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Risk Factors for Multisystem Inflammatory Syndrome in Children: A Case-Control Investigation

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Abstract

Background: In a 2020 pilot case-control study using medical records, we reported that non-Hispanic Black children were more likely to develop multisystem inflammatory syndrome in children (MIS-C) after adjustment for sociodemographic factors and underlying medical conditions. Using structured interviews, we investigated patient, household, and community factors underlying MIS-C likelihood.

Methods: MIS-C case patients hospitalized in 2021 across 14 US pediatric hospitals were matched by age and site to outpatient controls testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within 3 months of the admission date. Caregiver interviews queried race/ethnicity, medical history, and household and potential community exposures 1 month before MIS-C hospitalization (case-patients) or after SARS-CoV-2 infection (controls). We calculated adjusted odds ratios (aOR) using mixed-effects multivariable logistic regression.

Results: Among 275 case patients and 496 controls, race/ethnicity, social vulnerability and patient or family history of autoimmune/rheumatologic disease were not associated with MIS-C. In previously healthy children, MIS-C was associated with a history of hospitalization for an infection [aOR: 4.8; 95% confidence interval (CI): 2.1–11.0]. Household crowding (aOR: 1.7; 95% CI: 1.2–2.6), large event attendance (aOR: 1.7; 95% CI: 1.3–2.1), school attendance with

limited masking (aOR: 2.6; 95% CI: 1.1–6.6), public transit use (aOR: 1.8; 95% CI: 1.4–2.4) and co-resident testing positive for SARS-CoV-2 (aOR: 2.2; 95% CI: 1.3–3.7) were associated with increased MIS-C likelihood, with risk increasing with the number of these factors.

Conclusions: From caregiver interviews, we clarify household and community exposures associated with MIS-C; however, we did not confirm prior associations between sociodemographic factors and MIS-C.

Keywords

children; coronavirus disease 2019 (COVID-19); multisystem inflammatory syndrome in children; SARS-CoV-2; risk factors

Multisystem inflammatory syndrome in children (MIS-C) is a severe hyperinflammatory condition occurring between 2 and 6 weeks after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1–5] Risk factors for MIS-C remain unclear. Certain racial and ethnic minority groups have been disproportionately represented in case counts of coronavirus disease 2019 (COVID-19) and MIS-C. It is unclear whether specific community and household risk factors underlie the increased risk of these groups in developing SARS-CoV-2-associated complications.[1,3,4,6–14] In a pilot case-control study among patients hospitalized in 2020, after adjustment for sociodemographic and medical history, we reported MIS-C to be more frequent among patients with non-Hispanic Black race/ethnicity compared with outpatient controls who were at risk for but did not develop MIS-C.[12] Our previously published pilot study captured data through medical record abstraction. However, race and ethnicity are most accurately ascertained through patient or caregiver reports,[15–17] as are specific community and household exposures.

MIS-C as a clinical syndrome has many features similar to Kawasaki disease.[18] It may also share pathophysiology with autoimmune diseases, such as systemic lupus erythematosus,[19,20] which can be associated with a family history of rheumatologic disease. Previous studies reporting increased autoantibody levels among children with MIS-C[20,21] support the need to investigate the potential association between a family history of underlying rheumatologic and autoimmune disease, and patient history of prior infections, atopy and immune deficiency.[22] Potential frequency of SARS-CoV-2 antigenic exposure may also be associated with MIS-C, as the SARS-CoV-2 spike protein is immunogenic.[23,24] In this case-control investigation using caregiver report, we evaluated associations of MIS-C with race/ethnicity, family history of rheumatologic and autoimmune disease, patient medical history and multiple individual-level household and community measures of potential SARS-CoV-2 exposure that may have occurred after infection.

METHODS

Study Design

For this case-control investigation, we conducted surveillance for children hospitalized and diagnosed with MIS-C at 14 US pediatric health centers within the Overcoming COVID-19 network between January 1 and December 31, 2021. Demographic characteristics, clinical history and household and community exposures were collected through parent/caregiver

interviews. Vaccine data among children who were vaccine-eligible were collected and verified with electronic medical records, state immunization information systems or COVID-19 vaccination cards.[25–27]

Ethics

This protocol was reviewed and approved by the Boston Children's Hospital Institutional Review Board (IRB), by participating sites, and by the US Centers for Disease Control and Prevention (CDC). The activity was conducted consistent with applicable federal law and CDC policy. This report conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for case-control studies.[28] Patient caregivers were provided the option to verbally decline to participate upon contact.

Population

Eligible MIS-C case-patients included children admitted to participating site hospitals meeting diagnostic criteria for MIS-C per the original 2020 CDC case definition,[29] with laboratory evidence of current or recent SARS-CoV-2 infection including real-time polymerase chain reaction (RT-PCR), antigen or antibody testing. Site-matched outpatient controls were identified by site investigators by screening outpatient medical records of SARS-CoV-2 testing centers, pediatric clinics or emergency departments affiliated with the case-patient hospital. Controls included children with positive RT-PCR, nucleic acid amplification test or antigen tests 3 months before or after the corresponding case-patients date of admission (Figure, Supplemental Digital Content 2, http://links.lww.com/INF/E981), and presumed to be at risk for developing MIS-C. Approximately two controls were frequency-matched to case-patients by category within a particular prespecified age group (0–4 years, 5–11 years, 12–15 years and 16–20 years) and by the site to promote equivalent age distributions and geographic representation between study arms.

Parent/caregiver interview

MIS-C hospital admission date among case-patients and positive SARS-CoV-2 test result date among controls were considered study index events. Because MIS-C typically occurs between 2 and 6 weeks after SARS-CoV-2 infection,[1–5] primary household and environmental exposures of interest were queried relative to 1 month before hospitalization among MIS-C case-patients, and 1 month after a SARS-CoV-2-positive test for outpatient controls. This was performed to evaluate potential exposures that may have occurred in the month following SARS-CoV-2 infection and to ensure control patients did not develop MIS-C. Caregivers of MIS-C patients were contacted (through 3 attempts) by telephone after discharge using the contact information available from the patient medical record or administration data or approached for an interview during their child's hospitalization for MIS-C if the patient was still hospitalized at the time of enrollment. Patients were ineligible to be included as controls if they were admitted to the hospital for potential COVID-19 or MIS-C illness between SARS-CoV-2 diagnosis and caregiver interview. With site approval, participants were offered a $25 gift card as compensation for their time.

The interview included caregiver-reported demographic factors, including age, sex, zip code and race/ethnicity. Patient medical history, including the reported history of autoimmune or

rheumatologic disease (such as Kawasaki disease, rheumatoid/juvenile idiopathic/psoriatic arthritis, inflammatory bowel syndrome, systemic lupus erythematosus and type 1 diabetes), prior history of hospitalization for an infection, primary immunodeficiency and other disorders were also collected. Household and community exposure data collected included (1) household crowding (defined as the total number of co-residents per household, divided by the total number of rooms, excluding the kitchen and bathrooms),[30] (2) attendance at an indoor event with ≥10 people with and without masking, (3) attendance at school or a daycare setting ≥2 days a week with and without masking, (4) use of public transportation, (5) presence of a household member who tested positive for SARS-CoV-2 infection and (6) history of repeated prior SARS-CoV-2 infections, as indicated by having had more than 1 positive SARS-CoV-2 viral test at least 1 month apart. The entire interview instrument is included in "Parent/patient interview instrument," Table, Supplemental Digital Content 3, http://links.lww.com/INF/E981.

Statistical Analysis

This investigation was powered a priori to detect an odds ratio (OR) of 1.95 given an exposure prevalence among controls of 10%, with 250 case-patients and 500 controls. Analyses were considered exploratory; therefore, no adjustments for multiple comparisons were performed. Continuous variables, including age and the CDC's social vulnerability index (SVI),[31] were compared between study arms using Wilcoxon rank-sum tests for nonpara-metric comparison of medians. For comparison of frequencies of binomial and categorical variables, Mantel-Haenszel χ tests or Fisher's exact tests were used, as appropriate. A kappa (κ) test was used among case-patients to assess agreement between caregiver-reported race/ethnicity compared with race/ethnicity obtained from medical records.

The association between risk factors of interest and MIS-C was evaluated through mixed effects multivariable logistic regression, including hospital site as a random effect to account for between-site heterogeneity and any residual confounding by the site. Plausible relationships between covariates and exposures and disease were plotted using directed acyclic graphs[32,33] before assessing multicollinearity of potential binary and categorical covariates using tetrachoric or polychoric correlation coefficients, respectively, given the propensity of Pearson correlation coefficients to bias correlations between ordinal and binary variables towards zero,[34] and variance inflation factors.[35] After removing collinear variables, factors were retained in multivariable logistic regression models if their removal altered the full model effect estimate by ≥10%. Potential interactions were identified by variable reduction if they altered the OR point estimate by >35% or changed the directionality of association; interaction terms were then added and retained if they were significant ($\alpha = 0.10$).[36] Interactions identified through multivariable models were further explored through stratified analyses. Data analysis was performed in SAS version 9.4 (SAS Institute, Cary, NC) and R version 1.4.1717.

RESULTS

From 565 potentially eligible MIS-C case-patients and 2269 potentially eligible outpatient SARS-CoV-2-positive controls, 275 enrolled case-patients and 496 enrolled controls were included in this analysis (Fig. 1). The 275 enrolled MIS-C case-patients were like the 290 non-enrolled MIS-C case-patients for age, sex, race and ethnicity, SVI and disease severity (Table, Supplemental Digital Content 4, http://links.lww.com/INF/E981). Between 8 and 45 MIS-C case-patients were enrolled across each of the 14 US pediatric hospitals (Table, Supplemental Digital Content 5, http://links.lww.com/INF/E981). Case-patients and controls were well-matched on the date of hospital admission or the date of a positive test, and while all case-patients were admitted in 2021, 44% of patients were identified during the first 3 months of the year.

Descriptive analyses indicated that MIS-C case-patients and controls were well-balanced on sex, age and census region (Table 1). The most common age group among MIS-C case patients was 5–11 years, reflecting the population distribution of previously reported CDC national passive surveillance data for MIS-C.[37,38] Among MIS-C case-patients, there was moderate agreement in race/ethnicity reported from caregivers compared with the medical record ($\kappa = 0.70$; $P < 0.001$); however, caregiver-reported race/ethnicity resulted in the resolution of 26 of 27 patients with unknown race/ethnicity data from case-patient medical records. Additionally, 12 additional non-Hispanic Black and 10 additional Hispanic children were identified through caregiver reports relative to information abstracted from the medical record (Figure, Supplemental Digital Content 6, http://links.lww.com/INF/E981). Race, ethnicity and SVI were balanced across both study arms, indicating no association with MIS-C in this analysis.

Previous history of underlying medical conditions (11.6% vs. 21.0%), including a history of recurrent infections[39,40] (5.8% vs. 10.9%), occurred more frequently in controls. Family history of rheumatologic or autoimmune disease was similar in MIS-C case-patients and controls (33.8% and 36.1%, respectively) (Table 1); no MIS-C case-patients had a medical history of a rheumatologic or autoimmune disorder. Over 85% of patients were not eligible for vaccination at the time of their hospitalization, and the sample size was not sufficient to independently evaluate the association between vaccination and progression to MIS-C after infection (Table 1).

Analysis of the collinearity of household and community exposures variables is shown in Table, Supplemental Digital Content 7, http://links.lww.com/INF/E981. After the removal of collinear variables, models were adjusted for sex, race/ethnicity, presence of ≥1 underlying medical condition, history of >1 prior SARS-CoV-2 infection and additional model-specific confounders, as specified in Table, Supplemental Digital Content 8, http://links.lww.com/INF/E981. Results of the final multivariable analyses are shown in Fig. 2. The likelihood of MIS-C was positively associated with caregiver reports of in-person school attendance ≥2 days per week with little to no mask-wearing [adjusted odds ratio (aOR) = 2.6; (95% CI: 1.1–6.6)] or attending a large (≥10 people) event [aOR: 1.5; (95% CI: 1.2—1.9)], including attending a large indoor event with little to no masking [aOR: 2.3; (95% CI: 1.5—3.7)]. MIS-C was also more likely among children who used public

transportation [aOR: 1.8; (95% CI: 1.4—2.4)]. Household factors associated with MIS-C included household crowding, defined as households with >1 resident per room [aOR: 1.7; (95% CI: 1.2—2.6)], and having a household member test positive for SARS-CoV-2 [aOR: 2.2; (95% CI: 1.3—3.7)]. Household residence type was not associated with MIS-C. Controls were more likely to have a caregiver-reported history of >1 prior SARS-CoV-2 infection [aOR: 0.4 (95% CI: 0.2—0.7)], which was asked as whether the child had tested positive more than once, with at least 1 month between tests. Hispanic/Latino children [aOR: 0.70; (95% CI: 0.5—0.9)] were likewise less likely to develop MIS-C compared with non-Hispanic White children (Fig. 2), and this association remained after analyzing separately by both race and ethnicity (Table, Supplemental Digital Content 9, http://links.lww.com/INF/E981). The presence of underlying health conditions was more common in controls (Fig. 2), which could influence SARS-CoV-2 testing decisions and increase its frequency. However, the proportion of case-patients and controls with a history of having tested positive more than once, at least 1 month apart who had underlying conditions, did not significantly differ (Material, Supplemental Digital Content 10, http://links.lww.com/INF/E981). Previous history of hospitalization (>24 hours) for any infection was more likely among MIS-C case-patients [aOR: 2.7; (95% CI: 1.0–7.3)]; however, this association was significant only among children without underlying health conditions [aOR: 4.8; (95% CI: 2.1–11.0)] (Fig. 2).

The association of increased likelihood of MIS-C increased with more caregiver-reported potential exposures. Compared with children with no high-risk potential exposures, defined as household or community exposures significantly associated with increased MIS-C likelihood (Fig. 2), relative MIS-C likelihood increased serially among children with two exposures [aOR: 3.1; (95% CI: 1.9—5.0)], 3 exposures [aOR: 5.8; (95% CI: 3.2—10.5)] and 4 exposures [aOR: 13.8 (95% CI: 3.3—56.9)] (Table 2).

DISCUSSION

This 2021 investigation of MIS-C patients and SARS-CoV-2-positive outpatients at risk for MIS-C, using caregiver-reported demographic characteristics, did not confirm previously described disparities in MIS-C likelihood after infection by race, ethnicity or SVI. Our results suggest that patient and family medical history of underlying rheumatologic or autoimmune disease, including prior history of Kawasaki disease, are not independent risk factors for developing MIS-C after SARS-CoV-2 infection. Caregiver reports of factors related to the increased potential for household and community exposures to SARS-CoV-2 were associated with a higher likelihood of developing MIS-C compared with controls with SARS-CoV-2 infections who did not develop MIS-C, and this risk increased with the number of potential reported exposures. History of a prior hospitalization for at least 24 hours for infection was higher among children who developed MIS-C and who did not have underlying health conditions compared with controls that were at risk for developing MIS-C, however, this report was overall infrequent.

We did not confirm the results of our pilot study of patients presenting with MIS-C in 2020, which indicated that non-Hispanic Black children had higher odds of developing MIS-C after SARS-CoV-2 infection compared with non-Hispanic White children after adjustment

for sociodemographic and underlying health factors.[12] While there was some disagreement between the race reported in the medical record and by caregiver report in 2021, it was not as large as anticipated, making it less likely that using chart abstraction in 2020 accounted for the discrepancy in findings.[12] This finding is consistent with US CDC MIS-C national surveillance data, reporting a decrease in MIS-C diagnoses among Black relative to White children over time.[37,38] Consistent with prior reports, MIS-C case-patients tend to be otherwise healthy, with fewer underlying conditions than pediatric patients presenting with COVID-19;[1,4,5,37,41–45] however, this finding does not preclude previous hospitalization (≥24 hours) for an infection, which was more likely among MIS-C case-patients, for whom the odds of this hospitalization history were significantly higher specifically among children without any underlying condition. Our investigation also demonstrated that parent-reported patient history of previous positive viral tests at least 1 month apart was less likely among MIS-C case-patients. We are uncertain why controls were more likely to report a prior episode of SARS-CoV-2 infection. This finding did not differ by prior health status; therefore, it is unlikely that it was due to increased testing of patients with underlying conditions. Although prior infection could possibly confer protection against MIS-C, these patients did not undergo systematic serial testing for SARS-CoV-2. A separate evaluation of vaccine impact on clinical progression to MIS-C was not possible, given that the majority of children enrolled were not eligible for vaccination at the time of their illness.

Race, ethnicity and aggregate measures of community-level socio-demographic factors, such as the CDC's SVI,[31] may not fully account for heterogeneity between individual- or household-level risk factors.[46] We therefore also explored caregiver-reported household and community characteristics potentially associated with frequent or intense viral exposures during the MIS-C at-risk period (the month following SARS-CoV-2 infection) and found that several caregiver-reported exposures were independently associated with MIS-C. Although this was exploratory, and actual SARS-CoV-2 exposures were not possible to measure, the findings were supported by an increased MIS-C likelihood with each additional caregiver-reported exposure factor. Reported masking behaviors were associated with a decreased likelihood of MIS-C in this population of children who all had laboratory evidence of SARS-CoV-2 infection. While masking has been clearly shown to reduce the risk of SARS-CoV-2 infection,[47–50] school attendance ≥2 days per week was not associated with increased likelihood for MIS-C, but school attendance with reported little to no masking was. It is not possible to determine whether repeated exposures to SARS-CoV-2 or other factors in the child's environment, may increase the risk of MIS-C.

This study's strengths include the inclusion of a well-matched control group of at-risk SARS-CoV-2-positive outpatients and caregiver-reported demographic, clinical and household-and community characteristics. Our study referenced caregiver-reported race and ethnicity captured through the interview, a more accurate method for ascertainment of race and ethnicity compared with medical records[15–17] and accounted for key risk periods of exposure (eg, the month before hospitalization for MIS-C patients and the month after infection for outpatient SARS-CoV-2-positive controls). Our study, however, has several limitations. First, findings on household and community exposures are exploratory due to concerns of recall bias. For most patients, the time from index event to interview exceeded 150 days, which may affect the reliability of self-reported behaviors related specifically

to community exposures and mask-wearing. Second, unmeasured residual confounding is possible, such that concurrent infections, community factors or reported behaviors might represent factors that were not included in the analysis or measured in the study. Third, it was necessary to query exposures in the month before hospitalization for case-patients and the month after infection for controls to capture exposures during the at-risk period for MIS-C development. Although this may have introduced social desirability bias, particularly among caregivers of control outpatients disinclined to report that their child had attended a large event or school shortly after testing positive for SARS-CoV-2, caregivers of children with MIS-C were also likely aware of its association with SARS-CoV-2 exposure. Finally, viral sequencing results were not available to assess the differential impact of variant distribution by time and geographic region, but case-patients and controls were matched within a 3-month period, with index events occurring during periods of pre-Delta and Delta variant predominance. For unclear reasons, MIS-C incidence among those with SARS-CoV-2 infection has declined during the period of Omicron variant predominance.[51,52]

CONCLUSIONS

In this investigation of potential risk factors for developing MIS-C, we found that race, ethnicity, SVI and family history of rheumatologic or autoimmune disease were not associated during the second year of the COVID-19 pandemic. Previously healthy children with a history of hospitalization for infection were more likely to later develop MIS-C. Household and community exposures potentially reflective of repeated or high viral exposures in the month after SARS-CoV-2 infection were each independently associated with higher MIS-C likelihood among a population comprised entirely of children with SARS-CoV-2 infection. These associations may inform future investigations; in addition, our robust identification of factors that are not associated with MIS-C also informs future studies on MIS-C risk and pathophysiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Overcoming COVID-19 Investigators: See Supplemental Digital Content 1 http://links.lww.com/INF/E981 for list of collaborators.

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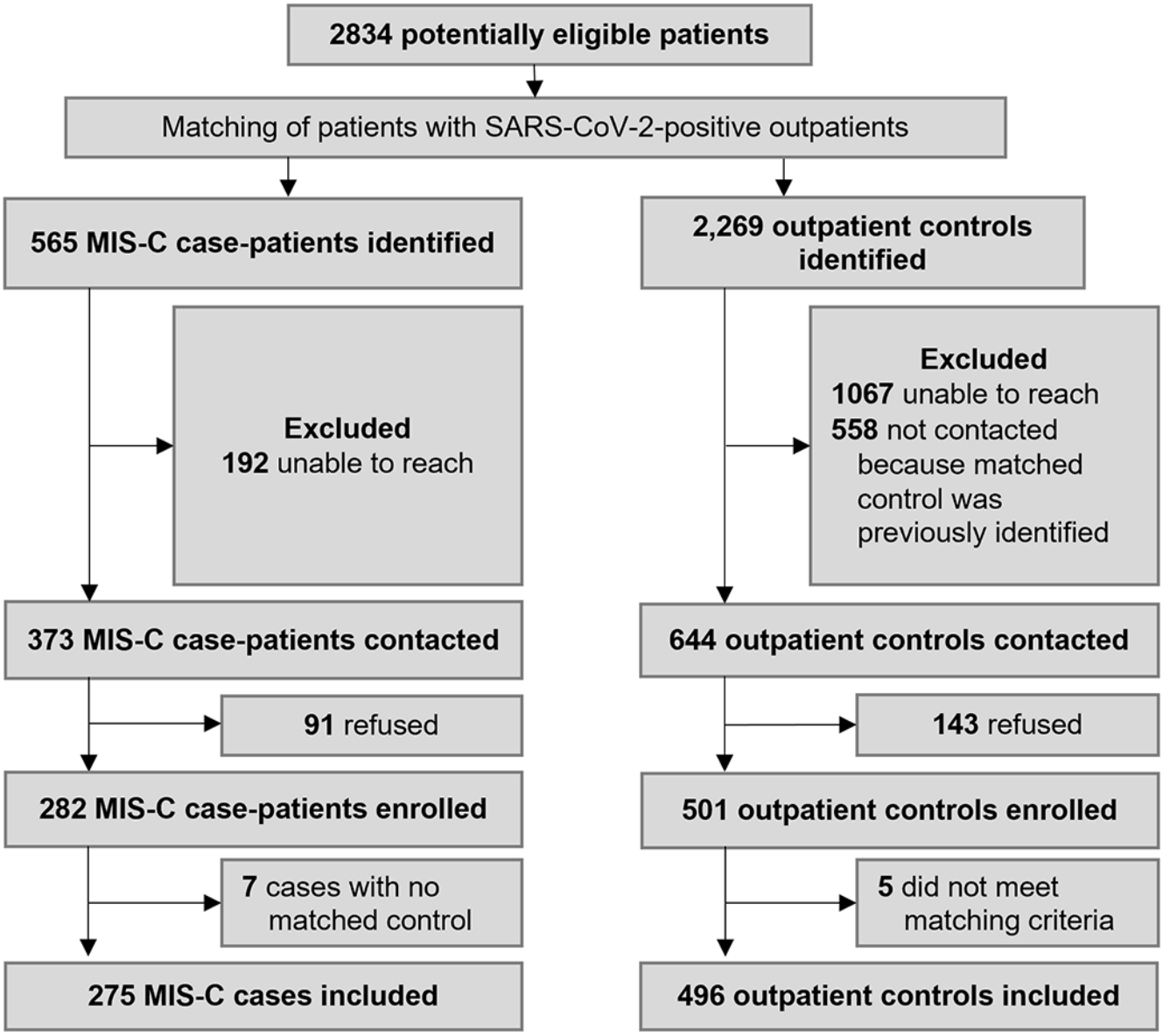

FIGURE 1.

Flow diagram for enrollment of case-patients and controls – Overcoming COVID-19 case-control study, January 1–December 31, 2021.

Characteristic	Cases No. (%) N=275	Controls No. (%) N=496	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Race/ethnicity				
Black, non-Hispanic	92/275 (33.5)	141/496 (28.4)	1.27 (0.89-1.80)	1.13 (0.76-1.66)
Hispanic/Latino of any race	42/275 (15.3)	105/496 (21.2)	0.78 (0.51-1.19)	0.70 (0.52-0.93)
Multiracial/Other/Unk	33/275 (12.0)	40/496 (8.1)	1.60 (0.96-2.69)	1.41 (0.81-2.45)
White, non-Hispanic	108/275 (39.3)	210/496 (42.3)	REF	REF
Household member work status				
Worked outside of the home	204/275 (74.2)	342/496 (70.0)	1.29 (0.93-1.80)	1.19 (0.85-1.66)
Worked in healthcare facility	55/275 (20.0)	88/496 (17.7)	1.16 (0.80-1.69)	1.04 (0.79-1.54)
Household and community exposures				
Divides time between >1 home	55/274 (20.1)	93/495 (18.8)	1.09 (0.75-1.57)	1.17 (0.81-1.69)
Household crowding	103/274 (37.6)	143/496 (28.8)	1.49 (1.09-2.03)	1.73 (1.16-2.56)
Attendance at large event	106/269 (39.4)	129/489 (26.4)	1.77 (1.28-2.44)	1.65 (1.32-2.07)
Held indoors	84/268 (31.3)	106/487 (21.8)	1.57 (1.12-2.21)	1.51 (1.20-1.92)
Limited masking	36/263 (13.7)	34/485 (7.3)	2.10 (1.28-3.45)	2.32 (1.47-3.66)
Public transportation	87/275 (31.6)	105/496 (21.2)	1.72 (1.24-2.40)	1.79 (1.37-2.35)
In-person school	172/275 (62.5)	283/493 (57.4)	1.24 (0.92-1.68)	1.09 (0.83-1.42)
Limited masking	20/259 (7.7)	17/476 (3.6)	2.27 (1.17-4.42)	2.63 (1.05-6.60)
Household member tested positive	143/275 (52.0)	169/496 (34.2)	2.08 (1.54-2.81)	2.17 (1.27-3.70)
Relevant clinical history				
History of >1 prior SARS-CoV-2 infection	15/275 (5.5)	67/496 (13.5)	0.37 (0.21-0.66)	0.41 (0.23-0.71)
History of hospitalization for an infection	30/275 (10.9)	24/496 (4.8)	2.41 (1.38-4.21)	2.74 (1.03-7.31)
With any underlying condition	6/32 (18.8)	15/104 (14.4)	1.37 (0.48-3.88)	1.68 (0.33-8.51)
Without any underlying condition	24/243 (9.9)	9/392 (2.3)	4.67 (2.13-10.21)	4.78 (2.08-10.97)
Residence type				
Apartment of condominium	43/273 (15.8)	92/488 (18.9)	0.80 (0.53-1.19)	0.97 (0.71-1.34)
Multi-family	12/273 (4.4)	25/488 (5.1)	0.82 (0.40-1.66)	0.73 (0.35-1.49)
Single family	218/273 (79.9)	371/488 (76.0)	REF	REF

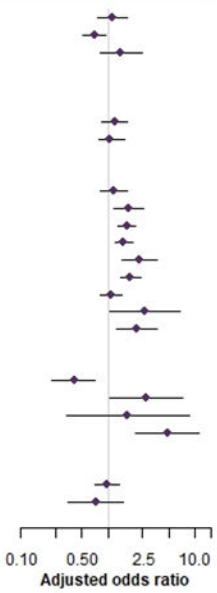

FIGURE 2.

Unadjusted and adjusted odds ratios reflecting the relative likelihood of exposure in the 1 month before hospitalization (for MIS-C case-patients) and 1 month after a positive SARS-CoV-2 viral test (for outpatient controls) – Overcoming COVID-19 case-control study, January 1–December 31, 2021. MIS-C indicates multisystem inflammatory syndrome in children; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1.

Distribution of self-reported demographic characteristics and patient and family medical history among MIS-C case patients and outpatient controls with SARS-CoV-2 infection.

Characteristic	Participants, No., %, (95% CI[c])		
	Case-patients (N=275)	Controls (N=496)	*P*-value[c]
Sex	**n (%)**	**n (%)**	
Male	172 (62.5)	281 (56.7)	0.11
Age			
0–4 years	55 (20.0)	99 (20.0)	0.96
5–11 years	136 (49.5)	239 (48.2)	
12–15 years	62 (22.5)	113 (22.8)	
16-20 years	22 (8.0)	45 (9.1)	
Race and ethnicity [a]			
Non-Hispanic Black	92 (33.5)	141 (28.4)	0.05
Hispanic/Latino of any race (except NHPI/AIAN)	42 (15.3)	105 (21.2)	
Non-Hispanic White	108 (39.3)	210 (42.3)	
Non-Hispanic other, multiracial, or unknown	33 (12.0)	40 (8.1)	
Census region [b]			
Region 1: Northeast	54 (19.6)	107 (21.6)	0.86
Region 2: Midwest	62 (22.5)	101 (20.4)	
Region 3: South	121 (44.0)	226 (45.6)	
Region 4: West	38 (13.8)	62 (12.5)	
Social vulnerability index			
Mean (SD)	0.48 (0.17)	0.48 (0.17)	0.98
Median (IQR)	0.49 (0.35-0.60)	0.46 (0.35-0.62)	0.97
Patient and family medical history			
Any underlying medical condition	32 (11.6)	104 (21.0)	0.001
Asthma	17 (6.2)	50 (10.1)	0.07
History of recurrent infections	16 (5.8)	54 (10.9)	0.02
History of hospitalization (for more than 24 hours) for an infection	30 (10.9)	24 (4.8)	0.002
Child prescribed Epi-Pen or other epinephrine autoinjector	11 (4.0)	37 (7.5)	0.06
Eczema	26 (9.5)	70 (14.1)	0.06
Family history of autoimmune or rheumatologic disease	93 (33.8)	179 (36.1)	0.53
Rheumatoid / juvenile idiopathic / psoriatic arthritis	35 (12.7)	86 (17.3)	0.09
Inflammatory bowel disease	16 (5.8)	41 (8.3)	0.21
Systemic lupus erythematosus	18 (6.5)	18 (3.6)	0.07
Type 1 diabetes	37 (13.5)	56 (11.3)	0.38
Other autoimmune or rheumatologic disease	17 (6.2)	42 (8.5)	0.25
Vaccine-eligible	46 (16.7)	66 (13.3)	0.20

Characteristic	Participants, No., %, (95% CI[C])		
	Case-patients (N=275)	Controls (N=496)	*P*-value[C]
Fully vaccinated (2 doses at least 14 days prior to hospitalization or positive COVID-19 test)	2 (4.3)	4 (6.1)	0.56*
Partially vaccinated	2 (4.3)	5 (7.6)	
Unvaccinated	40 (86.9)	56 (84.8)	
First dose within 14 days of hospitalization	2 (4.3)	1 (1.5)	

[a]Patients who were NH/PI, AI/AN, and Asian were grouped together into the “non-Hispanic other, multiracial, or unknown” due to limited sample size. One White patient and one Black patient with unknown ethnicity were grouped into the non-Hispanic White and non-Hispanic Black groups, respectively.

[b]Patients representing census regions were enrolled by site, as follows: Region 1 (Northeast): Massachusetts, Pennsylvania; Region 2 (Midwest): Indiana, Iowa, Ohio; Region 3 (South): Arkansas, Louisiana, Mississippi, Texas, Tennessee; Region 4 (West): California, Colorado.

[c]P-values calculated by Cochran Mantel Haenszel chi-square unless otherwise noted by an asterisk (*), reflecting p-values calculated through Fisher’s exact test.

Table 2.

Association of the sum of caregiver-reported household and community exposures associated with MIS-C likelihood.

Total high-risk exposures*	No./Total cases (%) N=275	No./Total controls (%) N=496	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
1	91 (33.1)	216 (43.5)	1.57 (1.00 - 2.47)	1.54 (0.97 - 2.44)
2	91 (33.1)	115 (23.2)	2.96 (1.85 - 4.72)	3.09 (1.91 - 5.01)
3	50 (18.2)	35 (7.1)	5.34 (3.00 - 9.48)	5.75 (3.17 – 10.45)
4	9 (3.3)	3 (0.6)	11.21 (2.88 - 43.68)	13.76 (3.33 - 56.86)
0	34 (12.4)	127 (25.6)	REF	REF

[a]High risk caregiver-reported exposures within the month before hospitalization (for case-patients) or after a positive SARS-CoV-2 test (for controls) were those that were found to be independently associated with higher MIS-C likelihood. These exposures included household crowding (>1 person per room within the child's household), attendance at a large event (gathering with ≥10 people), use of public transit, in-person schooling with limited masking, and having a household member test positive for SARS-CoV-2.