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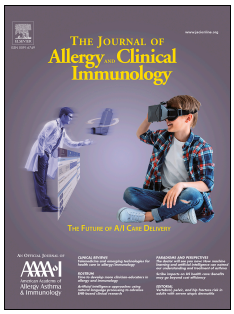

Risk factors for SARS-CoV-2 infection and transmission in households with asthmatic and allergic children. A prospective surveillance study

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Risk factors for SARS-CoV-2 infection and transmission in households with asthmatic and allergic children. A prospective surveillance study

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DISCLAIMER**:** Drs. Fulkerson's and Togias' authorship does not constitute endorsement by the National Institute of Allergy and Infection Diseases, the National Institutes of Health or any other Agency of the United States Government.

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ABSTRACT

Background: Whether children and people with asthma and allergic diseases are at increased risk for SARS-CoV-2 infection is unknown.

Objective: To determine SARS-CoV-2 infection incidence in households with children, and whether self-reported asthma and/or other allergic diseases are associated with infection and household transmission.

Methods: Biweekly nasal swabs and weekly surveys were conducted for six months within 1,394 households (N=4,142 participants) to identify incident SARS-CoV-2 infections from May 2020-February 2021, a pandemic time period largely pre-vaccine and pre-emergence of SARS-CoV-2 variants. Participant/household infection and household transmission probabilities were calculated using time-to-event analyses, and factors associated with infection and transmission risk determined using regression analyses.

Results: 147 households (261 participants) tested positive for SARS-CoV-2. Household SARS-CoV-2 infection probability was 25.8%; participant infection probability was similar for children (14.0%,CI:8.0-19.6%), teenagers (12.1%,CI:8.2-15.9%), and adults (14.0%,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 (aHR=1.04,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,CI:0.32-0.81); higher BMI was associated with increased infection risk (aHR per 10-point increase:1.09,CI:1.03-1.15). Household secondary attack rate was 57.7%. Asthma was not associated with household transmission, but transmission was lower in households with food allergy (aOR=0.43,CI:0.19-0.96,p=0.04).

Conclusion: Asthma does not increase risk of SARS-CoV-2 infection. Food allergy is associated with lower infection risk, while BMI is associated with increased infection risk. Understanding how these factors modify infection risk may offer new avenues for infection prevention.

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

Capsule Summary: In a multi-center SARS-CoV-2 surveillance study, conducted among asthmatic/allergic disease cohorts, participants with self-reported asthma were not at increased risk for infection. However, self-reported food allergy and increasing BMI were associated with decreased and increased risk for infection, respectively.

Key Words: SARS-CoV-2, COVID-19, Food allergy, body mass index, asthma, infection, transmission

Abbreviations: severe acute respiratory syndrome virus 2 (SARS-CoV-2), Coronavirus Disease 2019 (COVID-19), Angiotensin Converting Enzyme 2 (ACE2), quantitative polymerase chain reaction (qPCR), adjusted odds ratio (aOR), adjusted hazards ratio (aHR)

INTRODUCTION

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, two potential risk factors for severe COVID-19 that did not emerge from these analyses were being a child or having asthma.(3) Children and people with asthma are established risk groups who typically experience significant morbidity from many respiratory viruses and are target groups for vaccine preventable respiratory viral diseases.(4-6) Early mechanistic studies have proposed that atopy may protect against SARS-CoV-2 infection. Individuals with atopic, but not non-atopic asthma, express lower airway levels of *ACE2*, the SARS-CoV-2 receptor, as do those with allergic or type 2 airway inflammation(7-10), suggesting a potential mechanism for this unanticipated finding.

However, for individuals with asthma, 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. To address these questions, a prospective observational study is of essence. Importantly, the study population should not be selected using index participants who have already been afflicted by COVID-19 as this would constitute a major bias due 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.(11) Unfortunately, many epidemiologic studies assessing SARS-CoV-2 infection have been conducted using such biased population samples.(12-17)

To prospectively provide information regarding the above questions, the National Institute of Allergy and Infectious Diseases invited investigators with extant pediatric asthma and allergic diseases 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. HEROS involved 18 cohorts from 12 US cities (SFigure 1).

METHODS

Study Design and Population

We recruited households of children (<13 years) and teenagers (13-21 years) who were participating in NIH-funded cohorts that focused on asthma/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 care-giver collected biweekly nasal swabs were conducted between May 15, 2020 and February 1, 2021. On alternating weeks, if anyone had developed symptoms a pre-specified algorithm prompted an additional illness event sampling of all household members. Full details of the study protocol are described elsewhere [NCT04375761]. The IRBs of all participating institutions and the HHS Office of Human Research Protections deemed this a public health surveillance study.

SARS-CoV-2 Testing

qPCR testing for SARS-CoV-2 was conducted on nasal swabs using the Centers for Disease Control (CDC) SARS-CoV-2 N1/N2, and the RNaseP housekeeping gene assays (STable 1). N1 and N2 cycle threshold (Cq) values are reported as the average of the duplicate assays analyzed (excluding values Cq $\geq$ 40), and the overall Cq for a sample as the average of N1 and N2 averages. Viral Cq values were normalized to RNase P expression levels 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), 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 if ill completed a twenty-symptom survey. qPCR-confirmed infection events were classified as symptomatic or not, based on one or more symptoms (STable 2) experienced during, or immediately before/after infection (+/-14 days).

Statistical analysis

Participant and household level infection probabilities were estimated using Kaplan-Meier analyses. Associations between infection and self-reported asthma/allergic diseases, age, and other exploratory risk factors were evaluated with extended Cox proportional hazards models. Baseline hazards were stratified by study site. 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 used robust "sandwich" standard errors to account for clustering of participants in households; household-level models controlled for the average age of 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 $p<0.10$.

Generalized estimating equation (GEE) logistic regression was used to model the odds of household transmission, symptomatic infection, and participant-level non-transmission while controlling for participant and household demographics. For full statistical analysis details see Supplementary Methods.

RESULTS

Cohort description

The study population analyzed includes 4,142 participants who contributed at least one nasal swab from 1,394 households evaluated between May 15, 2020 to February 1, 2021 (Table 1A,SFigure 2). 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 (SFigure 3). Households had a mean of 4.4 total and 3.0 enrolled members. 52.2% of enrollees were children or teens; average age was 10.2 years (Table 1B). A large percentage (42.5%) of enrolled households 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% caregiver (CG) and children/teenagers (C&T), respectively, including food allergy (CG=10.2%, C&T=20.7%), eczema (CG=10.2%, C&T=24.0%), and upper respiratory allergy ("hay fever", "allergic rhinitis," CG=47%, C&T44.5%).

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 rate was higher for the illness-triggered (6.3%) versus the bi-weekly surveillance swabs (0.97%, OR:6.81,95% Confidence Interval (CI):4.64-10.00, SFigure 4), although 92.1% of infections were detected through biweekly surveillance. The HEROS 7-day rolling SARS-CoV-2 incidence among adults and teens tracks with U.S. nationwide data reported by the CDC in the same groups (Figure 1A). Among children we observe a higher wave of infection in late 2020, than observed in CDC data, likely due to our prospective design that screened subjects for infection regardless of symptoms. This allowed us

to identify asymptomatic infections that 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%). Using a Kaplan-Meier time to event analysis 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%(CI:10.3-17.5%), and was similar between children (14.0%,CI: 8.0-19.6%), teens (12.1%,CI: 8.2-15.9%), and adults (14.0%, CI: 9.5-18.4%,Figure 1B). However, the proportion of symptomatic infections varied significantly by age group; 24.5% of infections were symptomatic in children, 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 (aHR=1.04,CI:0.73-1.46, Figure 2A), nor in secondary analyses considering childhood asthma, adult asthma, and obese asthma separately (STable 3). Neither eczema (aHR=1.06, CI:0.75-1.50) nor upper respiratory allergy (aHR=0.96, CI:0.73-1.26) were associated with infection risk (STable 3). 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, CI:0.32-0.81, Figure 2B, STable 3). Neither asthma ($\Delta\log_{10}$viral load=-0.42, CI:-1.10-0.26, p=0.22), food allergy ($\Delta\log_{10}$viral load=0.88, CI:-0.06-1.81, p=0.07), eczema ($\Delta\log_{10}$viral load=0.46, CI:-0.27-1.20, p=0.22), nor upper respiratory allergy ($\Delta\log_{10}$viral load=0.36, CI:-0.21-0.93, p=0.22) 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 HEROS, through measurement of allergen specific IgE on a subset of HEROS participants. Specifically, we measured IgE to 112 allergens and allergen components (online Supplement), including 30 food allergens, in 1053 of

the HEROS participants, to examine the correspondence 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 two food allergy variables, we found 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 HEROS. To evaluate whether the overall atopic character of those with self-reported food allergy was higher, we compared the mean number of positive tests to any allergen/allergen component (of the 112 food and aeroallergen tests conducted) between those that did and did not report food allergy. We found the mean number of positive tests was significantly higher among those who self-reported food allergy (mean number of positive test=9.47) versus those who did not report food allergy (mean number of positive tests=2.91, $p < 2 \times 10^{-16}$), suggesting a greater level of general atopy among those with self-reported food allergy. Moreover, those with asthma, but not food allergy, exhibited on average only 4.61 positive antigen tests, 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 STable 3. Exposure to a symptomatic household member was associated with an 87.39-fold (adjusted hazard ratio (aHR),CI: 58.02-131.63) increase in infection risk, whereas exposure to an asymptomatically infected household member was associated with a 27.80-fold increase in risk (CI:17.16–45.03,Figure 2A). Age and sex were not significantly associated with infection risk. Minority race/ethnicity was associated with 59% increased infection risk (aHR:1.59,CI:1.15-2.21, Figure 2A).

Participants who were overweight or obese (63.0% adults, 14.7% teenagers, and 22.3% children) had a 41% increased risk of infection (aHR:1.41,CI:1.06–1.87, Figure 2C). Moreover, there was a strong linear relationship between BMI and infection risk, with every 10-point increase in BMI percentile increasing risk of SARS-CoV-2 infection by 9% (aHR:1.09,CI:1.03-1.15, Figure 2D). BMI percentile was not associated with peak viral load of infection events ($\Delta \log_{10}$viral load per 10 point increase=0.07, CI:-0.05-0.20, p=0.25).

Risk factors for household infection

In total, 147(10.5%) households experienced one or more SARS-CoV-2 infection(s). Accounting for the length of follow up, the probability of household infection was 25.8%(CI:11.2-38.1%) during the study period (SFigure 5). Households with an asthmatic participant were not at increased risk for infection, nor were households including participants with any other allergic disease (Table 2). We observed an increase in SARS-CoV-2 infection risk among households with a member attending in-person school (aHR:1.67,CI:1.09-2.57) and among minority race/ethnicity households (aHR:1.52,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,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,CI:0.74-1.00). We found no association between household infection risk and the following exposures in the prior 30 days: a household member attending daycare, healthcare appointments, social gatherings, grocery store visits, traveling, or getting takeout food (Table 2), nor with household characteristics: number of members in the household or smoking.

Within-household transmission of SARS-CoV-2

Of the 97 positive households with sufficient follow-up for this analysis (see online Supplement), 41 had a single member with a documented infection (no household transmission), while 56 had multiple members with documented infections (likely household transmission, SFigure 6), 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 (SFigure 6). Among the remaining transmitting households, members tested positive for SARS-CoV-2 concurrently (SFigure 6). Using Kaplan-Meier analysis, the probability of transmission to an individual household member was 41.2% within the first 50 days (CI:32.3-49.0%, SFigure 7); 88.3% of household transmissions occurred within 14 days of the first household member becoming infected.

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

To identify household characteristics associated with transmission, we compared transmitting to non-transmitting households (STable 4). Having an asthmatic in the household was not associated with transmission (aOR=0.64, CI:0.33-1.23). Upper respiratory allergy and eczema were also not significantly associated with increased odds of household transmission (aOR=0.71, CI: 0.27-1.84; aOR=1.85, CI: 0.65-5.21). However, transmissions were significantly less likely in households with food allergy (aOR=0.43, CI:0.19-0.96, p=0.04). 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/teenagers, there was a 21% decrease in odds of being a transmitting household (aOR:0.79, CI:0.69-0.89).

Characteristics of non-transmitting household members

Since the index case was unclear in many transmitting households, we analyzed participant-level characteristics associated with non-transmission by comparing non-transmitters (n=41) to possible transmitters (n=140, STable 5). Neither asthma, food allergy, upper respiratory allergy nor eczema were associated with non-transmission (STable 5). Age group was associated with non-transmission: teenagers had 6.15-fold increased odds (aOR,CI:2.49-15.21) of being a non-transmitter relative to children, and 3.55-fold increased odds (aOR,CI:1.56-8.08) of being a non-transmitter relative to adults. Being overweight or obese was associated with 55% lower odds of non-transmission (aOR:0.45,CI:0.25-0.82). Viral load was strongly associated with transmission (SFigure 8), with a 14% increase in the odds of being a non-transmitter for every 10-fold decrease in peak viral load (aOR=0.86,CI:0.74-0.99). Presence of symptoms, race/ethnicity, and sex were not significantly associated with non-transmission.

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, STable 2. There was no association between odds of symptomatic infection and asthma, food allergies, eczema, upper respiratory allergy, or overweight/obesity (STable 6). Symptomatic infection was associated with age (Figure 3A). Teenagers and adults had 2.78-fold (aOR,CI:1.05-7.36) and 6.02-fold (aOR,CI:2.83-12.78) higher odds of symptoms, respectively, compared with children (STable 6).

Children had significantly lower mean viral load compared to adults (-0.82 $\log_{10}$(viral load),CI:-1.61to-0.03), but did not significantly differ from teenagers (-0.47 $\log_{10}$(viral load), CI:-1.42 to 0.48, Figure 3B,STable 7). Viral loads were highly similar between symptomatic and asymptomatic infections up to ~age 10, whereas viral loads in subjects >10 years of age were generally higher for those with symptomatic vs. asymptomatic illnesses (SFigures 9A,B,STable 8). The odds of a

symptomatic vs. asymptomatic infection increased with higher peak viral load among teenagers and adults, whereas this relationship was not observed among children (Figure 3C,STable 9).

DISCUSSION

We conducted a unique, prospective, longitudinal SARS-CoV-2 surveillance study of more than 1300 households and over 4,000 participants, a study population enriched for asthma and other allergic conditions. Public health measures in place at the time of our study (May 2020-Feb 2021), which severely limited unnecessary person-to-person contact, necessitated we conduct the HEROS study activities remotely, without direct participant contact. Specifically, the study was exclusively conducted at the participants' homes and involved detailed training and frequent electronic/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 (alpha-omicron), providing key epidemiological data on this early stage of the pandemic, which will inform management of this and future respiratory virus pandemics.

We found that children, teenagers, and adults had similar probability of SARS-CoV-2 infection during the pre-vaccine period of the pandemic. However, children (<13 years) were much more likely to have asymptomatic infection compared with 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 using validated questionnaires, previously shown to accurately capture asthma and atopic disease.(18-21) 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, nor 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 report.

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 and 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 due to the inclusion of non-food allergic subjects in the food allergy group, thus driving the results toward the null. Moreover, we found high correspondence between self-reported food allergy and food allergen-specific IgE measurements conducted in a subset of HERO subjects. Regarding the possibility that biology enriched among food allergic subjects 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.(9) Moreover, *in vitro* experiments have found interleukin-13 stimulation of the airway epithelium both lowers ACE2 levels and inhibits SAR-CoV-2 infection;(9, 22) similarly, experimentally induced airway allergic reactions also lead to reduced ACE2 gene expression.(7) It is not known whether this is also the case in food allergic individuals, but it is tempting to speculate that type 2 inflammation, a characteristic of food allergy(23), 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 to both those without food allergy, and even those with asthma. Alternatively, the lower infection risk observed among food allergic participants could also be explained in part by differences in risk behaviors, such as less eating out among food allergic individuals. However,

449 we assessed this biweekly and observed only slightly lower levels of exposures (SFigure 10)
450 among households with food allergic individuals.
451
452 Obesity/being overweight, a factor previously associated with severe COVID-19 disease, was
453 associated with increased infection risk. Our results demonstrate that BMI exerts an effect on
454 infection risk linearly throughout the population BMI range. Lower BMI individuals were also more
455 likely to be non-transmitters within households. Potential biological mechanisms underlying this
456 effect, include increased ACE2 expression in obese subjects,(24) or neutrophilic airway
457 inflammation also described in obese individuals which has been associated with increased viral
458 replication for several respiratory viruses.(25, 26) Previous studies have also found the risk for
459 asthma exacerbations, which often are triggered by viral infections, is increased among obese
460 subjects with asthma, but we did not find an increased risk of SARS-CoV-2 infection among the
461 subset of individuals with obesity and asthma.(27, 28)
462
463 We found both the average age of children/teenagers, but also of caregivers were risk factors for
464 a household becoming infected, although with differing directions of effect. We hypothesize that
465 the association between older age of children/teenagers and increased infection risk may result
466 from a greater number of social interactions and group activities experienced by older children,
467 putting these households at higher infection risk. Households with younger caregivers were also
468 at higher infection risk and we hypothesize that this may, again, be due to greater social
469 interactions, as well as obligations outside the household. The only exposure significantly
470 associated with infection of households was having a member attending in-person school. The
471 high risk of household infection associated with in-person school attendance may be explained
472 by unrecognized asymptomatic infections among children/teenagers attending school and
473 resultant transmission to other children and households.
474

Once a SARS-CoV-2 infection was introduced into a household, we found a high household SAR, with over 57% of infected households experiencing one or more transmissions and a 41% probability of infection for at-risk household members. This is substantially higher than 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 – November 2020, prior to the wide-spread emergence of SARS-CoV-2 variants of concern, and in particular the more infectious Delta- and Omicron-variants. Moreover, infections were likely missed due 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 this may be driven by fewer and/or less physical social interactions between older children/teenagers and other household members, relative to younger children.
Viral loads were highly variable among participants, but did not significantly differ by self-reported asthma, food allergy, or other atopic conditions. This result was surprising, given bronchial airway epithelial cells from individuals with asthma have previously been shown to have impaired anti-viral response and attenuated viral clearance.(29) 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, a larger proportion of children with high viral loads may be asymptomatic compared to adults. Therefore, children may serve as efficient transmitters, with very high

asymptomatic infection, high viral loads, and close physical interactions within their household. Teenagers are similarly less likely than adults to be symptomatic, but more likely to introduce infection into a household, and 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. While 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 (STable 10). Although 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. While 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. Since the HEROS study population is enriched for asthma and allergic diseases, it is possible that those results are only partially generalizable to the larger U.S. population. Moreover, our study was largely conducted prior to the availability of COVID vaccines and before the wide-spread emergence of new variants of concern (alpha-omicron) in the U.S., therefore it is unclear how our results will translate to the current situation. 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 that food allergic participants were at lower risk for both infection and transmission, and 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 explaining these observations may offer new pathways for disease prevention.

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TABLES

Table 1A: Subject Characteristics. Mean (SD), Median (Inter-Quartile Range) or N (%)

Table 1B: Household Characteristics. Mean (SD), Median (Inter-Quartile Range) or N (%)

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

FIGURES

Figure 1. Subject level SARS-CoV-2 incidence and probability of infection.

A. Rolling incidence (7-day) of SARS-CoV-2 infection among adults, teens, and children, compared to U.S. nationwide data collected by the CDC for the same time period.

B. KM curve for probability of subject-level SARS-CoV-2 infection in children, teenagers, and adults by calendar time.

Figure 2. Food allergy and obesity are associated with decreased and increased SARS-CoV-2 infection risk, respectively.

A. Adjusted hazards ratios 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. * HR from model adjusted for age, sex, race/ethnicity, and exposure to an infected household member.

B. KM curve for probability of SARS-CoV-2 infection across study time by food allergy status.

C. KM 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, adjusting for age, sex, race/ethnicity, exposure to an infected household member, food allergy and number of bedrooms per person.

Figure 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.

Table 1A: Subject Characteristics. Mean (SD), Median (Inter-Quartile Range) or N (%)

Variable	Caregivers	Index Children and Siblings
N	1978	2164
SARS-CoV-2 Positive	124 (6.3%)	137 (6.3%)
Age (years)	41.14 (7.92)	10.18 (4.95)
Age Category		
Child, <5 years	0 (0.0%)	282 (13.0%)
Child, 5-12 years	1 (0.1%)	1087 (50.2%)
Teen	6 (0.3%)	795 (36.7%)
Adult, 21-40 years	906 (45.8%)	0 (0.0%)
Adult, >=40 years	1065 (53.8%)	0 (0.0%)
Sex: Male	604 (30.6%)	1123 (52.1%)
Race/Ethnicity Other than Non-Hispanic White	654 (33.7%)	884 (41.8%)
Current Smoking	185 (9.4%)	3 (0.1%)
Asthma	439 (22.2%)	711 (32.9%)
Upper Respiratory Allergies	929 (47.0%)	963 (44.5%)
Food Allergies	202 (10.2%)	447 (20.7%)
Eczema	202 (10.2%)	520 (24.0%)
Atopic Conditions (excluding asthma)	1030 (52.1%)	1231 (56.9%)
BMI Category		
Normal	759 (38.8%)	1251 (64.2%)
Overweight	488 (25.0%)	307 (15.8%)
Obese	708 (36.2%)	391 (20.1%)
BMI Percentile	81.59 (21.04)	63.47 (31.74)
High Cholesterol	258 (13.0%)	19 (0.9%)
Hypertension	312 (15.8%)	17 (0.8%)
Number of nasal swabs analyzed, Median (IQR)	10 (6-12)	10 (6-12)
Length of nasal swab follow up (weeks)	19.94 (8.36)	19.58 (8.60)
Number of surveillance swabs expected		
10 swabs	319 (16.1%)	369 (17.1%)
14 swabs	1659 (83.9%)	1795 (82.9%)
Percent of surveillance swabs received	64.6 (27.8)	63.5 (28.3)
Month of first nasal swab		
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%)

Table 1B: Household Characteristics. Mean (SD), Median (Inter-Quartile Range) or N (%)

Variable	
N	1394
Number of Household Mebers Enrolled, Median (IQR)	3 (2-4)
Total Number of Household Members, Median (IQR)	4 (4-5)
SARS-CoV-2 Positive	147 (10.5%)
Average age of enrolled caregivers (years)	41.09 (7.58)
Average age of enrolled children (years)	10.33 (4.69)
Race/Ethnicity Other than Non-Hispanic White	582 (42.5%)
Smoking in the Household	174 (12.5%)
Number of Bedrooms in the Household, Median (IQR)	3 (3-4)
Pets in the Household	814 (58.4%)

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

		Adjusting for Number Enrolled + Age + Race				Multivariable			
		HR	95% Confidence Interval		P Value	HR	95% Confidence Interval		P Value
Family Characteristics	**Comparison**								
Average age of caregivers	5 year increase	0.87	0.75	1.01	0.0731	0.86	0.74	1.00	0.0503
Average age of children and teenagers	1 year increase	1.06	1.01	1.12	0.0296	1.07	1.01	1.13	0.0228
Race/Ethnicity	Other Race/Ethnicity vs NHW	1.37	0.92	2.04	0.1167	1.52	1.02	2.27	0.0407
Smoking in the household	Yes vs No	0.82	0.46	1.47	0.5090				
Number of household members	1 person increase	0.99	0.86	1.13	0.8315				
Number of subjects enrolled	1 person increase	1.23	1.01	1.50	0.0380	1.21	0.99	1.47	0.0633
Asthma in household	Yes vs No	0.82	0.57	1.19	0.2978				
Food allergy in household	Yes vs No	0.89	0.61	1.32	0.5746				
Upper respiratory allergy in household	Yes vs No	1.01	0.69	1.49	0.9472				
Eczema in household	Yes vs No	0.85	0.59	1.22	0.3679				
Exposures in the Past 30 Days									
In person school	Yes vs No	1.77	1.16	2.69	0.0081	1.67	1.09	2.57	0.0192
Work	Yes vs No	1.42	0.95	2.13	0.0859	1.29	0.86	1.95	0.2209
Daycare	Yes vs No	0.97	0.56	1.69	0.9239				
Travel outside of home city	Yes vs No	1.04	0.72	1.48	0.8496				
Healthcare appointments	Yes vs No	0.91	0.65	1.28	0.5856				

Getting takeout food	Yes vs No	1.02	0.67	1.55	0.9269
Going to social gatherings	Yes vs No	1.35	0.81	2.24	0.2456
Going to the grocery store	Yes vs No	0.84	0.48	1.47	0.5501

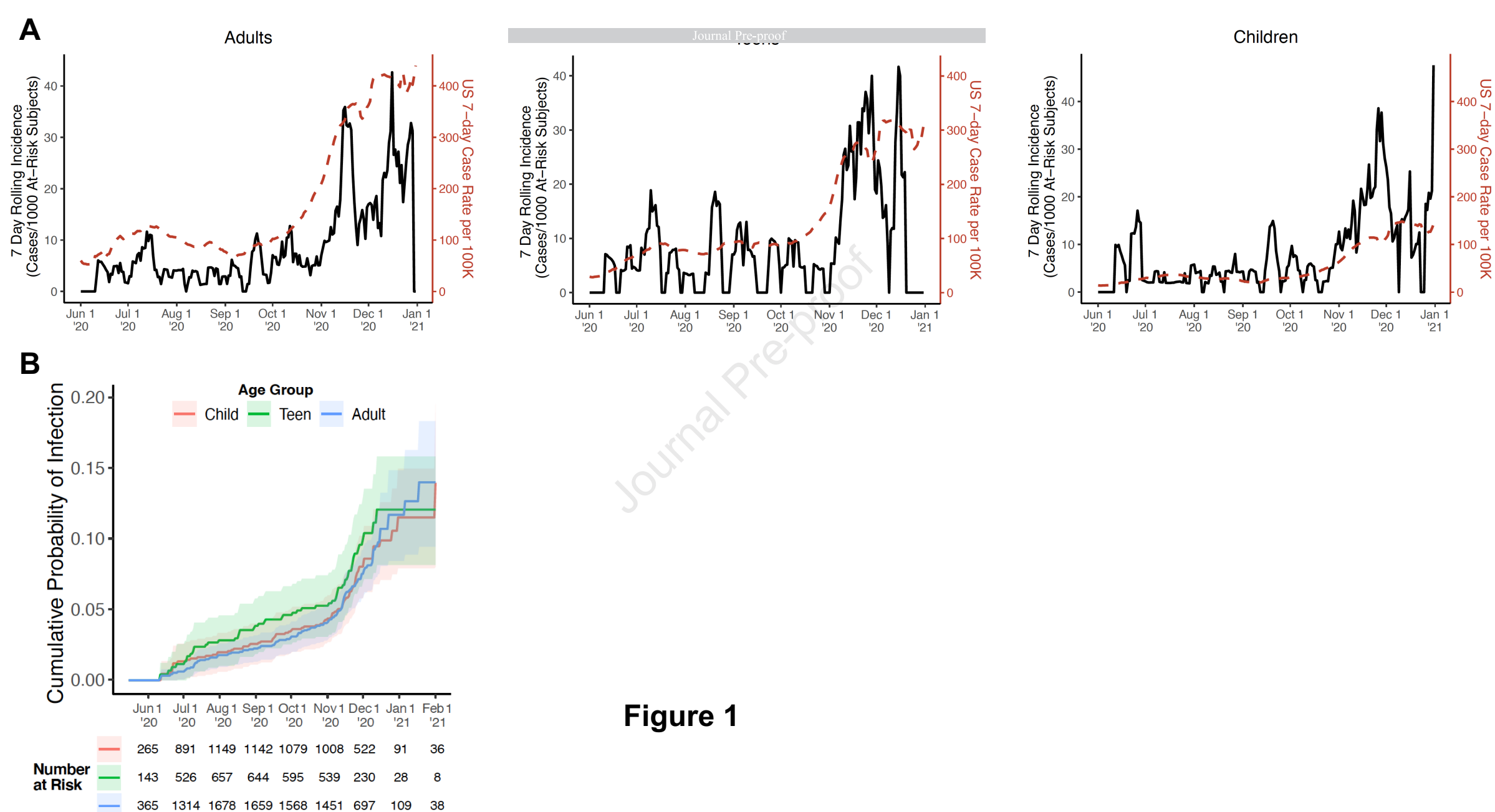

Figure 1

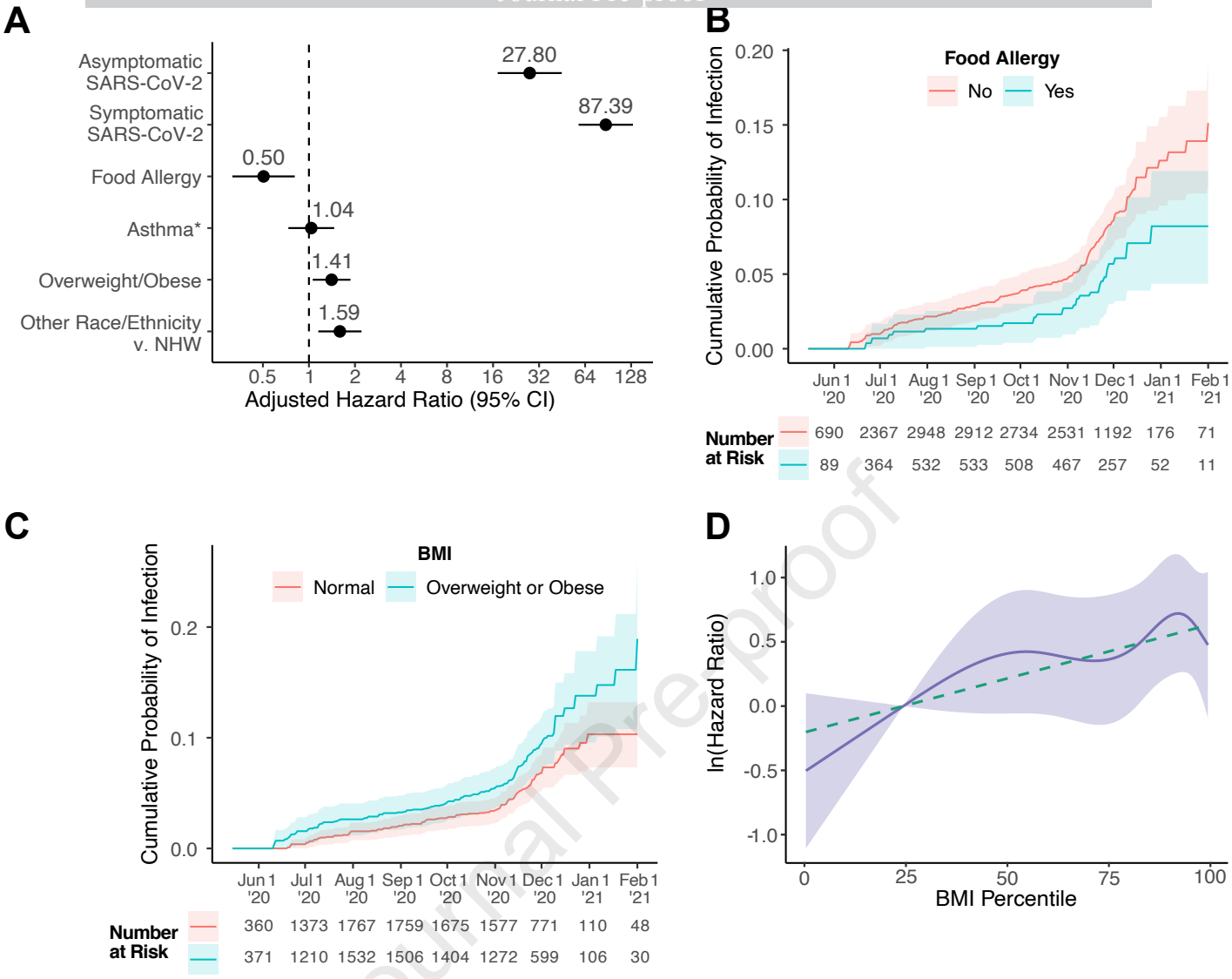

Figure 2

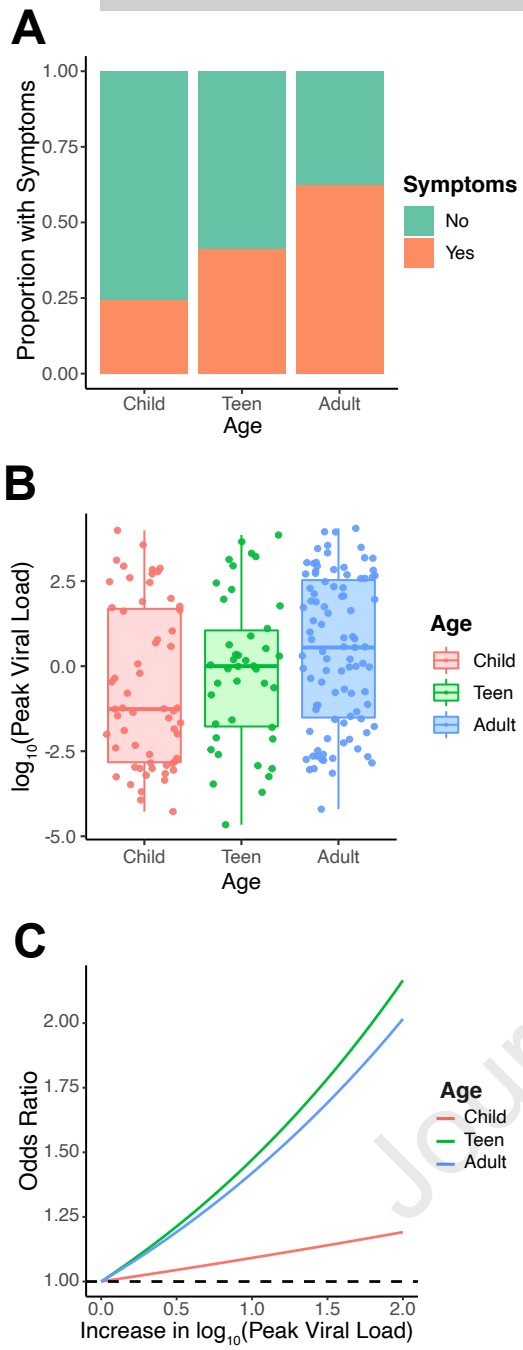

Figure 3