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Risk factors for SARS-CoV-2 infection and transmission in households with children with asthma and allergy: A prospective surveillance study

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Background: Whether children and people with asthma and allergic diseases are at increased risk for severe acute respiratory syndrome virus 2 (SARS-CoV-2) infection is unknown.

Objective: Our aims were to determine the incidence of SARS-CoV-2 infection in households with children and to also determine whether self-reported asthma and/or other allergic

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diseases are associated with infection and household transmission.

Methods: For 6 months, biweekly nasal swabs and weekly surveys were conducted within 1394 households (N = 4142 participants) to identify incident SARS-CoV-2 infections from May 2020 to February 2021, which was the pandemic period largely before a vaccine and before the emergence of SARS-CoV-2 variants. Participant and household infection and household transmission probabilities were calculated by using time-to-event analyses, and factors associated with infection and transmission risk were determined by using regression analyses.

Results: In all, 147 households (261 participants) tested positive for SARS-CoV-2. The household SARS-CoV-2 infection probability was 25.8%; the participant infection probability was similar for children (14.0% [95% CI = 8.0%-19.6%]), teenagers (12.1% [95% CI = 8.2%-15.9%]), and adults (14.0% [95% CI = 9.5%-18.4%]). Infections were symptomatic in 24.5% of children, 41.2% of teenagers, and 62.5% of adults. Self-reported doctor-diagnosed asthma was not a risk factor for infection (adjusted hazard ratio [aHR] = 1.04 [95% CI = 0.73-1.46]), nor was upper respiratory allergy or eczema. Self-reported doctor-diagnosed food allergy was associated with lower infection risk (aHR = 0.50 [95% CI = 0.32-0.81]); higher body mass index was associated with increased infection risk (aHR per 10-point increase = 1.09 [95% CI = 1.03-1.15]). The household secondary attack rate was 57.7%. Asthma was not associated with household transmission, but transmission was lower in households with food allergy (adjusted odds ratio = 0.43 [95% CI = 0.19-0.96]; *P* = .04).

Conclusion: Asthma does not increase the risk of SARS-CoV-2 infection. Food allergy is associated with lower infection risk, whereas body mass index is associated with increased infection risk. Understanding how these factors modify infection risk may offer new avenues for preventing infection. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *SARS-CoV-2, COVID-19, food allergy, body mass index, asthma, infection, transmission*

Early in the severe acute respiratory syndrome virus 2 (SARS-CoV-2) pandemic, studies focused on understanding risk factors for the severe forms of coronavirus disease 2019 (COVID-19).[1] These studies identified older age, minority race/ethnicity, obesity, and several comorbidities as significant risk factors for severe COVID-19.[2] Unexpectedly, 2 potential risk factors for severe COVID-19 that did not emerge from these analyses were being a child and having asthma.[3] Children and people with asthma are established risk groups that typically experience significant morbidity from many respiratory viruses and are target groups for vaccine-preventable respiratory viral diseases.[4,5] Early mechanistic studies have proposed that atopy may protect against SARS-CoV-2 infection. Individuals with atopic asthma express lower airway levels of angiotensin-converting enzyme 2 (*ACE2*), the SARS-CoV-2 receptor, as do those with allergic or type 2 airway inflammation,[6-9] suggesting a potential mechanism for this unanticipated finding.

For individuals with asthma, however, the risk of SARS-CoV-2 infection, whether asymptomatic or mildly symptomatic, is unknown. Furthermore, few data are available as to how people with other allergic conditions may be affected by SARS-CoV-2.

Abbreviations used

ACE2:	Angiotensin-converting enzyme 2
aHR:	Adjusted hazard ratio
aOR:	Adjusted odds ratio
BMI:	Body mass index
CDC:	US Centers for Disease Control and Prevention
COVID-19:	Coronavirus disease 2019
Cq:	Quantification cycle
HEROS:	Human Epidemiology and Response to SARS-CoV-2
OR:	Odds ratio
SAR:	Secondary attack rate
SARS-CoV-2:	Severe acute respiratory syndrome virus 2

To address these questions, a prospective observational study is of essence. Importantly, the study population should not be selected by using index participants who have already been infected with COVID-19, as this would constitute a major bias owing to changes in the behavior of people surrounding such individuals. Also, because a large proportion of children may have asymptomatic infection, a study based on individuals who have already developed COVID-19 could result in unintended exclusion of this important subgroup.[10] Unfortunately, many epidemiologic studies assessing SARS-CoV-2 infection have been conducted by using such biased population samples.[11-16]

To prospectively provide information regarding the aforementioned questions, the National Institute of Allergy and Infectious Diseases invited investigators with extant pediatric asthma and allergic disease cohorts to participate in the Human Epidemiology and Response to SARS-CoV-2 (HEROS) study, a longitudinal surveillance study of households enriched for children and adults with asthma and other allergic diseases. The HEROS study involved 18 cohorts from 12 US cities (see Fig E1 in the Online Repository at www.jacionline.org).

METHODS

Study design and population

We recruited households of children (aged <13 years) and teenagers (aged 13-21 years) who were participating in National Institutes of Health–funded cohorts that focused on asthma and/or allergic disease. In addition to the cohort-participating child, enrollment required a household caregiver; an additional household child and adult could also be enrolled. Self- or caregiver-collected biweekly nasal swabs were conducted between May 15, 2020, and February 1, 2021. On alternating weeks, if anyone developed symptoms, a prespecified algorithm prompted an additional illness event sampling of all household members. Full details of the study protocol are described elsewhere (National Clinical Trials identifier NCT04375761). The institutional review boards of all participating institutions and the Health and Human Services Office of Human Research Protections deemed this a public health surveillance study.

SARS-CoV-2 testing

Quantitative PCR testing for SARS-CoV-2 was conducted on nasal swabs by using the US Centers for Disease Control and Prevention (CDC) SARS-CoV-2 N1/N2 and RNaseP housekeeping gene assays (see Table E1 in the Online Repository at www.jacionline.org). N1 and N2 assay quantification cycle (Cq) threshold values were reported as the average of the duplicate assays analyzed (excluding Cq values ≥40). The overall Cq value for a sample was reported as the average of the N1 and N2 Cq averages. Viral Cq values were normalized to expression levels of RNase P for each assay N1 and N2 and transformed from $\log_2$ scale into viral load values

(viral load(N_x) = $2^{Cq(RNaseP) - Cq(Nx)}$, where N_x is either N1 or N2) and then averaged across N1 and N2 assays to generate a relative viral load value for each sample.

Symptoms

Weekly, households were asked about any ill household members and ill individuals were asked to complete a 20-symptom survey. Quantitative PCR–confirmed infection events were classified as symptomatic or not symptomatic based on 1 or more symptoms (see Table E2 in the Online Repository at www.jacionline.org) experienced during or immediately before and/or after infection (±14 days).

Statistical analysis

Participant- and household-level infection probabilities were estimated by using Kaplan-Meier analyses. Associations between infection and self-reported asthma and/or allergic diseases, age, and other exploratory risk factors were evaluated with extended Cox proportional hazards models. Baseline hazards were stratified by study site. The participant-level models controlled for age, sex, race/ethnicity, and exposure to a family member testing positive for SARS-CoV-2 within the past 14 days, and they used robust "sandwich" SEs to account for clustering of participants in households; the household-level models controlled for the average age of the enrolled caregivers and children, household race/ethnicity, and the number of household members enrolled. Individual risk factors were first considered in separate models before fitting a multivariable model including all factors with a P value less than .10.

Generalized estimating equation logistic regression was used to model the odds of household transmission, symptomatic infection, and participant-level nontransmission while controlling for participant and household demographics. For full statistical analysis details, see the Supplementary Methods in the Online Repository at www.jacionline.org).

RESULTS

Cohort description

The study population analyzed included 4,142 participants who were from the 1,394 households evaluated between May 15, 2020, to February 1, 2021, and contributed at least 1 nasal swab from (Table I and see Fig E2 in the Online Repository at www.jacionline.org). The mean number of swabs per participant was 8.9 (SD = 4.1), with 65.6% of the expected 55,236 surveillance swabs successfully collected and screened for SARS-CoV-2 (see Fig E3 in the Online Repository at www.jacionline.org). The households had a mean of 4.4 total members and 3.0 enrolled members; 52.2% of the enrollees were children or teens, and their average age was 10.2 years (Table II). A large percentage of enrolled households (42.5%) were of races/ethnicities other than White, non-Hispanic. Asthma was self-reported by 22.2% of caregivers and 32.9% of children and teenagers.

One or more atopic conditions other than asthma were self-reported by 52.1% and 56.9% of caregivers and children and teenagers, respectively, including food allergy (10.2% of caregivers and 20.7% of children and teenagers), eczema (10.2% of caregivers and 24.0% of children and teenagers), and upper respiratory allergy (eg, "hay fever," "allergic rhinitis" [47% of caregivers and 44.5% of children and teenagers]).

Participant-level SARS-CoV-2 infection incidence

A total of 382 samples tested positive for SARS-CoV-2 (1.04%), corresponding to 261 participants from 147 households (10.5% of households). The positivity was higher for the illness-triggered surveillance swabs (6.3%) than for the biweekly surveillance swabs (0.97% [odds ratio (OR) = 6.81] [95% CI = 4.64-10.00]) (see Fig E4 in the Online Repository at www.jacionline.org), although 92.1% of infections were detected through biweekly surveillance. The HEROS study 7-day rolling SARS-CoV-2 incidence among adults and teens tracked with the US nationwide data reported by the CDC for the same groups (Fig 1, *A*). Among children, we observed a higher wave of infection in late 2020 than was observed in the CDC data, likely owing to our prospective design, which screened subjects for infection regardless of symptoms. This allowed us to identify asymptomatic infections, which were much more common in children (discussed later). Overall, 6.3% of participants tested positive for SARS-CoV-2 while under study observation, with similar proportions among children (6.1%), teens (6.7%), and adults (6.2%). When a Kaplan-Meier time-to-event analysis was used to account for the length of participants' follow-up and rolling study enrollment, the individual probability of infection during the study period was 14.0% (95% CI = 10.3%-17.5%) and was similar between children (14.0% [95% CI = 8.0%-19.6%]), teens (12.1% [95% CI = 8.2%-15.9%]), and adults (14.0% [95% CI = 9.5%-18.4%]) (Fig 1, *B*). However, the proportion of symptomatic infections varied significantly by age group: 24.5% of infections in children were symptomatic versus 41.2% in teenagers and 62.5% in adults.

Assessing self-reported asthma and atopic conditions as risk factors for SARS-CoV-2 infection

Current asthma was not associated with infection risk in our primary analysis (adjusted hazard ratio [aHR] = 1.04 [95% CI = 0.73-1.46] [Fig 2, *A*]) or in secondary analyses considering childhood asthma, adult asthma, and obese asthma separately (see Table E3 in the Online Repository at www.jacionline.org). Neither eczema (aHR = 1.06 [95% CI = 0.75-1.50]) nor upper respiratory allergy (aHR = 0.96 [95% CI =0.73-1.26]) was associated with infection risk (see Table E3). However, participants reporting food allergy (31.1% adults, 28.7% teenagers, and 40.2% children) were at 50% lower risk of SARS-CoV-2 infection (aHR = 0.50 [95% CI = 0.32-0.81]) (Fig 2, *B* and see Table E3). Neither asthma ($\Delta\log_{10}$viral load = –0.42 [95% CI = –1.10 to 0.26]; P = .22) nor food allergy ($\Delta\log_{10}$viral load = 0.88 [95% CI = –0.06 to 1.81]; P = .07) nor eczema ($\Delta\log_{10}$viral load = 0.46 [95% CI = –0.27 to 1.20]; P = .22) nor upper respiratory allergy ($\Delta\log_{10}$viral load = 0.36 [95% CI = –0.21-0.93]; P = .22) were associated with peak viral load of infection events. Given the potential for individuals to overreport food allergy, we next sought to evaluate the accuracy of self-reported food allergy in the HEROS study through measurement of allergen-specific IgE level in a subset of HEROS study participants. Specifically, we measured levels of IgE to 112 allergens and allergen components (see the Supplementary Methods), including 30 food allergens, in 1053 of the HEROS study participants to examine the concordance of self-reported and IgE-determined food allergy. Among these 1053 subjects, 136 (12.9%) reported food allergy versus 98 subjects for whom we detected IgE to food allergens (9.3%). Examining the overlap between these 2 food allergy variables, we found that 39.0% of those with self-reported food allergy also tested positive for food-specific IgE versus only 4.9% with food allergen IgE among those who did not report food allergy. This concordance between self-report and food allergen IgE measurement strongly supports the accuracy of self-reported food allergy determination in the HEROS study. To evaluate whether the overall atopic character of those with self-reported food allergy

TABLE I. Subject characteristics

Variable	Caregivers	Index children and siblings
Subjects (no.)	1978	2164
SARS-CoV-2–positive, no. (%)	124 (6.3%)	137 (6.3%)
Age (y), mean (SD)	41.14 (7.92)	10.18 (4.95)
Age category, no. (%)		
Child, <5 y	0 (0.0%)	282 (13.0%)
Child, 5-12 y	1 (0.1%)	1087 (50.2%)
Teen	6 (0.3%)	795 (36.7%)
Adult, 21-40 y	906 (45.8%)	0 (0.0%)
Adult, ≥40 years	1065 (53.8%)	0 (0.0%)
Male sex, no. (%)	604 (30.6%)	1123 (52.1%)
Race/ethnicity other than non-Hispanic White, no. (%)	654 (33.7%)	884 (41.8%)
Current smoking, no. (%)	185 (9.4%)	3 (0.1%)
Asthma, no. (%)	439 (22.2%)	711 (32.9%)
Upper respiratory allergies, no. (%)	929 (47.0%)	963 (44.5%)
Food allergies, no. (%)	202 (10.2%)	447 (20.7%)
Eczema, no. (%)	202 (10.2%)	520 (24.0%)
Atopic conditions (excluding asthma), no. (%)	1030 (52.1%)	1231 (56.9%)
BMI category, no. (%)		
Normal	759 (38.8%)	1251 (64.2%)
Overweight	488 (25.0%)	307 (15.8%)
Obese	708 (36.2%)	391 (20.1%)
BMI percentile, mean (SD)	81.59 (21.04)	63.47 (31.74)
High cholesterol, no. (%)	258 (13.0%)	19 (0.9%)
Hypertension, no. (%)	312 (15.8%)	17 (0.8%)
Nasal swabs analyzed (no.), median (IQR)	10 (6-12)	10 (6-12)
Duration of nasal swab follow-up (wk)	19.94 (8.36)	19.58 (8.60)
Surveillance swabs expected, no. (%)		
10	319 (16.1%)	369 (17.1%)
14	1659 (83.9%)	1795 (82.9%)
Percentage of surveillance swabs received, mean (SD)	64.6 (27.8)	63.5 (28.3)
Month of first nasal swab, no. (%)		
May	314 (15.9%)	349 (16.1%)
June	1026 (51.9%)	1100 (50.8%)
July	526 (26.6%)	582 (26.9%)
August	91 (4.6%)	108 (5.0%)
September	12 (0.6%)	14 (0.6%)
October	6 (0.3%)	10 (0.5%)
November	2 (0.1%)	1 (0.0%)

IQR, Interquartile range.

TABLE II. Household characteristics

Variable	Value
Households (no.)	1394
Household members enrolled (no.), median (IQR)	3 (2-4)
Total household members, (no.), median (IQR)	4 (4-5)
SARS-CoV-2–positive, no. (%)	147 (10.5%)
Age of enrolled caregivers (y), mean (SD)	41.09 (7.58)
Age of enrolled children (y), mean (SD)	10.33 (4.69)
Race/ethnicity other than non-Hispanic White, no. (%)	582 (42.5%)
Smoking in the household, no. (%)	174 (12.5%)
Bedrooms in the household (no.), median (IQR)	3 (3-4)
Households with pets, no. (%)	814 (58.4%)

IQR, Interquartile range.

was stronger, we compared the mean number of positive test results to any allergen or allergen component (of the 112 food and aeroallergen tests conducted) between those who did and did not report food allergy. We found that the mean number of positive tests was significantly higher among those who self-reported food allergy (a mean of 9.47 positive test results) versus those who did not report food allergy (a mean of 2.91 positive tests [$P < 2 \times 10^{-16}$]), suggesting a greater level of general atopy among those with self-reported food allergy. Moreover, on average, those with asthma but not food allergy exhibited only 4.61 positive antigen test results, substantiating the highly atopic nature of those with self-reported food allergy, even relative to those with asthma ($P = 1.8 \times 10^{-7}$).

Other risk factors for SARS-CoV-2 infection

Other demographic factors and health characteristics associated with time to infection are listed in Table E3. Exposure to a symptomatic household member was associated with an 87.39-fold increase in infection risk (aHR) (95% CI = 58.02-131.63), whereas exposure to an asymptomatically infected household member was associated with a 27.80-fold increase in risk (95% CI = 17.16-45.03 [Fig 2, *A*]). Age and sex were not significantly associated with infection risk. Minority race/ethnicity was associated with a 59% increased risk of infection (aHR = 1.59 [95% CI = 1.15-2.21]) (Fig 2, *A*).

Participants who were overweight or obese (63.0% adults, 14.7% teenagers, and 22.3% children) had a 41% increased risk of

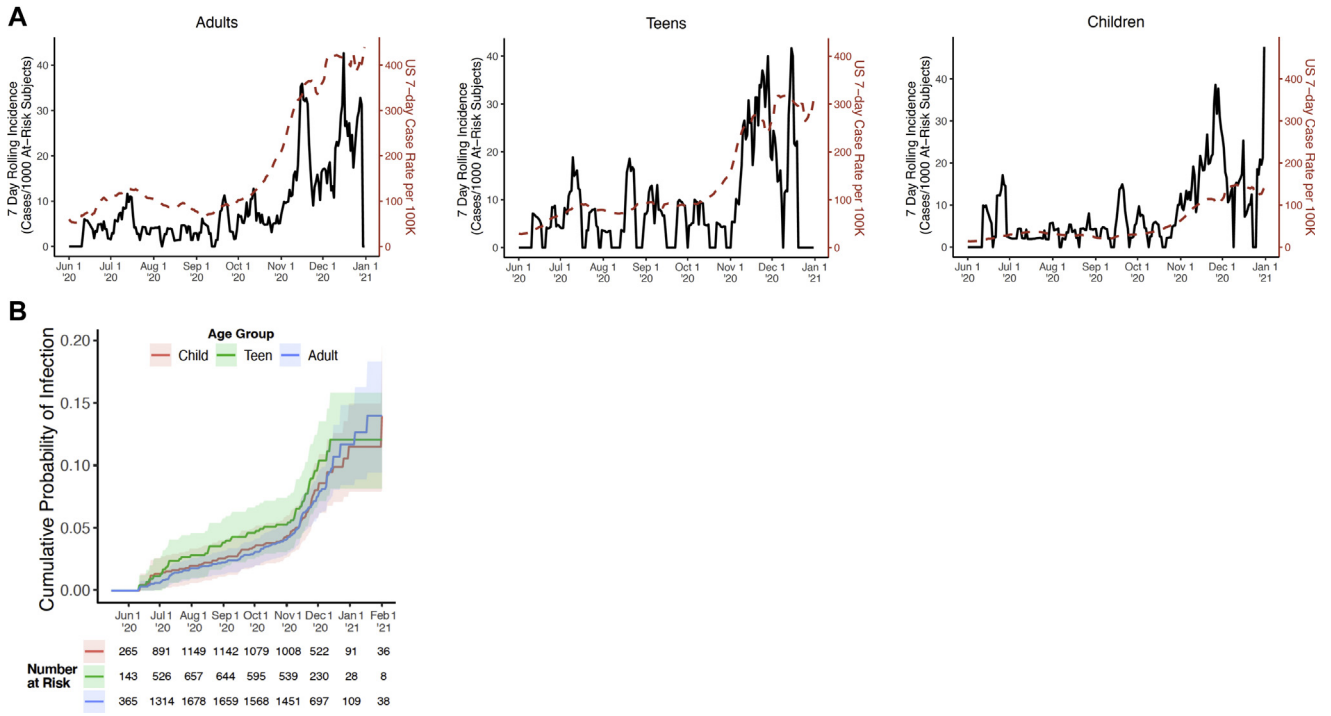

FIG 1. Subject-level SARS-CoV-2 incidence and probability of infection. **A,** Rolling (7-day) incidence of SARS-CoV-2 infection among adults, teens, and children, compared with US nationwide data collected by the CDC for the same time period. **B,** Kaplan-Meier curve for probability of subject-level SARS-CoV-2 infection in children, teenagers, and adults by calendar time.

infection (aHR = 1.41 [95% CI = 1.06-1.87]) (Fig 2, *C*). Moreover, there was a strong linear relationship between body mass index (BMI) and infection risk, with every 10-point increase in BMI percentile increasing the risk of SARS-CoV-2 infection by 9% (aHR = 1.09 [95% CI = 1.03-1.15]) (Fig 2, *D*). BMI percentile was not associated with peak viral load of infection events ($\Delta\log_{10}$viral load per 10-point increase = 0.07 [95% CI = –70.05 to 0.20]; $P = .25$).

Risk factors for household infection

In total, 147 households (10.5%) experienced 1 or more SARS-CoV-2 infection(s). When the duration of follow-up was taken into account, the probability of household infection was 25.8% (95% CI = 11.2%-38.1%) during the study period (see Fig E5 in the Online Repository at www.jacionline.org). Households with an asthmatic participant were not at increased risk for infection, nor were households that included participants with any other allergic disease (Table III). We observed an increase in SARS-CoV-2 infection risk among households with a member attending in-person school (aHR = 1.67 [95% CI = 1.09-2.57]) and among racial/ethnic minority households (aHR = 1.52 [95% CI = 1.02-2.27]). Household age composition was associated with infection risk. For every year increase in the average age of children and teenagers within a household, there was a 7% increase in household infection risk (aHR =1.07 [95% CI = 1.01-1.13]). In contrast, every 5-year increase in average age of household caregivers was associated with a 14% decrease in household infection risk (aHR = 0.86 [95% CI = 0.74-1.00]). We found no association between household infection risk and the following types of exposure of household members in the prior 30 days: attending day care, attending a health care appointment, attending a social gathering, visiting a grocery store, traveling, or getting takeout food (Table III); nor was there an association with either the number of members in the household or smoking in the household.

Within-household transmission of SARS-CoV-2

Of the 97 SARS-CoV-2–positive households with sufficient follow-up for this analysis (see the Supplementary Methods), 41 had a single member with a documented infection (no household transmission), whereas 56 had multiple members with documented infections (likely household transmission [see Fig E6 in the Online Repository at www.jacionline.org]), for a household secondary attack rate (SAR) of 57.7%. An index case was identified in only 15 households, with 26.7% being children, 20.0% teenagers, and 53.3% adults (see Fig E6). Among the remaining transmitting households, members tested positive for SARS-CoV-2 concurrently (see Fig E6). With use of Kaplan-Meier analysis, the probability of transmission to an individual household member was 41.2% within the first 50 days (95% CI = 32.3%-49.0% [see Fig E7 in the Online Repository at www.jacionline.org]); 88.3% of household transmissions occurred within 14 days of the first household member becoming infected.

Risk factors for within-household transmission of SARS-CoV-2

To identify household characteristics associated with transmission, we compared transmitting households with nontransmitting households (see Table E4 in the Online Repository at www.jacionline.org). Having an asthmatic household member was not

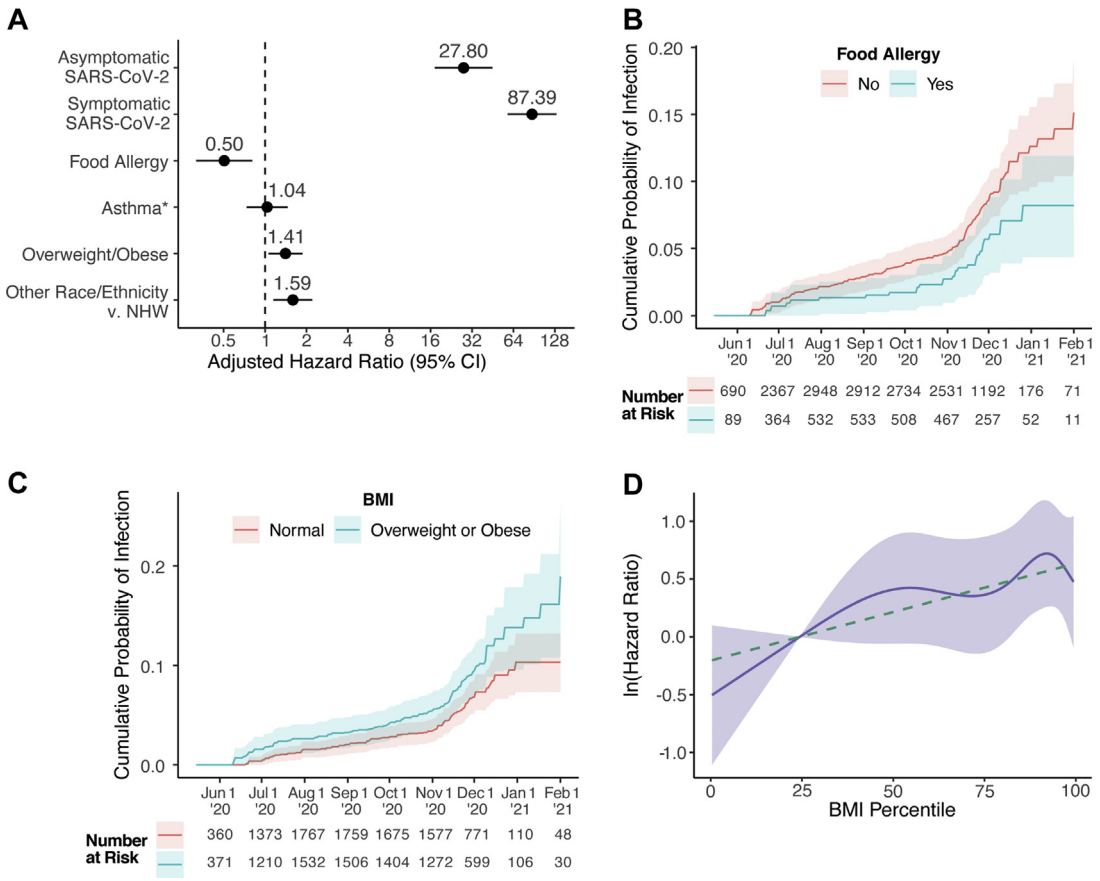

FIG 2. Food allergy and obesity are associated with decreased and increased SARS-CoV-2 infection risk, respectively. **A,** aHRs for SARS-CoV-2 infection of important demographic and health factors from the final multivariable model, including age, sex, race/ethnicity, exposure to an infected household member, overweight/obesity, food allergy, and number of bedrooms per person. *Hazard ratio (HR) from the model adjusted for age, sex, race/ethnicity, and exposure to an infected household member. **B,** Kaplan-Meier curve for the probability of SARS-CoV-2 infection across study time by food allergy status. **C,** Kaplan-Meier curve for probability of SARS-CoV-2 infection across study time by obesity. **D,** Linear relationship between HR for SARS-CoV-2 infection and BMI percentile, with adjustment for age, sex, race/ethnicity, exposure to an infected household member, food allergy, and number of bedrooms per person.

associated with transmission (adjusted OR [aOR] = 0.64 [95% CI = 0.33-1.23]). Upper respiratory allergy and eczema were also not significantly associated with increased odds of household transmission (aOR = 0.71 [95% CI = 0.27-1.84] and aOR = 1.85 [95% CI = 0.65-5.21], respectively). However, transmissions were significantly less likely in households with food allergy (aOR = 0.43 [95% CI = 0.19-0.96]; P = .04). There were no associations between transmission and number of household members, bedrooms per person, household race/ethnicity, or smoking in the household. However, the average age of children and teenagers in the household was associated with household transmission; for every year increase in the average age of the children and teenagers, there was a 21% decrease in the odds of being a transmitting household (aOR = 0.79 [95% CI = 0.69-0.89]).

Characteristics of nontransmitting household members

Because the index case in many transmitting households was unclear, we analyzed participant-level characteristics associated with nontransmission by comparing nontransmitters (n = 41) with possible transmitters (n = 140) (see Table E5 in the Online Repository at www.jacionline.org). Neither asthma nor food allergy nor upper respiratory allergy nor eczema were associated with nontransmission (see Table E5). Age group was associated with nontransmission: teenagers had 6.15-fold increased odds (aOR [95% CI = 2.49-15.21]) of being a nontransmitter relative to children and 3.55-fold increased odds (aOR [95% CI = 1.56-8.08]) of being a nontransmitter relative to adults. Being overweight or obese was associated with 55% lower odds of nontransmission (aOR = 0.45 [95% CI = 0.25-0.82]). Viral load was strongly associated with transmission (see Fig E8 in the Online Repository at www.jacionline.org), with a 14% increase in the odds of being a nontransmitter for every 10-fold decrease in peak viral load (aOR = 0.86 [95% CI = 0.74-0.99]). Presence of symptoms, race/ethnicity, and sex were not significantly associated with nontransmission.

The relationship between symptomatic infections and viral load by age

We found that 44.6% of infections were symptomatic, with 73.1% of symptomatic infections involving at least 3 symptoms (see Table E2). There was no association between odds of

TABLE III. Associations between household characteristics and hazard of SARS-CoV-2 infection, controlling for average age of the enrolled caregivers, average age of the enrolled children, number of household members enrolled, and race/ethnicity

Family characteristic comparison		Adjusting for No. of enrolled + age + race			Multivariable		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Average caregiver age	5-y increase	0.87	0.75-1.01	.0731	0.86	0.74-1.00	.0503
Average child/teenager age	1-y increase	1.06	1.01-1.12	.0296	1.07	1.01-1.13	.0228
Race/ethnicity	Other race/ethnicity vs NHW	1.37	0.92-2.04	.1167	1.52	1.02-2.27	.0407
Smoking in the household	Yes vs no	0.82	0.46-1.47	.5090			
Household members	1-person increase	0.99	0.86-1.13	.8315			
Subjects enrolled	1-person increase	1.23	1.01-1.50	.0380	1.21	0.99-1.47	.0633
Asthma in household	Yes vs no	0.82	0.57-1.19	.2978			
Food allergy in household	Yes vs no	0.89	0.61-1.32	.5746			
Upper respiratory allergy in household	Yes vs no	1.01	0.69-1.49	.9472			
Eczema in household	Yes vs no	0.85	0.59-1.22	.3679			
Exposures in the past 30 days							
In-person school	Yes vs no	1.77	1.16-2.69	.0081	1.67	1.09-2.57	.0192
Work	Yes vs no	1.42	0.95-2.13	.0859	1.29	0.86-1.95	.2209
Day care	Yes vs no	0.97	0.56-1.69	.9239			
Travel outside home city	Yes vs no	1.04	0.72-1.48	.8496			
Health care appointments	Yes vs no	0.91	0.65-1.28	.5856			
Getting takeout food	Yes vs no	1.02	0.67-1.55	.9269			
Going to social gatherings	Yes vs no	1.35	0.81-2.24	.2456			
Going to the grocery store	Yes vs no	0.84	0.48-1.47	.5501			

HR, Hazard ratio; *NHW*, non-Hispanic white.

symptomatic infection and asthma, food allergies, eczema, upper respiratory allergy, or overweight/obesity (see Table E6 in the Online Repository at www.jacionline.org). Symptomatic infection was associated with age (Fig 3, *A*). Teenagers and adults had 2.78-fold (aOR [95% CI = 1.05-7.36]) and 6.02-fold (aOR [95% CI = 2.83-12.78]) higher odds of symptoms, respectively, than children did (see Table E6).

Children had significantly lower mean viral loads than adults did (–0.82 $\log_{10}$(viral load) [95% CI = –1.61 to –0.03]), but their viral loads did not significantly differ from those of teenagers (–0.47 $\log_{10}$(viral load) [95% CI = –1.42 to 0.48]) (Fig 3, *B* and see Table E7 in the Online Repository at www.jacionline.org). Viral loads were highly similar between symptomatic and asymptomatic infections in individuals up to about age 10 years, whereas viral loads in subjects older than 10 years were generally higher for those with symptomatic versus asymptomatic illnesses (see Fig E9, *A* and *B* and Table E8 in the Online Repository at www.jacionline.org). The odds of a symptomatic versus asymptomatic infection increased with higher peak viral load among teenagers and adults, whereas this relationship was not observed among children (Fig 3, *C* and see Table E9 in the Online Repository at www.jacionline.org).

DISCUSSION

We conducted a unique prospective, longitudinal SARS-CoV-2 surveillance study of more than 1300 households and more than 4000 participants—a study population that was enriched for asthma and other allergic conditions. The public health measures in place at the time of our study (May 2020-Feb 2021), which severely limited unnecessary person-to-person contact, necessitated that we conduct the HEROS study activities remotely, without direct participant contact. Specifically, the study was conducted exclusively at the participants' homes and involved detailed training and frequent electronic and/or phone communications to complete repetitive online questionnaires and in-house biosample collections. Our study largely preceded the widespread deployment of SARS-CoV-2 vaccines and the emergence of SARS-CoV-2 variants of concern (from Alpha to Omicron), providing key epidemiologic data on this early stage of the pandemic that will inform management of this and future respiratory virus pandemics.

We found that children, teenagers, and adults had similar probabilities of SARS-CoV-2 infection during the prevaccine period of the pandemic. However, children (aged <13 years) were much more likely to have asymptomatic infection than were teenagers and adults. To examine the association between asthma/atopic diseases and infection risk, we relied on participant self-report of these conditions. However, these disease determinations were ascertained by using validated questionnaires that were previously shown to accurately capture asthma and atopic disease.[17-20] Participants with self-reported asthma, eczema, and upper respiratory allergy were not at increased risk for SARS-CoV-2 infection. Individuals with asthma and other allergic conditions were also not more likely to have symptomatic infection or higher SARS-CoV-2 viral loads. Further, infected households with asthmatic individuals were not at increased risk of transmission. As nearly all SARS-CoV-2 infections were not severe and many were asymptomatic, we could not assess asthma as a risk factor for severe disease; neither did we assess the severity and management of asthma and respiratory allergic disease in this article.

We unexpectedly found that self-report of food allergy was associated with lower risk of SARS-CoV-2 infection and household transmission. The nature of this association is unclear; the use of self-report could have resulted in misclassification of participants for this trait. However, misclassification of food allergy status would be more likely to lead to a false-negative result owing to the inclusion of subjects without food allergy in the food allergy group, thus driving the results toward the null.

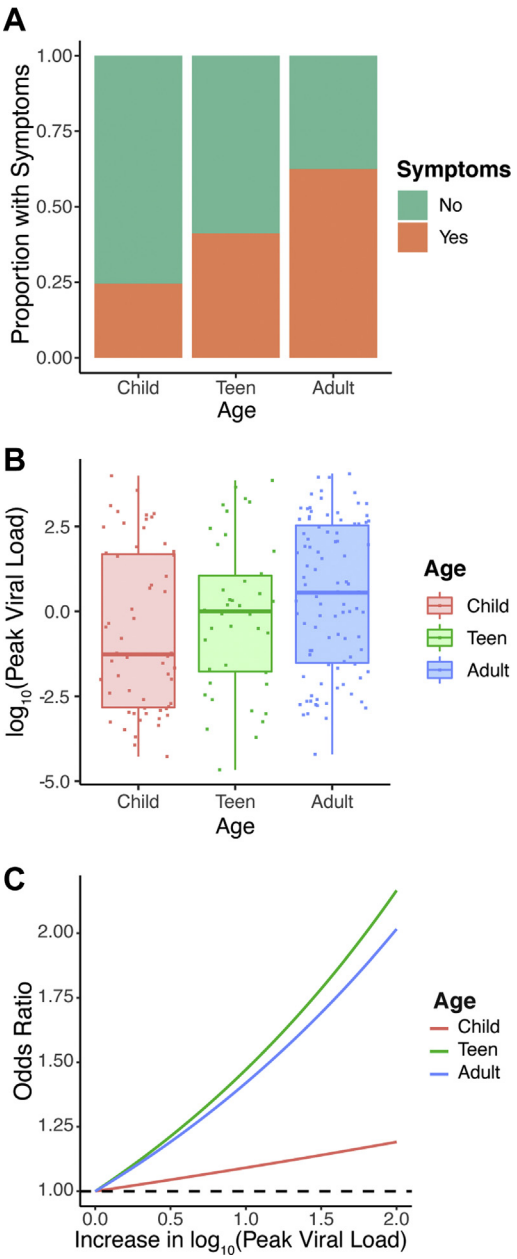

FIG 3. The relationship between symptomatic infections and viral load is modified by age. **A,** Frequency of symptomatic infections by age group. **B,** Boxplots illustrating peak viral load by age group. **C,** Relationship between odds of symptomatic infection and peak viral load, by age group.

Moreover, we found high concordance between self-reported food allergy and measurements of food allergen–specific IgE level conducted in a subset of HERO subjects. It is possible that pathobiology common among subjects with food allergy underlies this association. In children with type 2 cytokine–high asthma, lower *ACE2* gene expression, the primary receptor for SARS-CoV-2, has been reported in airway epithelium.[8] Moreover, *in vitro* experiments have found that IL-13 stimulation of the airway epithelium both lowers ACE2 levels and inhibits SARS-CoV-2 infection[8,21]; similarly, experimentally induced airway allergic reactions also lead to reduced *ACE2* gene expression.[7] Whether this is also the case in individuals with food allergy is not known, but it is tempting to speculate that type 2 inflammation, a characteristic of food allergy,[22] may reduce airway ACE2 levels and thus the risk of infection. Supporting this possibility, we found significantly greater levels of general atopy among those with self-reported food allergy relative both to those without food allergy and those with asthma. Alternatively, the lower infection risk observed among participants with food allergy could also be explained in part by differences in risk behaviors, such as less eating out among individuals with food allergy. However, we assessed this biweekly and observed only slightly lower levels of exposures (see Fig E10 in the Online Repository at www.jacionline.org) among households that include individuals with food allergy.

Being obese or overweight, which is a factor previously associated with severe COVID-19 disease, was associated with increased infection risk. Our results demonstrate that BMI exerts an effect on infection risk linearly throughout the population BMI range. Individuals with a lower BMI were also more likely to be nontransmitters within households. Potential biologic mechanisms underlying this effect include increased *ACE2* expression in obese subjects,[23] or neutrophilic airway inflammation, which has also been described in obese individuals and has been associated with increased viral replication for several respiratory viruses.[24,25] Previous studies have also found that the risk for asthma exacerbations, which are often triggered by viral infections, is increased among obese subjects with asthma, but we did not find an increased risk of SARS-CoV-2 infection among the subset of individuals with obesity and asthma.[26,27]

We found that both the average age of children/teenagers and that of caregivers were risk factors for a household becoming infected, although with differing directions of effect. We hypothesize that the association between older age of children/teenagers and increased infection risk may result from a greater number of social interactions and group activities experienced by older children, putting these households at higher infection risk. Households with younger caregivers were also at higher infection risk, and we hypothesize that this too may be due to greater social interactions, as well as to obligations outside the household. The only exposure significantly associated with infection of households was having a member attending in-person school. The high risk of household infection associated with in-person school attendance may be explained by unrecognized asymptomatic infections among children/teenagers attending school and the resultant transmission to other children and households.

Once a SARS-CoV-2 infection was introduced into a household, we found a high household SAR, with more than 57% of infected households experiencing 1 or more transmissions and a 41% probability of infection for at-risk household members. This probability is substantially higher than that in a recent SARS-CoV-2 household transmission meta-analysis, which estimated the SARS-CoV-2 SAR to be 18.9%.[1] This difference highlights an important feature of our study, which included routine surveillance with nasal sampling of household participants regardless of symptoms, in contrast to many studies involved in the meta-analysis, which initiated transmission evaluation and/or identified subsequent infections based on symptoms. The majority of samples screened in our study were collected from May 2020 to November 2020, before the widespread emergence of SARS-CoV-2 variants of concern, and in particular, the more infectious Delta and Omicron variants. Moreover, infections were likely missed owing to our biweekly surveillance and missed

collections; thus, our SAR is likely an underestimation and reinforces the highly contagious nature of this evolving virus.

Age of children/teenagers in the household was the most significant risk factor for within-household viral transmission, with a 21% decrease in odds of transmission for every year increase in average age. We postulate that this may be driven by fewer and/or less physical social interactions between older children/teenagers and other household members relative to those between younger children and other household members.

Viral loads were highly variable among participants, but they did not differ significantly by self-reported asthma, food allergy, or other atopic conditions. This result was surprising, given that bronchial airway epithelial cells from individuals with asthma have previously been shown to have impaired antiviral response and attenuated viral clearance.[28] The range of viral loads among children was comparable to that of teenagers and adults despite high asymptomatic infection rates. Thus, the relationship between viral load and symptoms was attenuated among young children. Consequently, when children and adults with high viral loads are compared, a larger proportion of children with high viral loads may be asymptomatic. Therefore, children may serve as efficient transmitters, as they commonly exhibit asymptomatic infection, can have high viral loads, and require close physical interactions within their household. Teenagers are similarly less likely than adults to be symptomatic, but they are more likely to introduce infection into a household and are therefore arguably more likely to contribute to community transmission.

Despite the strengths of this study, there are important limitations to be considered. A significant proportion of nasal collections were missed (34.4%) during the study period. Although this likely resulted in an underestimation of the incident infection rate, it could also cause underestimation of the risk associated with asthma, obesity, or minority race/ethnicity groups (see Table E10 in the Online Repository at www.jacionline.org). Even though it is the standard in the field, our use of validated questionnaires to identify asthma and allergic diseases by self-report of physician-diagnosed disease likely resulted in some amount of misclassification although study participants in asthma and allergic disease cohorts may be more likely to have laboratory or clinically confirmed disease. Although the primary goals of the HEROS study were to determine the impact of asthma and other atopic conditions on risk of infection and transmission, we did evaluate and present results for several other potential risk factors. Because the HEROS study population is enriched for asthma and allergic diseases, it is possible that these results are only partially generalizable to the larger US population. Moreover, our study was largely conducted prior to the availability of COVID vaccines and before the widespread emergence of new variants of concern (from Alpha to Omicron) in the United States; therefore, how our results will translate to the current situation is unclear. Lastly, although we defined multiple concurrent infections as resulting from a household transmission event(s), per the standard in the field,[1] we cannot rule out that among some of these households, multiple infections were concurrently acquired from the community.

In conclusion, HEROS, the household surveillance study of SARS-CoV-2 infection and transmission in a population of children and adults enriched for self-reported asthma and atopic conditions, provides some of the strongest evidence to date that asthma is not a risk factor for SARS-CoV-2 infection, symptoms, higher viral loads, or transmission events. Transmission risk is high in households with children, 75% of whom remain asymptomatic. We also report a number of intriguing findings requiring further investigation, including the fact that participants with food allergy were at lower risk for both infection and transmission and the fact that increasing BMI may be a risk factor for SARS-CoV-2 infection. Different types of systemic and airway inflammation may contribute to the variable infection risk, and understanding the mechanisms underlying these observations may offer new pathways for disease prevention.

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Clinical implications: Asthma is not associated with SARS-CoV-2 infection or household transmission. Understanding the nature of the relationship between food allergy and/or BMI and risk of SARS-CoV-2 infection may identify new targets for infection prevention.

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