TABLE II. Adjusted associations between *S aureus* nasal colonization and asthma and wheeze

Outcomes, OR [95% CI]	Whole population (age 6 to 85 y)	Age 6 to 30 y	Age 31 to 85 y	*S aureus* and age interaction
Sample size	n = 16,234	n = 8,703	n = 7,531	
Wheeze outcomes:				
Wheeze in the past year†	1.02 [0.87, 1.20]	**1.35 [1.06, 1.73]***	0.85 [0.68, 1.06]	***P* = .006**
Wheeze during exercise†	1.00 [0.82, 1.19]	1.27 [0.95, 1.70]	0.84 [0.67, 1.08]	*P* = .06
Nocturnal wheeze§	1.05 [0.84, 1.34]	**1.52 [1.15, 2.00]****	0.79 [0.53, 1.18]	***P* = .01**
Emergency room visit for wheezing‡	**1.28 [1.00, 1.62]***	**1.50 [1.10, 2.03]***	1.11 [0.70, 1.78]	*P* = .26
Wheeze limits activities‡	1.11 [0.89, 1.38]	**1.41 [1.05, 1.90]***	0.97 [0.72, 1.29]	***P* = .03**
Medication for wheezing§	0.93 [0.75, 1.14]	**1.52 [1.08, 2.14]***	**0.64 [0.48, 0.84]****	***P* < .001**
Miss work or school due to wheeze‡¶	1.03 [0.77, 1.39]	**1.42 [1.04, 1.94]***	0.61 [0.32, 1.20]	***P* = .01**
Asthma outcomes:				
Asthma diagnosis ever†	1.07 [0.92, 1.23]	1.25 [0.99, 1.56]	0.92 [0.76, 1.11]	***P* = .04**
Current asthma†	1.08 [0.87, 1.35]	1.27 [0.95, 1.70]	0.93 [0.71, 1.22]	*P* = .06
Asthma attack in past year§	**1.37 [1.03, 1.83]***	1.42 [0.92, 2.19]	1.31 [0.94, 1.84]	*P* = .64
Emergency room visit for asthma‖	1.44 [0.89, 2.31]	**1.97 [1.05, 3.73]***	0.85 [0.37, 1.94]	*P* = .09

OR are (odds for colonized)/(odds for noncolonized).
Adjusted models use survey weighting and account for gender, ethnicity, obesity, smoking in the home, episode of flu, number of health care visits, poverty income ratio, and household size.
Whole-population and within-age-stratum models use age as a continuous variable.
Models with the *S aureus* * age interaction term use age as a binary variable.
Boldface: $P < .05$: *$P < .05$; **$P < .01$.
†≤1% missing data.
‡1% to 4% missing data.
§5% to 7% missing data.
‖8% to 10% missing data.
¶Excluding 2,120 participants over 65 years old.

Prospective studies are needed to unpack not only the direction of causation, but also the host factors and underlying inflammatory mechanisms by which *S aureus* is associated with wheeze and asthma outcomes. Whether the epidemic of *S aureus* may drive the concurrent epidemic of asthma is unknown, but understanding the role of *S aureus* on respiratory outcomes could identify novel intervention efforts to reduce the burden of disease in younger populations.

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Postmenopausal hormone therapy and asthma-related hospital admission

To the Editor:

There is considerable evidence that female sex hormones are involved in the asthma pathogenesis. Asthma is most prevalent in boys during childhood but after puberty it is more common in

METHODS

Study population

NHANES, a nationally representative survey conducted approximately every 2 years, includes data on demographic characteristics, health status, and nutrition of noninstitutionalized US residents ages 1 to 85 years old.[E1] Details on the conduct of NHANES surveys have previously been described[E1] and are available online at http://www.cdc.gov/nchs/nhanes.htm. This survey was approved by the NHANES Institutional Review Board/NCHS Research Ethics Review Board (IRB/ERB), and all participants gave written informed consent. Analysis was limited to participants age 6 to 85 years, precluding children under 5 years of age, due to the difficulties in diagnosing asthma in this age group.

Asthma outcomes

All participants were queried directly or by proxy (for participants ages 6 to 16 years old) regarding respiratory symptoms. This analysis includes respiratory outcomes related to self-reported symptoms of wheeze in the past 12 months: "{have you/has SP [Sample Person]} had wheezing or whistling in {your/his/her} chest?" (wheeze in the past year); "has {your/SP's} chest sounded wheezy during or after exercise or physical activity?" (wheeze during exercise); "how many times {have you/has SP} gone to the doctor's office or the hospital emergency room for 1 or more of these attacks of wheezing or whistling?" (emergency room visit for wheezing); "how often, on average, has {your/SP's} sleep been disturbed because of wheezing?" (nocturnal wheeze); "how much did {you/SP} limit {your/his/her} usual activities due to wheezing or whistling?" (wheeze limits activities); "{have you/has SP} taken medication, prescribed by a doctor, for wheezing or whistling?" (medication for wheezing); and "how many days of work or school did {you/SP} miss due to wheezing or whistling?" (miss work or school due to wheeze). This analysis includes respiratory outcomes related to asthma: "Has a doctor or other health professional ever told {you/SP} that {you have/SP has} asthma?" (asthma diagnosis ever); "{Do you/Does SP} still have asthma?" (current asthma); "During the past 12 months, {have you/has SP} had an episode of asthma or an asthma attack?" (asthma attack in the past year); and "During the past 12 months, {have you/has SP} had to visit an emergency room or urgent care center because of asthma?" (emergency room visit for asthma). Where questions were asked within a subpopulation limited to those reporting symptoms, participants not reporting any symptoms were assigned a value of 0. When questions were reported as a number or on an ordinal scale, variables were standardized to 1 for "ever" and 0 for "never."

S aureus measurement

Procedures for sampling and microbiological analysis of *S aureus* identified among participants in NHANES 2001-2004 have previously been described.[E2,E3] Briefly, all examined participants between the ages of 6 and 85 submitted culturette swabs (BD Diagnostics, Sparks, Md) from the anterior nares for culture and screening, using tube coagulase tests and Staphaurex agglutination assays (Remel, Lenexa, Kan).

Statistical analysis

Population-standardized prevalence rates were calculated using survey weighting and accounting for the multistage survey design, and unadjusted and adjusted associations between *S aureus* nasal colonization and asthma and wheeze outcomes were examined using logistic regression modeling to estimate ORs using Stata 13 (Stata, College Station, Tex). P values $\leq .05$ were considered statistically significant. *A priori*, covariates included self-reported age; gender; ethnicity; smoking in the home; flu, pneumonia, or ear infection in the past year; number of health care visits in the past year; family income using the family poverty income ratio (PIR); the household size; and body mass index (BMI). These covariates were included in final models because they are known to be associated with *S aureus* colonization and asthma and/or wheeze. Measured BMI was converted based on Centers for Disease Control and Prevention cut-off values for adults to categories of obesity using the following categorization method: underweight (BMI below 18.5 kg/m^2), normal (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), and obese (30.0 kg/m^2 and above). Percentile assignment for age and sex to categories of obesity was performed for children and youths aged 1 to 20 years old, using a previously described software package, using the following categorization method: underweight (<5th percentile), normal (5th percentile to <85th percentile), overweight (85th percentile to <95th percentile), and obese (≥95th percentile).[E4]

Potential age-dependency of relationships between colonization and asthma and wheeze outcomes was evaluated through exploratory data analysis, including stratification of analyses by age. Interactions between *S aureus* colonization and age were tested using categorical interaction terms in final statistical models (age ≤30 years vs >30 years * *S aureus* colonization). Interactions between *S aureus* colonization and continuous age also were calculated (NHANES variable ridageyr * *S aureus* colonization). Interactions between *S aureus* colonization and gender were evaluated.

RESULTS

Table I provides data on prevalence rates for asthma and wheeze outcomes in the NHANES 2001-2004 cohort among the 16,234 participants 6 to 85 years old (93% of 17,518 interviewed, and 100% of those examined) with complete data on *S aureus* nasal colonization and demographics. These data demonstrate that *S aureus*–colonized participants were slightly but significantly more likely to be male, non-Hispanic white, and come from a more affluent, nonsmoking household.

Prevalence rates for *S aureus* nasal colonization differed according to age, with a rate estimate of 30.1% [95% CI: 27.8%, 32.5%] for participants aged 6 to 30 years old and 28.2% [26.8%, 29.7%] for participants aged 31 to 85 years old. Participants 6 to 30 years old were 48% [95% CI: 38%, 59%] more likely to be *S aureus* colonized than those 31 to 85 years old ($P < .001$).

We performed additional analyses and sensitivity tests to evaluate the robustness of our results. In addition to the analyses of interactive effects between *S aureus* colonization and categorical age presented in Table II and Table E1, we found statistically significant interactions between *S aureus* colonization and continuous age for the following outcomes: wheeze in the past year, wheeze during exercise, nocturnal wheeze, medication for wheezing, and missing work or school for wheeze. These interactive effects support the general conclusion that the relationship between *S aureus* colonization and respiratory outcomes varies by age, with a positive association observed in younger participants that is not observed among older participants. Elimination of participants reporting heart disease or respiratory comorbidities such as emphysema and chronic bronchitis did not change the conclusions. Adjustment for program year (2001-02 vs 2003-04) also did not change the conclusions. Interactive effects with gender were explored using descriptive statistics, stratified models, and adjusted models with and without interaction terms. There was no evidence that the relationships between *S aureus* colonization and outcomes varied by gender (data not shown).

DISCUSSION

This is the first study to note differences in associations between *S aureus* colonization and asthma outcomes among children and young adults versus older participants. Several biologically plausible mechanisms could explain the observed relationships. First, because host responses, including specific IgE response and atopic status, may mediate the relationships between *S aureus* colonization and asthma and wheeze,[E5,E6]

children and young adults, who typically are more atopic,[E7] could be more susceptible to the respiratory effects of *S aureus* than older adults. It is also possible that the differences in relationships between *S aureus* colonization and asthma and wheeze outcomes are due to a cohort effect. Specifically, it is possible that individuals who were born more recently, and therefore were children at the time when *S aureus* became more widespread, were more likely to develop specific IgE sensitization, which increased susceptibility to respiratory effects of *S aureus* colonization. As the children and young adults from 2001 to 2004 age, they may continue to be susceptible to respiratory effects from *S aureus* colonization even as older adults. Finally, host mucosal immune responses to microbial pathogens are known to change with age, with immune maturation continuing until age 4 or 6 years, and then immune senescence commencing in later adulthood.[E8] For example, Bisgaard et al, in studying neonatal *S aureus* colonization, found no association with cumulative outcomes to age 5 related to persistent wheeze, asthma, and related outcomes.[E9] It is possible that colonization with *S aureus* causes asthma in school-age children and young adults and/or perpetuates existing asthma in school-age children and young adults but does not cause asthma in young children who were colonized as neonates. Future studies are needed to evaluate whether these possible mechanisms explain how the association between *S aureus* and wheeze and asthma outcomes varies by age.

These findings need to be replicated through prospective, longitudinal cohorts. Because this study was cross-sectional, and our finding of relationships between *S aureus* nasal colonization and asthma and wheeze outcomes could be due to reverse causation, future studies should test the effect of eradication of *S aureus* colonization on asthma. In addition, evaluation of bacterial factors such as presence and expression of SE genes, and host factors such as atopic status, should be included in future work. While the effect sizes we identified in this study were modest, because nearly a third of the US population is nasally colonized with *S aureus* at any given time, the risk conferred by *S aureus* colonization would affect a significant proportion of the US population.

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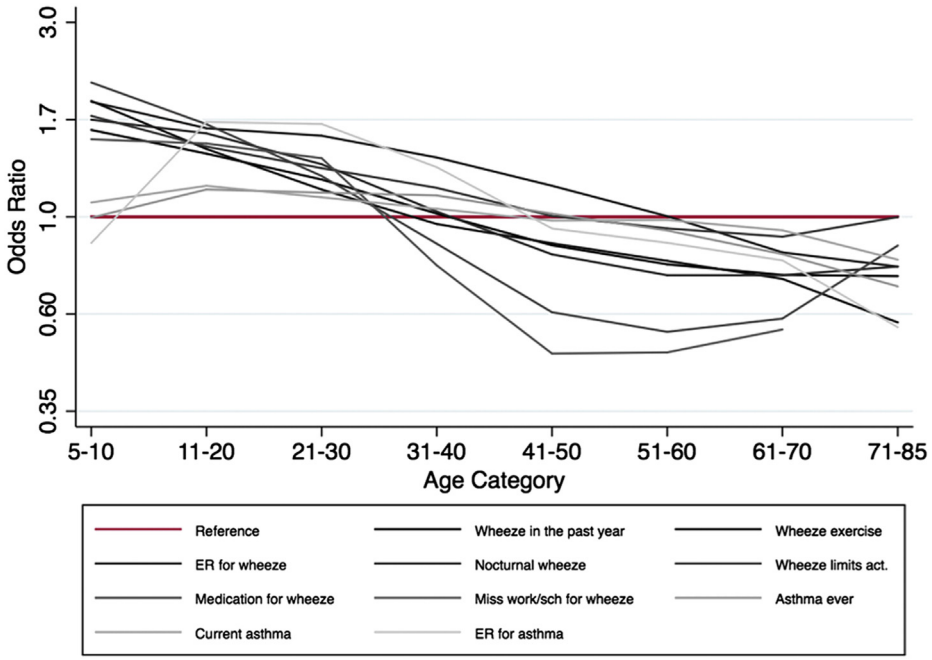

FIG E1. Smoothed associations between *S aureus* colonization and asthma-related outcomes. Lowess curves depicting relationships between relative odds of respiratory outcomes for *S aureus* colonization versus no *S aureus* colonization (*y axis*) and age (*x axis*). ORs, which depict (odds for colonized)/(odds for non-colonized), were first generated by logistic regression modeling of the *S aureus* colonization-respiratory outcome relationships and then the relationships between age and these ORs were depicted using Lowess smoothing.

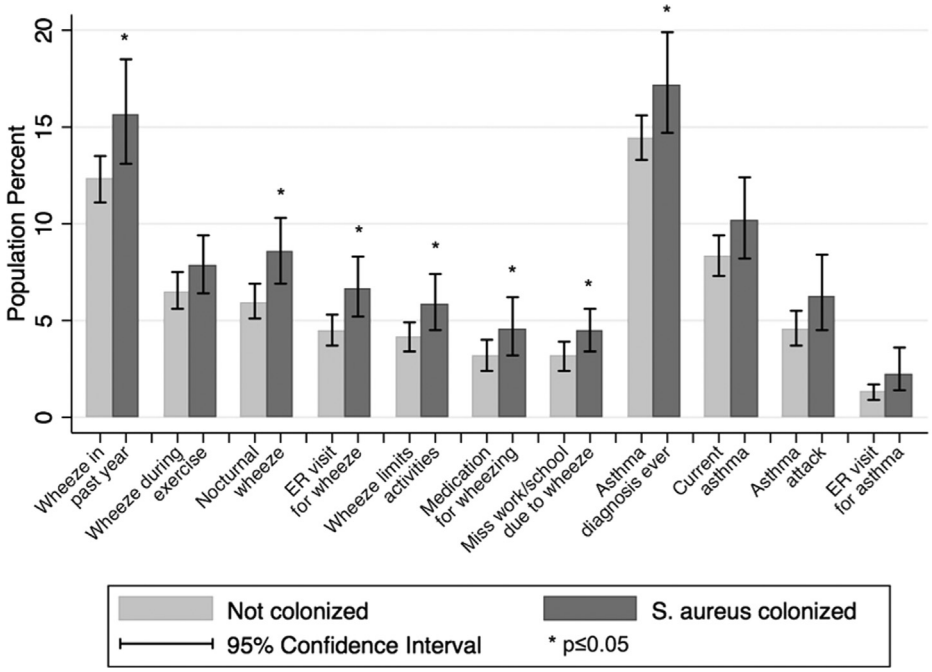

FIG E2. Population prevalence rates for asthma-related outcomes among 6- to 30-year-olds according to *S aureus* colonization status. Prevalence rates and confidence intervals were calculated using survey-weighted tabulation, and *P* values were calculated using Pearson x^2 analysis.

TABLE E1. Unadjusted associations between *S aureus* nasal colonization and asthma and wheeze

Outcomes, OR [95% CI]	Whole population (age 6-85 y)	Age 6-30 y	Age 31-85 y	*S aureus* and age interaction
Sample population, N (%)	n = 16,234	n = 8,703	n = 7,531	
Wheeze outcomes:				
Wheeze in the past year†	1.04 [0.91, 1.20]	**1.32 [1.06, 1.64]***	0.90 [0.73, 1.11]	***P* = .02**
Wheeze during exercise†	1.00 [0.86, 1.18]	1.22 [0.93, 1.61]	0.86 [0.68, 1.08]	*P* = .07
Emergency room visit for wheezing‡	**1.25 [1.01, 1.56]***	**1.53 [1.17, 2.00]****	1.10 [0.73, 1.65]	*P* = .23
Nocturnal wheeze§	1.14 [0.93, 1.41]	**1.47 [1.11, 1.93]****	0.93 [0.66, 1.32]	*P* = .06
Wheeze limits activities‡	1.07 [0.88, 1.31]	**1.44 [1.12, 1.86]****	0.92 [0.70, 1.22]	***P* = .02**
Medication for wheezing§	0.90 [0.76, 1.07]	**1.46 [1.15, 1.85]****	**0.66 [0.53, 0.81]****	***P* < .001**
Miss work or school due to wheeze§¶	1.15 [0.91, 1.45]	**1.45 [1.11, 1.89]****	0.75 [0.43, 1.30]	***P* = .04**
Asthma outcomes:				
Asthma diagnosis ever†	**1.15 [1.01, 1.33]***	**1.23 [1.01, 1.50]***	1.04 [0.87, 1.24]	*P* = .19
Current asthma†	1.14 [0.94, 1.39]	1.24 [0.96, 1.60]	1.02 [0.80, 1.30]	*P* = .20
Asthma attack in past year§	**1.43 [1.10, 1.86]***	1.40 [0.96, 2.04]	**1.38 [1.03, 1.86]***	*P* = .95
Emergency room visit for asthma‖	1.56 [0.93, 2.60]	1.77 [0.94, 3.33]	1.12 [0.53, 2.38]	*P* = .31

OR are (odds for colonized)/(odds for non-colonized).
All models use survey weighting.
Models with interaction terms treat age as a binary variable.
Boldface: $P < .05$: $*P < .05$, $**P < .01$.
†≤1% missing data.
‡1% to 4% missing data.
§5% to 7% missing data.
‖8% to 10% missing data.
¶Excluding 2120 participants over age 65 years.