Comparison of Persistent Symptoms Following SARS-CoV-2 Infection by Antibody Status in Nonhospitalized Children and Adolescents

Sarah E. Messiah, PhD, MPH,† Tianyao Hao, MS,‡ Stacia M. DeSantis, PhD,‡ Michael D. Swartz, PhD,‡ Yashar Talebi, MS,‡ Harold W. Kohl III, MSPH, PhD,§¶ Shiming Zhang, MS,‡ Melissa Valerio-Shewmaker, MPH, PhD,‖ Ashraf Yaseen, PhD,‡ Steven H. Kelder, MPH, PhD,§ Jessica Ross, BS,‡ Michael O. Gonzalez, MPH,‡ Leqing Wu, MS,‡ Lindsay N Padilla, MPH, MSW‡ Kourtney R. Lopez, BS,‡ David Lakey, MD,**†† Jennifer A. Shuford, MPH, MD,‡‡ Stephen J. Pont, MPH, MD,‡‡ and Eric Boerwinkle, PhD‡*

Background: The prevalence of long-term symptoms of coronavirus disease 2019 (COVID-19) in nonhospitalized pediatric populations in the United States is not well described. The objective of this analysis was to examine the presence of persistent COVID symptoms in children by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody status.

Methods: Data were collected between October 2020 and May 2022 from the Texas Coronavirus Antibody REsponse Survey, a statewide prospective population-based survey among 5-90 years old. Serostatus was assessed by the Roche Elecsys Anti-SARS-CoV-2 Immunoassay for detection of antibodies to the SARS-CoV-2 nucleocapsid protein. Self-reported antigen/polymerase chain reaction COVID-19 test results and persistent COVID symptom status/type/duration were collected simultaneously. Risk ratios for persistent COVID symptoms were calculated versus adults and by age group, antibody status, symptom presence/severity, variant, body mass index and vaccine status.

Results: A total of 82 (4.5% of the total sample [n = 1813], 8.0% pre-Delta, 3.4% Delta and beyond) participants reported persistent COVID symptoms (n = 27 [1.5%] 4–12 weeks, n = 58 [3.3%] >12 weeks). Compared with adults, all pediatric age groups had a lower risk for persistent COVID symptoms regardless of length of symptoms reported. Additional increased risk for persistent COVID symptoms >12 weeks included severe symptoms with initial infection, not being vaccinated and having unhealthy weight (body mass index ≥85th percentile for age and sex).

Conclusions: These findings highlight the existence of nonhospitalized youth who may also experience persistent COVID symptoms. Children and adolescents are less likely to experience persistent COVID symptoms than adults and more likely to be symptomatic, experience severe symptoms and have unhealthy weight compared with children/adolescents without persistent COVID symptoms.

Key Words: adolescents, children, coronavirus disease 2019, long coronavirus disease, pediatric, severe acute respiratory syndrome coronavirus 2

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As of June 21, 2022, over 13.5 million children in the United States have tested positive for coronavirus disease 2019 (COVID-19).[1] Previous studies have shown that symptomatic COVID-19 illness typically has a mild impact in children compared with adults.[1] Although most infected children do not require hospitalization, for those with symptomatic illness, acute symptoms of COVID-19 typically last about 2 weeks,[2,3] but have been reported to continue for much longer past initial onset.[4] Symptoms of COVID-19 that persist past recovery are commonly referred as postacute sequelae of SARS-CoV-2, post-COVID-19 syndrome, long-haul COVID or simply long COVID.[5,6] In adults, long COVID is recognized as a multisystem disease, with fatigue and dyspnea the most commonly reported long-term physical symptoms.[4] Less information is available in the literature that describes the long-term impact of COVID-19 among nonhospitalized pediatric populations, especially in the United States.

Most published research describing the impact of persistent COVID symptoms in children focuses on physical health, but recent studies have shown long COVID can also affect mental health.[7,8] Events such as school closures, lack of resources to support remote learning and social isolation can also negatively impact the child and their family's quality of life.[9] Thus, one of the major challenges of reporting accurate persistent COVID symptom prevalence estimates in the nonhospitalized pediatric population has been the

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From the *Department of Epidemiology, Human Genetics and Environmental Sciences, The University of Texas (UT) Health Science Center at Houston, School of Public Health in Dallas, and †Center for Pediatric Population Health, UTHealth School of Public Health and Children's Health System of Texas, Dallas, Texas; ‡Department of Biostatistics and Data Science, The University of Texas Health Science Center at Houston, School of Public Health in Houston, Houston, Texas; §The University of Texas Health Science Center at Houston, School of Public Health in Austin, and ¶Department of Kinesiology and Health Education, University of Texas at Austin, Austin, Texas; ‖Department of Health Promotion and Behavioral Sciences, The University of Texas Health Science Center at Houston, School of Public Health in Brownville, Brownsville, Texas; **University of Texas System, Austin, Texas; ††The University of Texas Health Science Center Tyler, Tyler, Texas; and ‡‡Texas Department of State Health Services, Austin, Texas.

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E.B., D.L., M.D.S., J.A.S., S.J.P. and M.V.-S. were responsible for the conception and design of the survey. D.L., S.J.P. and E.B. are the executive coordinators of the project. M.V.-S. led the relationship with regional Federally Qualified Health Centers. M.D.S., S.M.D., A.Y. and L.W. lead the data coordination components including survey operation, including the coordination of data acquisition and logistics. S.M.D., M.D.S. and S.Z. led all weighting calculations. M.V.-S. and S.E.M. developed the operational protocols for field work and were responsible for training the involved administrative and health personnel. S.E.M., TH, M.D.S. and S.M.D. were in charge of statistical analyses and table and figure design. J.R. lead all project coordination efforts. L.P. and K.R.L. coordinated participant interaction and recontact of participants. All remaining authors in the Texas CARES group contributed to participant recruitment, data acquisition, laboratory analyses and quality control for their respective populations. The first draft was written by S.E.M. and H.W.K. All authors had full access to all study data, contributed to data interpretation, critically reviewed the first draft and approved the final version and agreed to be accountable for the work.

Texas CARES investigators are committed to data sharing. Granular results and user-specified data summaries are currently publicly available on the Texas CARES portal (https://sph.uth.edu/projects/texascares/dashboard). When baseline recruitment is complete, a deidentified individual level dataset will be available for download from the same portal.

Address for correspondence: Sarah E. Messiah, PhD, MPH, Department of Epidemiology, Human Genetics and Environmental Sciences, sCenter for Pediatric Population Health, University of Texas Health Science Center School of Public Health, 2777 North Stemmons Freeway, Suite 8400, Dallas, TX 75207. E-mail: Sarah.E.Messiah@uth.tmc.edu.

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absence of a control or comparison group.[10] In 1 recent report summarizing 14 studies in the literature,[10] 5 studies included children and adolescents without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as controls and of these 2 did not find persistent symptoms to be more prevalent in children and adolescents with evidence of SARS-CoV-2 infection.

Similarly, a recently published meta-analysis assessed potential evidence of long-term post-COVID symptoms in those ≤19 years old.[11] The authors concluded that the frequency of the majority of reported persistent symptoms was similar in COVID-19 cases and controls and emphasized the importance of a control group to improve study rigor. These inconsistent findings are also supported in other studies that report a low prevalence of persistent symptoms in children (1.8%–4%),[2,12] while others report much higher estimates (24% to >30%)[13,14] and with multisystem involvement.[14] Both previously mentioned reviews[9,10] included only 2 studies with children,[15,16] and 1 study that included children from the United States,[7] respectively, neither of which included exclusively nonhospitalized children and adolescents. Therefore, we report here the prevalence of persistent symptoms in a population-based sample of ≤19 years old in the United States with known SARS-CoV-2 antibody status. It was hypothesized that persistent symptoms would be more prevalent in those with both positive natural antibody status and who experienced SARS-CoV-2 infection, versus those who were seropositive but symptomatic.

METHODS

Survey Design

Texas Coronavirus Antibody REsponse Survey (CARES) is an ongoing prospective population-based survey of a volunteer sample from the general population that includes participants ages 5–90 years. Participants can receive up to 3 free SARS-CoV-2 antibody tests over 6 months or about once every 3 months. Texas CARES is a partnership between the University of Texas Health Science Center at Houston, Texas Department of State Health Services, the University of Texas System and Clinical Pathology Laboratories, a laboratory facility with more than 200 statewide sites. All protocols were reviewed and approved by the University of Texas Health Science Center's Committee for the Protection of Human Subjects but also deemed public health practice by the Texas Department of State Health Services Institutional Review Board.

Survey Population

Texas CARES began enrolling participants across the state of Texas in October 2020. Families of potential pediatric participants were informed about the survey in several ways: via their healthcare provider, insurance carrier if they were Medicaid insured, media release, media (radio, billboard), social media campaign, community events and word of mouth. All information was delivered in English and Spanish.

Study Procedures

A parent or designated caregiver served as the proxy informed consent for children and adolescents to participate in Texas CARES. Adolescents ≥12 years old had the option to sign assent and complete the questionnaire. Participants who consented to enroll in Texas CARES first completed a short online questionnaire designed to collect demographic information, employment, baseline medical conditions and comorbidities, prior COVID-19 tests and diagnoses, physician diagnosis of COVID-19 and other chronic illnesses (eg, type 2 diabetes, asthma, hypertension), previous COVID-19 symptoms and severity and presence of persistent COVID symptoms. Once the participant completed the survey, orders were generated to be taken to a partner laboratory facility of their choice to complete the antibody status blood draw. Participants typically received their results within 48 hours.

Study Measures

SARS-CoV-2 Antibody Assay Roche Diagnostics

SARS-CoV-2 antibody status was assessed via the Roche Elecsys, Indianapolis, IN Anti-SARS-CoV-2 Immunoassay. The Roche assay detects high-affinity antibodies to SARS-CoV-2 using a modified recombinant protein representing the nucleocapsid (N) antigen for the determination of SARS-CoV-2 antibodies.[17] The assay relies on a double antigen sandwich format that enriches detection of higher affinity antibodies, which are more likely to be specific for SARS-CoV-2. The assay format is agnostic to the antibody isotype and can detect high-affinity antibodies of all isotypes; it preferentially detects IgG antibodies since these are most likely to evolve to become high affinity but can also detect IgM and IgA antibodies. The nucleocapsid antigen is abundantly expressed and is a useful target for sensitive detection of virus-specific antibodies. These features provide an optimal combination of high specificity and sensitivity for detection of exposure to SARS-CoV-2 in the general population, including pediatric populations. The test has a published sensitivity of 99.5% (95% confidence interval [CI]: 97.0%–100%) and 99.8% specificity (95% CI: 99.69%–99.88%) in diagnostic specimens (n = 2861).[17,18]

Electronic Questionnaire

An online, Research Electronic Data Capture[19,20] programmed questionnaire was designed to be completed in 10–15 minutes to capture previously described information by parent proxy. To increase validity and reproducibility, most questions and response formats were replicated from the COVID-19 PhenX Toolkit[21]and Behavioral Risk Factor Surveillance System questionnaires.[22] US Census race/ethnicity questions were also replicated.[23] The self-administered questionnaire was designed to flow after completion of informed consent using a seamless webpage transition to ease respondent burden and maximize survey completion.

Body Mass Index

Body weight categories were determined using the calculated body mass index (BMI; kg/m^2) from caregiver-reported height and weight of the child, which was then transformed to a standardized percentile distribution based on the Centers for Disease Control and Prevention (CDC) age- and sex-adjusted BMI growth charts.[24] Standardized weight categories are as follows: (1) underweight = <5th percentile; (2) healthy weight = 5th to <85th percentile; (3) overweight ≥85th to <95th percentile and (4): obesity ≥95th percentile.[25]

COVID Symptoms and Duration

The primary outcome for this analysis was the prevalence of persistent COVID-19 symptoms by SARS-CoV-2 antibody status. COVID-19 symptom assessment followed the CDC's standardized list.[26] Participants were asked if their initial symptoms were mild, moderate or severe. Length of COVID-19 symptoms was assessed via the following question: COVID-19 symptom length (4–12 weeks, >12 weeks, currently still have symptoms, never had symptoms). Following National Institute for Health and Care Excellence guidelines,[27] those who reported having at least 1 symptom for 4–12 weeks, or greater than 12 weeks, were defined as having long COVID.

Outcome Variable

The main outcome variable for this analysis was the presence of persistent COVID symptoms (Y/N) as captured via the survey question described above.

Exposure Variables

Exposure variables of interest included the variant time period that the participant was originally infected (pre-Delta vs. Delta period and beyond), confirmed by date of COVID-19 test, symptom status for initial COVID-19 illness (symptomatic/ asymptomatic), severity of symptoms, BMI group (healthy weight and unhealthy weight, defined as < or ≥85th percentile adjusted for age and sex,[24] respectively) and vaccine and social/ mental health.

Covariates

Covariates included age, sex and race/ethnicity.

Participants

The descriptive analysis included the estimation of the Texas census-adjusted and Roche assay-adjusted cross-sectional seroprevalence based on antibody test results in children and adolescents ≤19 years old. As per World Health Organization's COVID-19 sero-epidemiology protocol,[28] pediatric participants were stratified by the following age groups: 5–9 years, 10–14 years and 15–19 years and adult participants were greater than or equal to 20 years old.

Persistent COVID symptoms was defined as participants that self-reported having long-term COVID-19 symptoms either (1) 4–12 weeks or (2) >12 weeks after reporting a positive COVID-19 nasal or oral swab test or the serostatus tested positive, as this was the standard case definition when long COVID was first described by the CDC. The control group is defined as participants that did not report long-term symptoms after reporting a positive COVID-19 nasal or oral swab test or the serostatus tested positive.

Factors of interest are variant periods (pre-Delta and Delta and beyond), age (continuous age as well as categorical age), gender, race/ethnicity, language, geographic location (urban or rural area), BMI (calculated from self-reported height and weight and categorized according to the CDC convention), COVID-19 diagnosis, chronic disease (yes/no), antibody serostatus (positive/ negative), symptom status after reporting the COVID-19 infection (symptomatic/ asymptomatic), specific symptoms (headache, fatigue, congestion or runny nose, fever or chills, cough, sore throat, muscle or body aches, new loss of taste or smell, shortness of breath or difficulty breathing, diarrhea, nausea or vomiting), symptom severity (mild-moderate/severe), vaccination status (fully vaccinated/partially vaccinated/not vaccinated), social/mental health status (not impacted/mild-moderately impacted/severely impacted). A "missing" category for each variable is included in the analysis to maximize the sample size.

Statistical Analysis

Categorical variables were compared using Pearson χ^2 or Fisher exact test with or without simulated *P* values (based on 2000 replicates). The relative risk (RR) of persistent COVID symptoms at 4–12 weeks and >12 weeks was calculated using Poisson regression univariately for: categorical age, antibody serostatus, SARS-CoV-2 variant period, categorical BMI, symptom status, symptom severity and the vaccination status by persistent COVID symptom status. The RR is defined as the probability of persistent COVID symptoms divided by the probability of persistent COVID symptoms by key demographic characteristics. The adjusted RR was calculated using Poisson regression including all variables that had a significant univariate $P < 0.10$. The adjusted RR (95% CI) is defined as the exponentiation of the regression coefficient. All statistical analyses were performed in R version 4.0.2.

RESULTS

Those who reported persistent COVID symptoms by antibody serostatus and by pre-Delta (n = 451) versus Delta and beyond (n = 1362) variant time periods are summarized in Table 1. During the pre-Delta time period, the sample was older (51.9% 15–19 years old), but during Delta the sample included more 10–14 years old (44.1%). The samples were predominantly non-Hispanic White during both variant time periods (65.0%, 70.0%, respectively), urban residents (96.2%, 93.8%, respectively) and healthy weight (62.8%, 65.2%, respectively). The presence of at least 1 chronic disease was reported by 23.3% pre-Delta compared with 17.8% during Delta and beyond. Pre-Delta 79.6% of the sample had a COVID-19 diagnosis compared with 40.2% during the Delta variant time period. A total of 8.0% reported persistent COVID symptoms pre-Delta and 3.4% during Delta and beyond. Table 1 also included the weighted Texas population by key descriptive characteristics. In general, the analytical sample tended to be older, more non-Hispanic White and urban than the general Texas population.

Table 2 summarizes the characteristics of those who reported symptoms lasting from 4 to 12 weeks (n = 27) and those who reported symptoms lasting >12 weeks (n = 58) by serostatus. A total of 3 seronegative participants reported long symptoms. Of the 27 children and adolescents who reported persistent COVID symptoms lasting 4–12 weeks and were seropositive, 46.2% were 10–14 years old and 46.2% were 15–19 years old, while of the 58 children and adolescents who reported persistent COVID symptoms lasting >12 weeks and were seropositive, 21.4% were 10-14 years old and 69.6% were 15–19 years old. Regardless of duration of reported long symptoms, all were symptomatic. For the 2 long symptom groups, those who reported persistent COVID symptoms and were seropositive also reported mild to moderate symptoms (93.3%, 89.5%, respectively) or severe symptoms (6.7%, 10.5%, respectively) and the majority were not vaccinated (91.3%, 82.1%, respectively). About 30% of those who reported long symptoms lasting 4–12 weeks and who were seropositive reported their social/ mental health was either mild-moderately (25.0%) or severely (5.0%) impacted while about a third of both those who reported symptoms lasting >12 weeks (33.3%) or reported no long symptoms (35.2%) were mild-moderately impacted or severely impacted (4.2%, 3.1%, respectively).

Among those reporting symptoms lasting 4–12 weeks, the most commonly reported symptoms among those who were both seropositive and reported persistent COVID symptoms were new loss of taste and smell (6.7%), fatigue (60.0%), fever or chills (46.7%) and headache (40.0%). Among those reporting symptoms lasting >12 weeks, the most commonly reported symptoms among those who were both seropositive and reported persistent COVID symptoms were headache and fatigue (53.8% each, respectively), congestion or runny nose (41.0%), cough (35.9%) and fever or chills (30.8%) (Data not shown on tables).

When compared with the Texas CARES adult sample who reported persistent COVID symptoms for 4–12 weeks (n = 2171), all pediatric age groups were significantly less at risk for persistent COVID symptoms. Specifically, in univariate modeling 5–19 years old had 93% less risk (RR: 0.07, 95% CI: 0.02–0.27), 10–14 years old had 78% less risk (RR: 0.22, 95% CI: 0.13–0.37) and 15–19 years old had 77% less risk (RR: 0.23, 95% CI: 0.13–0.40) versus adults. Five to 9 years and 10–14 years old were less at risk for reporting persistent COVID symptoms that lasted 4–12 months versus 15–19 years old. Those who did not report vaccination information were almost 6 times more likely to report persistent symptoms lasting 4–12 months (RR: 5.76, 95% CI: 1.18–28.06) than those who were vaccinated (Table 3). Two other findings that were not statistically significant but of note included those who reported

TABLE 1. Descriptive, Clinical and Persistent COVID Symptom Characteristics, Pre-Delta Versus Delta and Beyond Variant Period (Through May 2022), Texas CARES Pediatric Population (n = 1813) Versus the Texas Weighted Population

	Pre-Delta Variant Period (n = 451)		Delta and Beyond Variant Period (n = 1362)	
Participant Characteristics	Sample Population*	Weighted Population†	Sample Population*	Weighted Population†
Age (years), mean (SD)	14.1 (3.7)	14.16 (3.69)	12.6 (3.7)	12.56 (3.65)
Age group, years, n (%)				
5–9	62 (13.7)	102 (23.7)	305 (22.4)	503 (36.4)
10–14	157 (34.8)	125 (29.0)	601 (44.1)	478 (34.6)
15–19	232 (51.4)	204 (47.3)	456 (33.5)	401 (29.0)
Sex, n (%)				
Female	230 (51.2)	223 (49.7)	685 (50.3)	664 (48.8)
Male	219 (48.8)	226 (50.3)	677 (49.7)	698 (51.2)
Ethnicity, n (%)				
Non-Hispanic White	293 (65.0)	140 (27.1)	954 (70.0)	457 (32.5)
Non-Hispanic Black	7 (1.6)	68 (13.2)	16 (1.2)	155 (11.0)
Hispanic	104 (23.1)	259 (50.2)	260 (19.1)	648 (46.1)
Asian	18 (4.0)	22 (4.3)	51 (3.7)	61 (4.3)
Other	29 (6.4)	27 (5.2)	81 (5.9)	85 (6.0)
Geographic location‡, n (%)				
Rural	16 (3.8)	44 (10.1)	79 (6.2)	218 (15.9)
Urban	407 (96.2)	365 (83.9)	1200 (93.8)	1076 (78.4)
Body mass index§				
Underweight	11 (2.6)		49 (3.8)	
Normal	268 (62.8)		833 (65.2)	
Overweight	69 (16.2)		210 (16.4)	
Obese	79 (18.5)		186 (14.6)	
COVID-19 diagnosis¶, n (%)	359 (79.6)		547 (40.2)	
Chronic disease, n (%)	105 (23.3)		242 (17.8)	
Persistent COVID symptoms‖				
No	415 (92.0)		1316 (96.6)	
4–12 weeks	10 (2.2)		17 (1.2)	
>12 weeks	26 (5.8)		29 (2.1)	

*$N_{missing}$ gender = 2; $N_{missing}$ geographic location = 28; $N_{missing}$ BMI = 101 for pre-Delta; $N_{missing}$ gender = 0; $N_{missing}$ geographic location = 83; $N_{missing}$ BMI = 293 for post-Delta.

†Based on latest census data, if available.

‡2010 census results for urban-rural ratio as reference (84.7%/15.3%).

§Standardized BMI categories are as follows: (1) underweight = <5th percentile; (2) healthy weight = 5th–85th percentile; (3) overweight = 85th–95th percentile and (4): obesity = >95th percentile.[26]

¶Self-reported positive diagnosis by either a doctor or a nasal/oral COVID-19 test.

‖National Institute for Health and Care Excellence.[28]

severe symptoms were more than 3 times at risk (RR: 3.59, 95% CI: 0.51–25.44) and those reporting at least 1 symptom with initial infection were 28% more at risk (RR: 1.28, 95% CI: 0.46–3.70) for reporting persistent COVID symptoms lasting 4–12 weeks versus those who reported mild-moderate symptoms, and those who reported no initial symptoms, respectively.

Results were similar when compared with the Texas CARES adult sample who reported persistent COVID symptoms for >12 weeks (n = 3620); all pediatric age groups were significantly less at risk for persistent COVID symptoms. Also similarly, those with severe symptoms with initial infection were over 3 and a half times at risk (RR: 3.60, 95% CI: 1.24–10.4) and those not vaccinated were 2.44 times at risk (RR: 2.44, 95% CI: 1.25–4.76) versus their respective counterparts. In fully adjusted models, those with unhealthy weight were 64% more likely (RR: 1.64, 95% CI: 0.96, 2.81, $P = 0.05$) to report persistent COVID symptoms for >12 weeks versus those with healthy weight (Table 3).

Coexistence of persistent symptom categories is presented in the UpSet plot in Figure 1A for those reporting persistent symptoms lasting 4–12 weeks and in Figure 1B for those reporting symptoms lasting >12 weeks. New loss of taste and/or smell was the most prevalent individual symptom reported for both groups and was also reported in combination with cough and brain fog/difficulty in thinking among both groups.

DISCUSSION

We report here one of the first population-based estimates of the prevalence of persistent COVID symptoms in children and adolescents in the United States, often called long COVID. Our findings show that 4.5% of the total sample reported persistent COVID symptoms beyond 4 weeks with more than twice the number reporting symptoms lasting >12 weeks (n = 58) versus 4–12 weeks (n = 27) and more than double did so during the pre-Delta (8.0%) versus Delta variant period and beyond (3.4%). Regardless of length, all those reporting long COVID symptoms were symptomatic upon initial SARS-CoV-2 infection. In general, all pediatric age groups were significantly less at risk for persistent COVID symptoms than adults in the same study. Those who (1) reported symptomatic initial infection; (2) severe symptoms; (3) not being vaccinated and (4) had obesity were at higher risk for reporting persistent COVID symptoms versus their counterparts, although some of the associations did not meet statistical significance. These findings contribute

TABLE 2. Long COVID Status 4–12 Weeks and >12 Weeks, by SARS-CoV-2 Antibody Status for Age, Symptom Characteristics, COVID-19 Test, Vaccine and Mental/Social Health Status (Total N = 1828)

	Persistent COVID Symptoms Lasting 4–12 weeks (n = 27)*			Persistent COVID Symptoms Lasting >12 weeks (n = 58)†			No Persistent COVID Symptoms (n = 1743)*†‡		
Participant Characteristics	Positive	Negative	*P*	Positive	Negative	*P*	Positive	Negative	*P*‖
Age									
Overall sample	26	1	1.000§	56	2	0.104¶	1631	112	0.095
5–9 years old, n (%)	2 (7.7)	0		5 (8.9)	1 (50.0)		343 (21.0)	19 (17.0)	
10–14 years old, n (%)	12 (46.2)	1 (100.0)		12 (21.4)	1 (50.0)		697 (42.7)	41 (36.6)	
15–19 years old, n (%)	12 (46.2)	0		39 (69.6)	0		591 (36.2)	52 (46.4)	
Symptom status, n (%)									
Symptomatic	14 (100.0)	1 (100.0)	—	40 (100)	1 (50.0)	0.048¶	641 (86.5)	90 (82.6)	0.269
Asymptomatic	0	0		0	1 (50.0)		100 (13.5)	19 (17.4)	
Symptom severity, n (%)									
Mild-moderate	14 (93.3)	1 (100.0)	1.000¶	34 (89.5)	2 (100.0)	1.000¶	737 (98.5)	108 (97.3)	0.339
Severe	1 (6.7)	0		4 (10.5)	0		11 (1.5)	3 (2.7)	
COVID-19 Dx, n (%)	15 (57.7)	1 (100.0)	1.000¶	40 (71.4)	2 (100.0)	1.000¶	751 (46.0)	112 (100.0)	<0.001
Vaccination status, n (%)									
Fully vaccinated	1 (4.3)	1 (100.0)	0.126§	10 (17.9)	1 (100.0)	—	410 (26.3)	52 (49.1)	<0.001
Partially vaccinated	1 (4.3)	0		0	0		129 (8.3)	12 (11.3)	
Not vaccinated	21 (91.3)	0		46 (82.1)	0		1022 (65.5)	42 (39.6)	
Social/mental health status, n (%)									
Not impacted	14 (70.0)	0	0.338§	30 (62.5)	0	0.042§	846 (61.7)	44 (46.8)	0.010
Mild-moderately impacted	5 (25.0)	1 (100.0)		16 (33.3)	1 (50.0)		483 (35.2)	44 (46.8)	
Severely impacted	1 (5.0)	0		2 (4.2)	1 (50.0)		43 (3.1)	6 (6.4)	

Dx indicates diagnosis.

— indicates quantity could not be calculated because of small sample size or empty cells.

*For those reporting symptoms lasting 4–12 weeks: $N_{missing}$ symptoms status = 12, $N_{missing}$ headache = 11, $N_{missing}$ fatigue = 11, $N_{missing}$ congestion or runny nose = 11, $N_{missing}$ fever or chills = 11, $N_{missing}$ cough = 11, $N_{missing}$ sore throat = 11, $N_{missing}$ muscle or body aches = 11, $N_{missing}$ new loss of taste or smell = 11, $N_{missing}$ shortness of breath or difficulty breathing = 11, $N_{missing}$ diarrhea = 11, $N_{missing}$ nausea or vomiting = 11, $N_{missing}$ symptom severity = 11, $N_{missing}$ vaccination status = 3, $N_{missing}$ social/mental health status = 6 for long COVID.

†For those reporting symptoms lasting >12 weeks: $N_{missing}$ symptoms status = 16, $N_{missing}$ headache = 17, $N_{missing}$ fatigue = 17, $N_{missing}$ congestion or runny nose = 17, $N_{missing}$ fever or chills = 17, $N_{missing}$ cough = 17, $N_{missing}$ sore throat = 17, $N_{missing}$ muscle or body aches = 17, $N_{missing}$ new loss of taste or smell = 17, $N_{missing}$ shortness of breath or difficulty breathing = 17, $N_{missing}$ diarrhea = 17, $N_{missing}$ nausea or vomiting = 17, $N_{missing}$ symptom severity = 18, $N_{missing}$ vaccination status = 1, $N_{missing}$ social/mental health status = 8 for long COVID.

‡$N_{missing}$ symptoms status = 893, $N_{missing}$ headache = 896, $N_{missing}$ fatigue = 896, $N_{missing}$ congestion or runny nose = 896, $N_{missing}$ fever or chills = 896, $N_{missing}$ cough = 896, $N_{missing}$ sore throat = 896, $N_{missing}$ muscle or body aches = 896, $N_{missing}$ new loss of taste or smell = 896, $N_{missing}$ shortness of breath or difficulty breathing = 896, $N_{missing}$ diarrhea = 896, $N_{missing}$ nausea or vomiting = 896, $N_{missing}$ symptom severity = 884, $N_{missing}$ vaccination status = 76, $N_{missing}$ social/mental health status = 277 for no long COVID.

§Fisher exact test for count data with simulated *P* value (based on 2000 replicates).

¶Fisher exact test for count data.

‖Pearson χ^2 test.

to a better understanding of the expected burden of long COVID disease in the pediatric population that was not hospitalized due to COVID-19 illness, and thus the pediatric healthcare resources that will be required.

Our overall prevalence estimate (4.5%) of persistent COVID symptoms findings in children and adolescents falls more toward the lower end of other studies that report prevalence estimates ranging from (1.8%–4%)[11,2] to >30%.[12] Our findings that children are less at risk for long COVID versus adults is similar to other recent studies. Specifically, a study that included 201 households (n = 507 participants, 56.4% children) in Italy showed children experienced long COVID months (77 days median follow-up post-SARS-CoV-2 diagnosis, interquartile range 47–169) after mild acute SARS-CoV-2 infection, but at less frequency and severity than co-habitant adults.[29] The authors note the importance of continued need for population-based studies, such as the study sample here, to further characterize long COVID in children and its impact on their families and society as a whole.

Results here are some of the first to report by variant time period (pre-Delta defined as before July 1, 2021) and to include a control group. Indeed, to date, most pediatric studies only have included a few hundred subjects; a recent meta-analysis reported the mean sample size of long COVID studies in pediatric patients being about 238 subjects.[30] Similarly, Zimmermann et al[10] found that of 14 studies reviewed, only 5 (36.7%) studies included control groups with other significant limitations including lack of clear inclusion criteria, heterogeneity between studies and selection bias due to low response rate.[8]

Although severe symptoms of COVID are relatively rare, persistent COVID symptoms have the potential to debilitate a child's day-to-day function and emotional well-being.[31] One study reported that 7 months post-initial COVID-19 (mild) illness, lung single-photon emission computed tomography and cardiopulmonary exercise test results showed pulmonary circulation dysfunction with possible peripheral microvascular and endothelial damage in a 14-year-old girl.[32] A multidisciplinary rehabilitation approach may be needed for those having more difficulty recovering from long COVID, offering age-specific coping strategies to target the distinct needs of children and adolescents. This includes optimizing daily cognitive functioning to facilitate academic performance as well as addressing mood and behavioral difficulties associated with persistent COVID symptom complications including anxiety and depression.[14,32]

Results here also showed that roughly a third of those reporting persistent COVID symptoms and those reporting no persistent symptoms reported their social/mental health status had been mildly/moderately impacted, while 6% of those who reported long symptoms lasting >12 weeks stated their mental/social health was severely impacted due to the pandemic. A systematic review that analyzed the impact of COVID-19 and past pandemics on child and adolescent mental health suggested this population is more likely to experience high rates of depression and anxiety during and after a pandemic.[8] Another national study reported 16 or more sick days (1205 [18.2%] vs. 2518 [11.6%]; $P < 0.0001$) and 16 or more days of school absence (695 [10.5%] vs. 1777 [8.2%]; $P < 0.0001$) among older adolescents with a positive SARS-CoV-2

TABLE 3. Risk of COVID Symptoms That Persist 4–12 Weeks and >12 Weeks in Children and Adolescents Versus Adults and by Variant, Weight and Symptom Status and Severity and Vaccine Status

	Symptoms Lasting 4–12 Weeks					Symptoms Lasting >12 Weeks				
Potential Risk Factors	Yes, N (%)*	No, N (%)*	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)†	*P*	Yes, N (%)*	No, N (%)*	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)†	*P*
Age group, years					<0.001†					<0.001†
5–9 years old	2 (0.1)	362 (1.4)	0.07 (0.02–0.27)	—		6 (0.2)	362 (1.4)	0.13 (0.06–0.28)	—	
10–14 years old	13 (0.6)	738 (2.8)	0.22 (0.13–0.37)	—		13 (0.4)	738 (2.8)	0.14 (0.08–0.23)	—	
15–19 years old	12 (0.5)	643 (2.4)	0.23 (0.13–0.40)	—		39 (1.1)	643 (2.4)	0.45 (0.33–0.61)	—	
20 years or older	2171 (98.8)	24,949 (93.5)	Reference			3620 (98.4)	24,949 (93.5)	Reference		
Age group, years					0.227†					<0.001†
5–9 years old	2 (7.4)	362 (20.8)	0.28 (0.06–1.23)	—		6 (10.3)	362 (20.8)	0.28 (0.12–0.65)	0.36 (0.15–0.87)	
10–14 years old	13 (48.1)	738 (42.3)	0.87 (0.40–1.90)	—		13 (22.4)	738 (42.3)	0.30 (0.16–0.55)	0.35 (0.18–0.66)	
15–19 years old	12 (44.4)	643 (36.9)	Reference	Reference		39 (67.2)	643 (36.9)	Reference	Reference	
Antibody serostatus					1.000‡					0.580‡
Positive	26 (96.3)	1631 (93.6)	0.89 (0.12–6.53)	—		56 (96.6)	1631 (93.6)	1.27 (0.32–0.51)	—	
Negative	1 (3.7)	112 (6.4)	Reference	Reference		2 (3.4	112 (6.4)	Reference	Reference	
SARS-CoV-2 variant					0.262†					<0.001§
Missing	0	12 (0.7)	0			2 (3.4)	12 (0.7)	2.34 (0.62–8.90)	2.96 (0.67–13.05)	
Post-Delta	17 (63.0)	1316 (76.0)	0.49 (0.23–1.07)	—		30 (51.7)	1316 (75.5)	0.37 (0.22–0.61)	0.64 (0.35–1.18)	
Pre-Delta	10 (37.0)	415 (24.0)	Reference	Reference		26 (44.8)	415 (23.8)	Reference	Reference	
Body mass index					0.937†					0.050§
Missing	1 (3.7)	110 (6.3)	0.51 (0.07–3.80)			1 (1.7)	110 (6.3)	0.31 (0.04–2.28)	0.46 (0.06–3.44)	
Unhealthy weight¶	7 (25.9)	514 (29.5)	0.77 (0.32–1.80)	—		25 (43.1)	514 (29.5)	1.62 (0.97–2.71)	1.64 (0.96–2.81)	
Healthy weight	19 (70.4)	1119 (64.2)	Reference	Reference		32 (55.2)	1119 (64.2)	Reference	Reference	
Symptom status					0.362†					0.004†
Missing	11 (40.7)	896 (51.4)	0.72 (0.25–2.07)			17 (29.3)	896 (51.4)	0.38 (0.20–0.74)	0.24 (0.04–1.60)	
>1 symptom	11 (40.7)	495 (28.4)	1.28 (0.46–3.70)	—		24 (41.4)	495 (28.4)	0.95 (0.52–1.74)	1.17 (0.60–2.25)	
0 or 1 symptom	5 (18.5)	352 (20.2)	Reference	Reference		17 (29.3)	352 (20.2)	Reference	Reference	
Symptom severity					0.141†					<0.001§
Missing	11 (40.7)	884 (50.7)	0.66 (0.31–1.43)			18 (31.0)	884 (50.7)	0.48 (0.27–0.83)	2.52 (0.43–14.73)	
Severe	1 (3.7)	14 (0.8)	3.59 (0.51–25.44)	—		4 (6.9)	14 (0.8)	5.30 (2.11–13.31)	3.60 (1.24–10.4)	
Mild-moderate	15 (55.6)	845 (48.5)	Reference	Reference		36 (62.1)	845 (48.5)	Reference	Reference	
Vaccination status					0.010†					0.019§
Missing	3 (11.1)	76 (4.4)	5.76 (1.18–28.06)			1 (1.7)	76 (4.4)	0.67 (0.09–5.09)	0.72 (0.1–5.75)	
Not vaccinated	21 (77.8)	1064 (61.0)	2.93 (0.88–9.81)	—		46 (79.3)	1064 (61.0)	2.12 (1.11–4.1)	2.44 (1.25–4.76)	
Vaccinated	3 (11.1)	603 (34.6)	Reference	Reference		11 (19.0)	603 (34.6)	Reference	Reference	

— indicates variable is not included in the model.

**P* value and adjusted relative risks calculated based on generalized linear mixed model results.

†Fisher exact test for count data with simulated *P* value (based on 2000 replicates) for those reporting symptoms lasting 4–12 weeks and Pearson χ^2 test for those reporting symptoms lasting >12 weeks.

‡Fisher exact test for count data for those reporting symptoms lasting 4–12 weeks and Fisher exact test for count data with simulated *P* value (based on 2000 replicates) for those reporting symptoms >12 weeks.

§Fisher exact test for count data.

¶BMI >85th percentile for age and sex.[25]

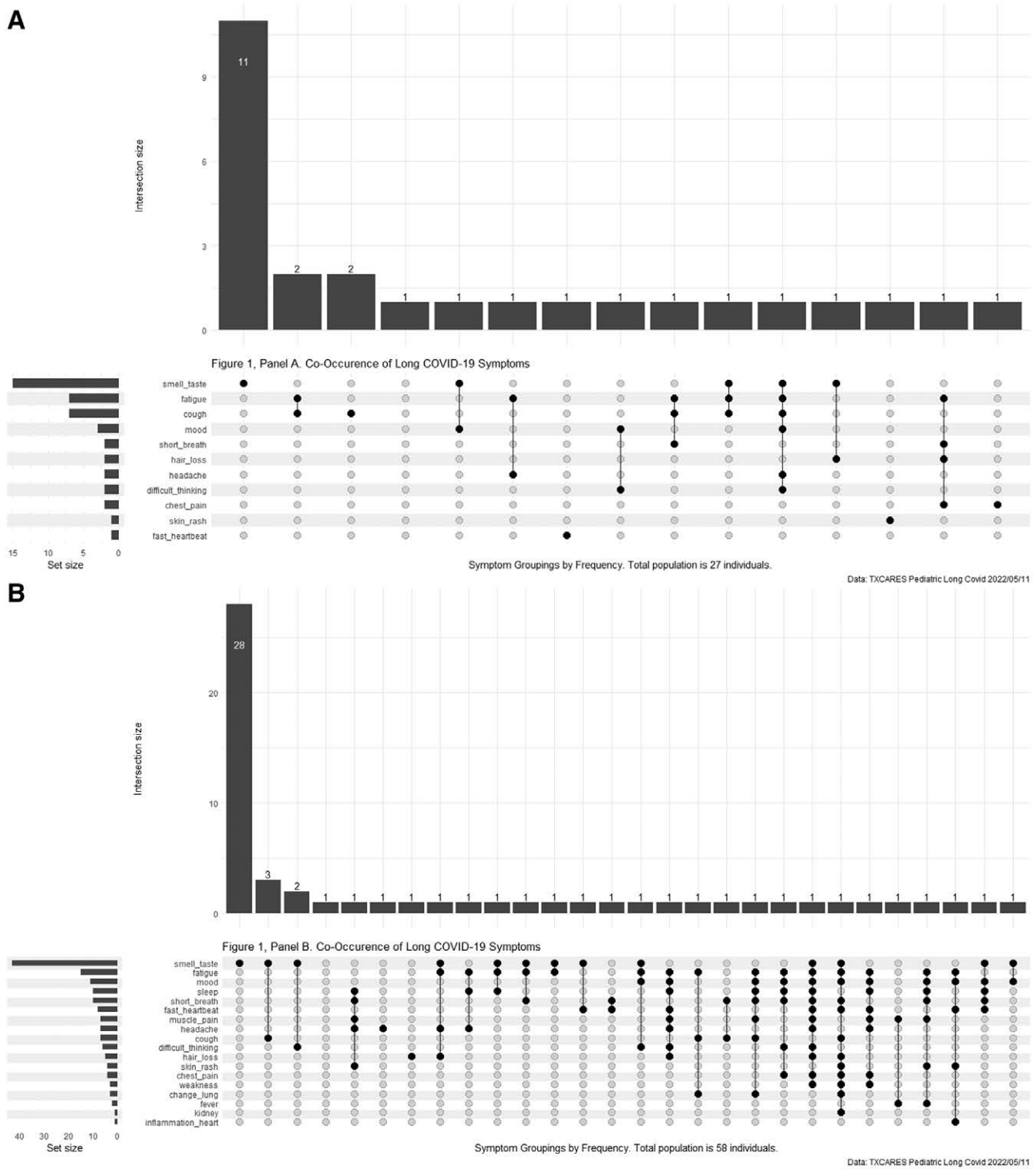

FIGURE 1. Co-Occurrence and individual long COVID-19 symptoms. A: UpSet plot representing the coexistence of persistent symptoms lasting for 4–12 months. The Y-axis values represent the number of participants who report experiencing an individual symptom or combination of symptoms. The X-axis represents the specific individual symptom or combination of symptoms. The lines below link multiple reported symptoms, which are indicated by the black circles. B: UpSet plot representing the coexistence of persistent symptoms lasting for >12 months. The Y-axis values represent the number of participants who report experiencing an individual symptom or combination of symptoms. The X-axis represents the specific individual symptom or combination of symptoms. The lines below link multiple reported symptoms, which are indicated by the black circles.

test.[33] While our results did not show mental health differences by persistent COVID symptom status, they highlight that well over 1 in 4 children have had some level of mental health impact during the pandemic. This may be compounded for those struggling with persistent COVID physical conditions as described here and suggest that not only clinical settings but schools and other community resources should be developed and be accessible to all families during COVID recovery. Interestingly, 3 participants reported persistent COVID symptoms but were seronegative. The challenge of persistent or long COVID conditions being attributable to actual infection or pandemic fatigue has been mentioned by others. Again, our study design helps disentangle this by providing seroprevalence data but also calls attention to youth who may need post-pandemic support but did not experience COVID-19 illness.[11]

Risk factors for persistent COVID symptoms continue to be an area of interest. Specifically, the association between childhood obesity and persistent COVID symptoms has yet to be assessed. Our findings show that youth with obesity may be more likely to report persistent COVID symptoms >12 weeks compared with those at a healthy weight. Similarly, a retrospective analysis in adult patients (n = 2839) found that moderate and severe obesity (BMI $\geq 35\ kg/m^2$) are associated with a greater risk of post-acute COVID-19.[34] These similar findings may be a result of elevated inflammation from excess adipose tissue but are in need of more research.

Limitations of the findings reported here should be noted. The first limitation is that all responses regarding persistent COVID symptoms were self-reported and thus subject to selection bias. Additionally, the definition of long COVID requires exclusion of alternative conditions, which is not allowable with a survey. Secondly, because the study design was based on nonrandom sampling of participants, unweighted analysis cannot provide precise estimates of seroprevalence by age group in the general Texas population. Population-level weights[35] were calculated based on the Texas population and thus may not be generalizable to other states or the United States in general; however, the diverse population mirrors that of the United States. The third limitation due to the sampling frame is another selection bias; that is, parents who suspected their child or an adult in the household may have been infected with SARS-CoV-2 may have been more likely to participate. However, over half of those with positive antibody status reported no symptoms during the pre-Delta time period and slightly less than half when Delta became the dominant variant and beyond. Finally, the power to detect significant predictors of reported symptoms lasting 4–12 weeks was very low and thus may be driving the insignificant results.

Strengths of the current study include the inclusion of a comparison/control group of those with no SARS-CoV-2 antibodies. Our study may not be as subject as others to selection and misclassification bias given the high proportion who were asymptomatic, regardless of serostatus. Another strength is our ability to examine a wide age range among children, the impact of initial disease symptom severity and pre-Delta versus Delta variants on the prevalence of persistent COVID symptoms.

CONCLUSIONS

Findings here show that nonhospitalized youth may also experience persistent COVID symptoms that last for at least several months. Risk factors include having severe symptoms with initial infection, not being vaccinated and having obesity. These findings have important implications to inform post-pandemic recovery as we learn more about those who are reporting chronic impacts of initial infections. In the case of the pediatric population, resources in both clinical and community/school settings can be developed to support this important subgroup of those infected with SARS-CoV-2, especially given the findings here that children who are experiencing persistent COVID symptoms may not have been hospitalized or experienced severe symptoms upon initial infection.

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