%, 12.9%]	.05
XIX	Current asthma*	1,315 (8.1%)	7.7% [6.4%, 9.3%]	7.3% [6.4%, 8.3%]	.19
XX	Asthma attack in past year‡	672 (4.4%)	4.6% [3.4%, 6.1%]	3.5% [3.0%, 4.0%]	.02
XXI	Emergency room visit for asthma§	206 (1.4%)	1.2% [0.7%, 1.9%]	0.8% [0.6%, 1.1%]	.13

The sample column displays absolute numbers and percentages.
S aureus rates are standardized to the population distribution.
Due to rounding, percents may not add up to 100%.
BMI category is based on percentile assignment for ages 1 to 20 and BMI for ages 21 to 85.
BMI, Body mass index; *Mex Am*, Mexican American; *NH*, non-Hispanic; *PIR*, poverty income ratio.
*≤1% missing data.
†1% to 4% missing data.
‡5% to 7% missing data.
§8% to 10% missing data.

and other sites.[9] However, *S aureus* nasal colonization often shows a high correlation with skin carriage.[9] Another limitation of this study is the potential for reverse causation, in which lower respiratory disease could be a risk factor for *S aureus* colonization, rather than vice versa. For example, lower respiratory disease or symptoms could cause more contact with health care facilities, and increased contact with health care facilities could promote *S aureus* colonization. However, our findings were robust to adjustment for the number of reported health care visits.