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Original Article

Association of Varying Clinical Manifestations and Positive Anti–SARS-CoV-2 IgG Antibodies: A Cross-Sectional Observational Study

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What's already known about this topic? Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces variable anti–SARS-CoV-2 IgG antibody responses. Clinical predictors of anti–SARS-CoV-2 IgG antibody responses are not fully understood.

What does this study add to our knowledge? Prolonged fever, anosmia, and receiving supplemental oxygen therapy and more severe disease phenotypes had strongest associations with positive IgG antibodies to the SARS-CoV-2 nucleocapsid protein.

How does this study impact current management guidelines? These symptom patterns can help predict the likelihood of having positive antibodies to SARS-CoV-2, and potentially guide occupational and clinical recommendations regarding vaccination and social distancing requirements.

BACKGROUND: The complex relationship between clinical manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and individual immune responses is not fully elucidated.

OBJECTIVE: To examine phenotypes of symptomatology and their relationship with positive anti–SARS-CoV-2 IgG antibody responses.

METHODS: An observational study was performed of adults (≥18 years) from 5 US states. Participants completed an electronic survey and underwent testing to anti–SARS-CoV-2 nucleocapsid protein IgG antibody between May and July 2020. Latent class analysis was used to identify characteristic symptom clusters.

RESULTS: Overall, 9507 adults (mean age, 39.6 ± 15.0 years) completed the survey; 6665 (70.1%) underwent antibody testing for anti–SARS-CoV-2 IgG. Positive SARS-CoV-2 antibodies were associated with self-reported positive SARS-CoV-2 nasal swab result (bivariable logistic regression; odds ratio [95% CI], 5.98 [4.83-7.41]), household with 6 or more members (1.27 [1.14-1.41]) and sick contact (3.65 [3.19-4.17]), and older age

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Abbreviations used
COVID-19- Coronavirus disease 2019
LCA- Latent class analysis
OR- Odds ratio
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

(50-69 years: 1.55 [1.37-1.76]; ≥70 years: 1.52 [1.16-1.99]), but inversely associated with female sex (0.61 [0.55-0.68]). Latent class analysis revealed 8 latent classes of symptoms. Latent classes 1 (all symptoms) and 4 (fever, cough, muscle ache, anosmia, dysgeusia, and headache) were associated with the highest proportion (62.0% and 57.4%) of positive antibodies, whereas classes 6 (fever, cough, muscle ache, headache) and 8 (anosmia, dysgeusia) had intermediate proportions (48.2% and 40.5%), and classes 3 (headache, diarrhea, stomach pain) and 7 (no symptoms) had the lowest proportion (7.8% and 8.5%) of positive antibodies. CONCLUSIONS: SARS-CoV-2 infections manifest with substantial diversity of symptoms, which are associated with variable anti−SARS-CoV-2 IgG antibody responses. Prolonged fever, anosmia, and receiving supplemental oxygen therapy had strongest associations with positive SARS-CoV-2 IgG. **(J Allergy Clin Immunol Pract 2021;9:3331-8)**

Key words: *COVID; Symptoms; Phenotype; Convalescent; Seroprevalence; Infection*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces variable humoral immune responses. Although most patients with coronavirus disease 2019 (COVID-19) develop SARS-CoV-2 IgA, IgM, and IgG antibodies over days and weeks following infection, target antigens and quantitative titers can vary.[1] The importance of antibody titers was demonstrated in 2 recent studies. One study showed an inverse correlation between IgG levels and persistence of viral shedding.[2] Another study showed a dose-dependent relationship between titers of anti−SARS-CoV-2 spike-protein IgG in transfused convalescent plasma and patient survival in COVID-19.[3] Assay- and antibody-dependent factors may impact antibody measurements and their use in determining individual immunity or population-level seroprevalence.[4,5] Importantly, such levels may also correlate with patient characteristics such as age and severity of illness in hospitalized patients.[2,6]

Little is known about the clinical and demographic predictors of positive anti−SARS-CoV-2 IgG antibody responses in patients with mild SARS-CoV-2 infections. We hypothesize that age, sex, and symptom severity among other factors impact the strength of anti−SARS-CoV-2 nucleocapsid protein IgG antibody response. In addition, symptoms of COVID-19 exhibit substantial variation.[7,8] The significance of such variation is unclear, particularly as it relates to variation in anti−SARS-CoV-2 IgG antibody responses. We additionally hypothesize that specific phenotypes of SARS-CoV-2 symptoms are predictors of IgG antibody responses to SARS-CoV-2 nucleocapsid protein. In this large-scale study, we examine the diversity of SARS-CoV-2 symptomatology and its relationship to IgG antibody responses in a convalesced population with a high SARS-CoV-2 seroprevalence.

METHODS

Study design

The study involved a 2-stage sampling design as previously described.[9] Stage 1 was designed to determine the self-reported symptoms and outcomes of SARS-CoV-2 in adults. Subjects were recruited by local not-for-profit and social service organizations within orthodox Jewish communities across 5 states (California, Connecticut, Michigan, New Jersey, and New York) between May 13 and July 6, 2020. A cross-sectional survey invitation was sent to adults; 12,626 individuals began the survey process, with 9,507 adults completing the survey (completion rate, 75.4%). In stage 2, a subset of 6665 adults (70.1% response rate) had antibody testing performed shortly after completing the survey. Electronic informed consent was taken and disclosure of the study purpose was done before beginning the survey. The study was open to all participants and did not require participants to have SARS-CoV-2 symptoms or exposures to participate. The study was approved by IntegReview institutional review board.

Survey

The survey was developed to determine the most common symptoms and outcomes of SARS-CoV-2 (see this article's Online Repository at www.jaci-inpractice.org). The survey included 81 data points including questions about patient demographics, contacts with other Covid-19−infected individuals in the household, symptoms of SARS-CoV-2, whether they tested positive for SARS-CoV-2 by nasal swab (yes/no), and required oxygen for SARS-CoV-2 throughout their illness. The survey was administered via the Health Insurance Portability and Accountability Act-compliant and secure Research Data Capture software.

Antibody measurement

Anti−SARS-CoV-2 antibody measurements were performed at the Mayo Clinic Laboratory (Rochester, Minn) using the Epitope Diagnostics ELISA (San Diego, Calif), established and used for clinical reporting of qualitative test for detection of IgM or IgG antibodies to the nucleocapsid protein from SARS-CoV-2. For the purposes of this study, IgG results were reported as described previously, with index value thresholds of greater than or equal to 1.21, less than or equal to 1.01, and 1.01 to 1.20 for positive, negative, and indeterminate results.[10]

Data analysis

Baseline characteristics were determined and summary statistics were estimated. Frequency and proportion of SARS-CoV-2 symptoms were estimated overall and in those with positive SARS-CoV-2 antibodies.

Latent class analysis (LCA) was used to examine phenotypical patterns of SARS-CoV-2 symptoms. LCA uses observed categorical or binary data to identify patterns, or latent classes. Conditional probabilities were estimated using maximum likelihood to characterize the latent classes by indicating the chance that a member would give a certain response (yes/no) for the specific symptom. Conditional probability plots are presented, where probabilities closer to 0 or 1 indicate lower or higher chances, respectively. LCA regression models examine the differential effects of individual

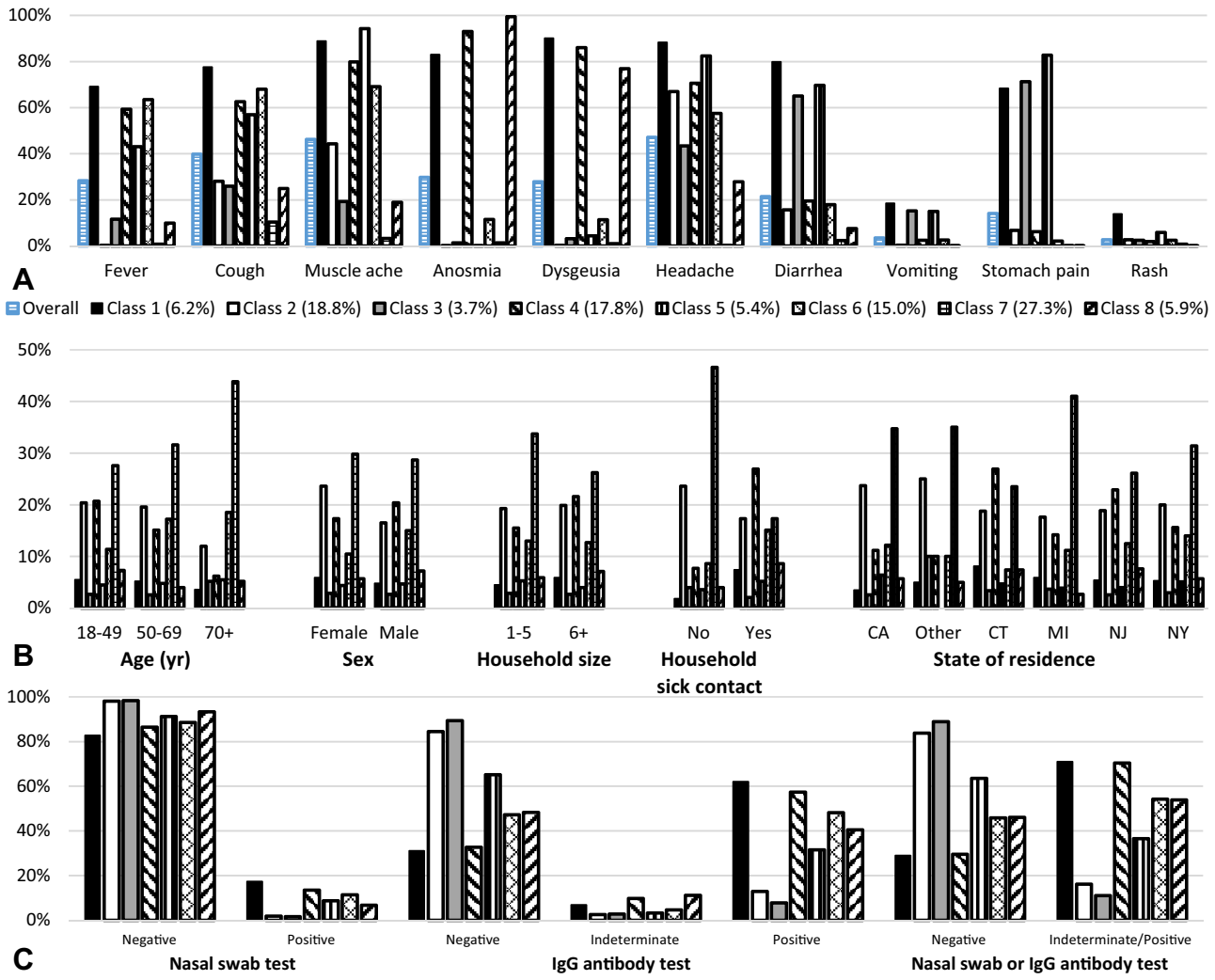

FIGURE 1. LCA of patterns of SARS-CoV-2 symptoms. LCA was used to examine patterns of binary variables of SARS-CoV-2 symptoms in adults. LCA used the observed binary data to identify homogeneous patterns; that is, n = 8 latent classes. Conditional probabilities were estimated using maximum likelihood to characterize the latent classes. (**A**) Conditional probability plots are presented, where probabilities closer to 0 or 1 indicate lower or higher chances, respectively. Overall distribution of SARS-CoV-2 symptoms. Class 1 Class 2 Class 3 Class 4 Class 5 Class 6 Class 7 Class 8. The proportion of respondents who are members of these classes is presented. (**B**) χ^2 tests were performed comparing (Figure 1, *B*) clinical characteristics and (**C**) SARS-CoV-2 nasal swab and/or IgG antibody positivity with class membership.

variables across unobserved classes. The ideal number of latent classes and best-fitting models were selected by minimizing the corrected Akaike information criterion and Bayesian information criterion and interpretability. χ^2 tests were used to test the associations of age, sex, household size (above or below the median household size), and the presence of sick contacts in the household with membership in the latent classes.

Among adults with positive SARS-CoV-2 antibodies, bivariable logistic regression models were constructed to determine whether demographic or household characteristics are associated with having at least 1 SARS-CoV-2 symptom or individual SARS-CoV-2 symptom (dependent variables). Crude odds ratio (OR) and 95% CI were estimated. Similarly, Poisson regression models were constructed to identify associations of the number of self-reported SARS-CoV-2 symptoms (dependent variable). Crude risk ratios and 95% CI were estimated. Multivariable models included sex (male/female), age (continuous), household size, and number of household sick contacts. Adjusted OR, relative risk, and 95% CI were estimated. Two- and 3-way statistical interactions were tested between covariables.

Bivariable logistic regression models were also constructed to determine whether demographic or household characteristics, SARS-CoV-2 symptoms, and latent classes of SARS-CoV-2 symptoms are associated with having positive SARS-CoV-2 antibody tests (binary dependent variables). OR and 95% CI were estimated. Multivariable models included all variables from the bivariable models (except for self-report of any symptoms or fever) and state of residence. Adjusted OR and 95% CI were estimated. Two- and 3-way statistical interactions were tested between covariables.

Bivariable logistic regression models were constructed to elucidate the impact of household size overall and number of children age 0 to 3, 4 to 10, or 11 to 17 years (independent variables) on positive

TABLE I. Associations of the pattern of symptoms (LCA) and SARS-CoV-2 IgG antibody positivity

	SARS-CoV-2 IgG antibodies					
	Negative/indeterminate (n = 4670)	Positive (n = 1995)				
Symptom class	Frequency (%)	Frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
1. All symptoms	127 (38.0)	207 (62.0)	**17.57 (13.38-23.08)**	**<.0001**	**15.69 (11.52-21.37)**	**<.0001**
2. Muscle ache, headache	1132 (87.1)	168 (12.9)	**1.60 (1.28-2.01)**	**<.0001**	**1.71 (1.32-2.21)**	**<.0001**
3. Headache, diarrhea, stomach pain	166 (92.2)	14 (7.8)	0.91 (0.52-1.61)	.74	0.79 (0.40-1.54)	.48
4. Fever, cough, muscle ache, anosmia, dysgeusia, headache	546 (42.6)	737 (57.4)	**14.55 (11.99-17.67)**	**<.0001**	**12.76 (10.15-16.06)**	**<.0001**
5. Fever, cough, muscle ache, headache, diarrhea, stomach pain	207 (68.5)	95 (31.5)	**4.95 (3.70-6.62)**	**<.0001**	**4.38 (3.14-6.12)**	**<.0001**
6. Fever, cough, muscle ache, headache	449 (51.8)	418 (48.2)	**10.04 (8.15-12.36)**	**<.0001**	**8.67 (6.81-11.04)**	**<.0001**
7. No symptoms	1779 (91.5)	165 (8.5)	1.00 (reference)	—	1.00 (reference)	—
8. Anosmia, dysgeusia	260 (59.5)	177 (40.5)	**7.34 (5.72-9.41)**	**<.0001**	**6.98 (5.27-9.25)**	**<.0001**

Bivariable logistic regression models were constructed with SARS-CoV-2 IgG test results (positive vs negative/indeterminate) as the dependent variable and symptom pattern (ordinal variable with 8 classes derived from LCA) as the independent variable. Crude ORs and 95% CI were estimated. Multivariable models included age, sex, household size, household sick contacts, self-report of a positive SARS-CoV-2 nasal swab test result as covariables, and state of residence. Adjusted ORs and 95% CI were estimated. Bold indicates statistical significance ($P < .05$).

SARS-CoV-2 antibodies (binary dependent variable). Multivariable models controlled for age, sex, and state of residence.

All data processing and statistical analyses were performed in SAS version 9.4.3 (SAS Institute, Cary, NC). Complete data analysis was performed; that is, subjects with missing data were excluded. A 2-sided *P* value of less than .05 was considered statistically significant.

RESULTS

Population characteristics

The survey cohort had a median (interquartile range) age of 36.0 (22.0) years, with 3777 females (39.7%) (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). The antibody cohort had a median (interquartile range) age of 37.0 (21.0) years, with 3068 females (46.0%).

Among all 9507 respondents in the survey cohort, 5828 respondents (61.3%) reported any SARS-CoV-2 symptoms (mean number of symptoms, 2.6 ± 2.2), with 603 (6.6%) reporting a positive PCR nasal swab result. The most commonly reported symptom was headache (47.1%), followed by muscle ache (46.3%), cough (39.8%), anosmia (29.8%), fever (28.3%), dysgeusia (27.9%), diarrhea (21.4%), stomach pain (14.1%), vomiting (3.5%), and rash (2.7%) (Figure 1).

Compared with the entire survey cohort, those with a positive SARS-CoV-2 IgG antibody test result (n = 2318 [34.8%]; mean number of symptoms, 4.0 ± 2.0 [variance, 4.1]) had numerically higher prevalences of all symptoms (muscle ache [64.8%], headache [58.6%], cough [58.5%], anosmia [56.4%], fever [53.4%], dysgeusia [52.1%], diarrhea [28.6%], stomach pain [16.1%], vomiting [5.0%]) except for rash (2.3%).

Predictors of SARS-CoV-2 symptoms

Among respondents with positive SARS-CoV-2 antibodies, 178 (8.9%) reported no SARS-CoV-2 symptoms. Self-report of any SARS-CoV-2 symptoms was associated with households with 6 or more members (bivariable logistic regression; OR [95% CI], 1.63 [1.20-2.22]) or a sick contact (6.50 [4.55-9.28]), and reporting a positive SARS-CoV-2 nasal swab test result (5.41 [2.37-12.32]). In multivariable models, significant associations were observed for age 50 to 69 years, household sick contacts, and having a positive SARS-CoV-2 nasal swab test result (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Similarly, the number of self-reported SARS-CoV-2 symptoms was associated with female sex (0.05 [0.004-0.09]), households with 6 or more members (bivariable Poisson regression; relative risk [95% CI], 0.13 [0.10-0.16]), a household sick contact (0.69 [0.66-0.72]), and having a positive SARS-CoV-2 nasal swab test result (0.18 [0.12-0.24]), but inversely associated with age (≥70 years (−0.28 [−0.40 to −0.16]) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). In multivariable models, the associations remained significant for age 70 years or more, female sex, household sick contacts, and having a positive COVID nasal swab result. There were no significant 2- or 3-way statistical interactions.

Patterns of SARS-CoV-2 symptoms

To identify statistically significant homogeneous patterns of SARS-CoV-2 symptoms (latent classes) among subjects based on their observed binary reporting of symptoms (n = 9311 with complete symptom data), we used LCA. The best-fit model had 8 classes. Conditional probabilities of having different SARS-CoV-2 symptoms are plotted in Figure 1, *A*.

Class 7 had the highest membership probability (27.3% of the survey cohort) and consisted of very low probabilities of any symptom (Table I). Class 2 had the next highest membership probability (18.8% of the survey cohort) and had higher probabilities of muscle ache and headache. Class 4 (17.8% of the survey cohort) had higher probabilities of fever, cough, muscle ache, anosmia, dysgeusia, and headache. Class 6 (15.0% of the survey cohort) had higher probabilities of fever, cough, muscle ache, and headache. Class 1 (6.2% of the survey cohort) had higher probabilities of all symptoms. Class 8 (5.9% of the survey cohort) had higher probability of anosmia and dysgeusia. Class 5 (5.4% of the survey cohort) had higher probabilities of fever, cough, muscle ache, headache, diarrhea, and stomach pain. Class 3 (3.7% of the survey cohort) had higher probabilities of headache, diarrhea, and stomach pain.

There were significant associations of latent class membership with age, sex, household size, and the presence of sick contacts in the household (χ^2, $P < .0001$ for all) (Figure 1, *B*). Membership

TABLE II. Associations of positive SARS-CoV-2 IgG antibodies

	SARS-CoV-2 IgG antibodies					
	Negative/indeterminate (n = 4670)	Positive (n = 1995)				
Variable	Frequency (%)	Frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age (y)						
18-49	3624 (72.4)	1379 (27.6)	1.00 (reference)	—	1.00 (reference)	—
50-69	880 (62.9)	520 (37.1)	**1.55 (1.37-1.76)**	**<.0001**	**2.09 (1.75-2.50)**	**<.0001**
≥70	154 (63.4)	89 (36.6)	**1.52 (1.16-1.99)**	**.002**	**2.68 (1.67-4.29)**	**<.0001**
Sex						
Male	2353 (65.4)	1244 (34.6)	1.00 (reference)	—	1.00 (reference)	—
Female	2317 (75.5)	751 (24.5)	**0.61 (0.55-0.68)**	**<.0001**	**0.66 (0.57-0.76)**	**<.0001**
Household size						
1-5	2196 (72.9)	815 (27.1)	1.00 (reference)	—	1.00 (reference)	—
≥6	2468 (68.1)	1159 (32.0)	**1.27 (1.14-1.41)**	**<.0001**	**1.23 (1.06-1.42)**	**.007**
Household sick contact						
No	1946 (85.1)	340 (14.9)	1.00 (reference)	—	1.00 (reference)	—
Yes	2221 (61.1)	1415 (38.9)	**3.65 (3.19-4.17)**	**<.0001**	**1.82 (1.55-2.14)**	**<.0001**
Any SARS-CoV-2 symptoms						
No	2375 (93.0)	178 (7.0)	1.00 (reference)	—		
Yes	2295 (55.8)	1817 (44.2)	**10.56 (8.96-12.45)**	**<.0001**		
Fever						
No	3897 (81.6)	881 (18.4)	1.00 (reference)	—		
Yes	773 (41.0)	1113 (59.0)	**6.37 (5.66-7.16)**	**<.0001**		
Peak fever *(deg F)*						
None	4002 (80.7)	955 (19.3)	1.00 (reference)	—	1.00 (reference)	—
100°F-102°F	612 (41.0)	882 (59.0)	**6.04 (5.33-6.84)**	**<.0001**	**1.61 (1.11-2.33)**	**.01**
103°F-106°F	56 (26.3)	157 (73.7)	**11.75 (8.59-16.07)**	**<.0001**	**2.22 (1.30-3.78)**	**.003**
Duration of fever (d)						
None	3897 (81.6)	881 (18.4)	1.00 (reference)	—	1.00 (reference)	—
1-2	603 (50.8)	583 (49.2)	**4.28 (3.74-4.90)**	**<.0001**	1.35 (0.93-1.94)	.11
3-6	147 (32.3)	308 (67.7)	**9.27 (7.52-11.43)**	**<.0001**	**2.77 (1.80-4.26)**	**<.0001**
≥7	23 (9.4)	222 (90.6)	**42.69 (27.62-65.99)**	**<.0001**	**9.81 (5.26-18.29)**	**<.0001**
Cough						
No	3178 (80.0)	794 (20.0)	1.00 (reference)	—	1.00 (reference)	—
Yes	1488 (55.6)	1188 (44.4)	**3.20 (2.87-3.56)**	**<.0001**	**1.47 (1.27-1.69)**	**<.0001**
Muscle ache						
No	2892 (80.9)	685 (19.2)	1.00 (reference)	—	1.00 (reference)	—
Yes	1774 (57.8)	1298 (42.3)	**3.09 (2.77-3.45)**	**<.0001**	**1.37 (1.17-1.60)**	**<.0001**
Anosmia						
No	3768 (81.0)	883 (19.0)	1.00 (reference)	—	1.00 (reference)	—
Yes	898 (44.9)	1101 (55.1)	**5.23 (4.67-5.87)**	**<.0001**	**2.77 (1.80-4.26)**	**<.0001**
Dysgeusia						
No	3833 (80.1)	952 (19.9)	1.00 (reference)	—	1.00 (reference)	—
Yes	833 (44.6)	1033 (55.4)	**4.99 (4.45-5.61)**	**<.0001**	**1.49 (1.23-1.82)**	**<.0001**
Headache						
No	2702 (76.9)	813 (23.1)	1.00 (reference)	—	1.00 (reference)	—
Yes	1964 (62.7)	1168 (37.3)	**1.98 (1.78-2.20)**	**<.0001**	1.05 (0.90-1.21)	.57
Diarrhea						
No	3855 (73.6)	1385 (26.4)	1.00 (reference)	—	1.00 (reference)	—
Yes	812 (57.6)	597 (42.4)	**2.05 (1.81-2.31)**	**<.0001**	**1.28 (1.08-1.53)**	**.005**
Vomiting						
No	4561 (70.9)	1871 (29.1)	1.00 (reference)	—	1.00 (reference)	—
Yes	105 (48.8)	110 (51.2)	**2.55 (1.94-3.35)**	**<.0001**	1.28 (0.87-1.87)	.21
Stomach pain						
No	4074 (71.1)	1654 (28.9)	1.00 (reference)	—	1.00 (reference)	—
Yes	593 (64.4)	328 (35.6)	**1.36 (1.18-1.58)**	**<.0001**	**0.75 (0.61-0.93)**	**.009**

(continued)

TABLE II. *(Continued)*

	SARS-CoV-2 IgG antibodies					
	Negative/indeterminate (n = 4670)	Positive (n = 1995)				
Variable	Frequency (%)	Frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Rash						
No	4547 (70.1)	1936 (29.9)	1.00 (reference)	—	1.00 (reference)	—
Yes	119 (72.6)	45 (27.4)	0.89 (0.63-1.26)	.50	**0.52 (0.33-0.82)**	**.005**
Received supplemental oxygen therapy						
No	4664 (70.8)	1925 (29.2)	1.00 (reference)	—	1.00 (reference)	—
Yes	4 (7.3)	51 (92.7)	**30.85 (11.40, 85.43)**	**<.0001**	**5.29 (1.34, 20.90)**	**<.0001**
Positive COVID test result by nasal swab						
No	4533 (72.9)	1683 (27.1)	1.00 (reference)	—	1.00 (reference)	—
Yes	131 (31.0)	291 (69.0)	**5.98 (4.83-7.41)**	**<.0001**	**2.08 (1.57-2.74)**	**<.0001**

Bivariable logistic regression models were constructed with SARS-CoV-2 IgG test results (positive vs negative/indeterminate) as the dependent variable and age, sex, household size, household sick contacts, any symptoms, any fever, peak fever, duration of fever, other individual symptoms, receiving supplemental oxygen therapy, self-report of a positive SARS-CoV-2 nasal swab test result, and duration of overall illness as the independent variables. Crude ORs and 95% CI were estimated. Multivariable regression model 1 included all variables from the bivariable models (except for self-report of any symptoms or fever), and state of residence. Adjusted OR and 95% CI were estimated. Bold indicates statistical significance ($P < .05$).

in classes 6 and 7 was highest in older age, whereas classes 1, 2, 4, and 8 were highest in younger age. Class 2 membership was highest in females, whereas classes 4, 6, and 8 were higher in males. Membership in classes 1, 4, and 8 was highest in households with 6 or more members, whereas membership in class 7 was highest in households with 5 members. Membership in classes 1, 4, 5, 6, and 8 was highest in households with a sick contact, whereas membership in classes 2, 3, and 7 was highest in households with no sick contacts.

Predictors of laboratory-confirmed SARS-CoV-2 IgG seropositivity

Demographics. Positive SARS-CoV-2 antibodies were associated with positive SARS-CoV-2 nasal swab result (bivariable logistic regression; OR [95% CI], 5.98 [4.83-7.41]), sick contact (3.65 [3.19-4.17]), older age (50-69 years: 1.55 [1.37-1.76]); ≥70 years: 1.52 [1.16-1.99]), and households with 6 or more members (1.27 [1.14-1.41]), but inversely associated with female sex (0.61 [0.55-0.68]) (Table II). The associations remained significant in multivariable regression models.

Household size. Multivariable regression models were constructed to determine whether presence of children of different age groups or having multiple adults in the household was associated with positive SARS-CoV-2 antibodies. Positive SARS-CoV-2 antibodies were associated with the presence of 1 or more child age 11 to 17 years (1.28 [1.16-1.42]) and more than 5 adults (3.37 [1.23-9.23]), inversely associated with a child age 0 to 3 years in the household (0.86 [0.78-0.95]), but not associated with a child age 4 to 10 years (0.99 [0.90-1.10]) (Table III). These associations remained significant in multivariable models controlling for age, sex, and state of residence.

Symptoms

The symptom most strongly associated with positive SARS-CoV-2 antibodies was fever (10.56 [8.96- 12.45]), especially higher peak temperatures (100°F-102°F: 6.04 [5.33-6.84]; 103°F-106°F: 11.75 [8.59-16.07]) and prolonged fevers (1-2 days: 4.28 [3.74-4.90]; 3-6 days: 9.27 [7.52-11.43]; ≥7 days: 42.69 [27.62-65.99]) (Table II). Anosmia (5.23 [4.67-5.87]) and dysgeusia (4.99 [4.45-5.61]) also had strong associations with positive SARS-CoV-2 antibodies, as did cough (3.20 [2.87-3.56]), muscle ache (3.09 [2.77-3.45]), headache (1.98 [1.78-2.20]), diarrhea (2.05 [1.81-2.31]), vomiting (2.55 [1.94-3.35]), stomach pain (1.36 [1.18-1.58]), and receiving supplemental oxygen therapy (33.49 [10.45-107.33]). In multivariable regression models, all symptoms remained significantly associated with positive SARS-CoV-2 antibodies, except for headache and vomiting.

Finally, latent classes 1 (all symptoms) and 4 (fever, cough, muscle ache, anosmia, dysgeusia, and headache) were associated with the highest proportion (62.0% and 57.4%) with positive antibodies, whereas classes 6 (fever, cough, muscle ache, headache) and 8 (anosmia, dysgeusia) were associated with intermediate proportions (48.2% and 40.5%), and classes 3 (headache, diarrhea, stomach pain) and 7 (no symptoms) had the lowest proportion (7.8% and 8.5%) of positive SARS-CoV-2 IgG antibody tests (Table I). There were no significant 2- or 3-way statistical interactions in any of the abovementioned multivariable models.

DISCUSSION

In this large-scale observational cohort, we demonstrate substantial diversity of symptoms from SARS-CoV-2 infection. The 5 most common symptoms reported in the survey cohort were headache, myalgia, cough, anosmia, and fever, whereas in patients with serologically confirmed COVID-19, the most common symptoms were similarly myalgia, headache, cough, anosmia, and fever. Certain clinical characteristics have particularly strong relationships with anti−SARS-CoV-2 IgG antibody response, including prolonged fever, anosmia, and receiving supplemental oxygen therapy, which is consistent with previous reports.[13]

We used LCA to further elucidate the COVID symptom complex and its relationship with IgG antibody responses. LCA is a statistical method used to identify a set of discrete subgroups or latent classes of individuals based on their responses to a set of categorical variables.[14] Adults who experienced all symptoms (class 1) and those who specifically had fever, cough, muscle

TABLE III. Association of household size with positive SARS-CoV-2 IgG antibodies

Other people in household at specific ages	SARS-CoV-2 IgG antibodies					
	Negative/indeterminate (n = 4670)	Positive (n = 1995)				
	Frequency (%)	Frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
0-3 y						
No	2431 (63.9)	1374 (36.1)	1.00 (reference)	—	1.00 (reference)	—
Yes	1823 (67.3)	886 (32.7)	**0.86 (0.78-0.95)**	**.005**	**0.85 (0.76-0.96)**	**.007**
4-10 y						
No	2027 (65.2)	1081 (34.8)	1.00 (reference)	—	1.00 (reference)	—
Yes	2227 (65.4)	1179 (34.6)	1.99 (0.90-1.10)	.89	1.01 (0.90-1.12)	.92
11-17 y						
No	2296 (68.0)	1081 (32.0)	1.00 (reference)	—	1.00 (reference)	—
Yes	1958 (62.4)	1179 (37.6)	**1.28 (1.16-1.42)**	**<.0001**	**1.32 (1.19-1.46)**	**<.0001**
≥18 y						
0	19 (79.2)	5 (20.8)	1.00 (reference)	—	1.00 (reference)	—
1	1539 (67.2)	750 (32.8)	1.85 (0.69-4.96)	.22	1.62 (0.60-4.42)	.34
2-5	2516 (65.2)	1345 (34.8)	2.03 (0.76-5.44)	.16	1.77 (0.65-4.80)	.27
>5	180 (52.9)	160 (47.1)	**3.37 (1.23-9.23)**	**.02**	**3.10 (1.12-8.61)**	**.03**

Bivariable logistic regression models were constructed with SARS-CoV-2 IgG test results (positive vs negative/indeterminate) as the dependent variable and presence of children ages 0-3, 4-10, or 11-17 y (0, ≥1) and number of other adults in the household (0, 1, 2-5, >5) as the independent variables. Crude ORs and 95% CIs were estimated. Multivariable regression models included age (continuous) and sex (male, female) as fixed-effects variables, and state of residence. Adjusted ORs and 95% CI were estimated. The age cutoffs were selected *a priori* on the basis of previous reports suggesting that younger children are least likely to transmit COVID, followed by older children, then adolescents and greatest transmission occurring in adults.[11,12] Bold indicates statistical significance ($P < .05$).

ache, anosmia, dysgeusia, and headache (class 4) were most likely to have positive anti—SARS-CoV-2 antibodies and self-reported SARS-CoV-2 PCR nasal swabs. Interestingly, anosmia and dysgeusia alone (class 8) were not associated with as robust an immune response as fever, cough, muscle ache, and headache (class 6). This appears to be in contrast to a previous study in health care workers, and may suggest an association with a more robust immunophenotype with class 6.[15] Similar to a previous study,[16] we found that headache was reported in all but 2 latent classes (7 and 8). These symptom patterns may be useful to predict the likelihood of having SARS-CoV-2 infection and related outcomes based on symptoms alone, and potentially guide occupational and public health recommendations regarding resource allocation. In addition, these symptom patterns can help predict which patients likely have positive IgG antibodies to SARS-CoV-2 and guide clinical recommendations regarding vaccination and social distancing requirements.

We found that households with more than 5 residents had more SARS-CoV-2 symptoms and positive antibodies in bivariable analyses. These associations were attenuated after controlling for sick contacts in multivariable models. That is, people living in larger households have more potential sick contacts during an outbreak. In particular, the presence of adolescents was associated with higher antibody positivity, but not younger children. These results have important ramifications for public health and school policy. First, sociocultural groups with more persons per household may be prone to higher rates of infections. Second, households with more persons, particularly adolescents, may warrant more caution with respect to mitigation strategies for preventing community-based spread of SARS-CoV-2 infection. Third, as schools and workplaces around the world develop policies to reopen in-person, it is important to distinguish between regions and sociocultural groups with typically larger versus smaller household sizes. Adolescents and adults who might become infected with SARS-CoV-2 in school and work can transmit the virus to far more people residing in a larger versus smaller households, thereby potentially increasing community spread.

Strengths of this study include the large sample size, inclusion of a wide age range, and spectrum of disease severity, including a fairly high proportion of younger adults and milder symptoms. This allowed for comparison of symptoms and IgG antibody responses as a function of age and symptom severity. However, there are limitations. This ambulatory cohort may not accurately reflect the symptomatology and serologic profiles of patients with more severe disease. Viral PCR positivity was assessed via survey rather than direct testing. Moreover, this cohort included persons from communities with early COVID-19 outbreaks, when PCR testing was not yet widely accessible across the United States. Many participants were unable to get PCR testing, leading to a low proportion (6%) who reported having a positive PCR test result; that is, patients who reported not having a positive PCR test result may not have been tested. Thus, it is possible that some participants who experienced COVID-19 symptoms had other viral illnesses. We analyzed antibodies to the nucleocapsid protein but not spike protein, which may have led to lower rates of antibody positivity. Data on travel history and contact tracing were not available. This was a largely Ashkenazi Jewish population. COVID-19 hit the Orthodox Jewish community in the United States particularly hard, especially in the early days when much was unknown. At that time of great loss, Jewish communities around the United States rallied to participate in research to help the millions of other people impacted by the pandemic. Although the cohort included broad representation of age and sex, there was limited racial diversity. It is additionally unclear whether seroconversion using currently available assays reflects immunity to SARS-CoV-2, especially because the absence of T-cell data in a large portion of our population overlooks a phenotype of immunity that may be especially important in asymptomatic patients.[17,18] This latter aspect

regarding cellular immunity patterns is an aspect that we are following up in future studies.

CONCLUSIONS

SARS-CoV-2 was associated with a heterogeneous profile of symptoms. Adults who experienced prolonged fevers and anosmia and received supplemental oxygen therapy, as well as those who experienced a multitude of symptoms in combination, had the highest odds of positive SARS-CoV-2 antinucleocapsid IgG. Future studies should examine the impact of these characteristics on other aspects of immunity to SARS-CoV-2.

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ONLINE REPOSITORY

TABLE E1. Population characteristics

Variable	SARS-CoV-2 survey (Survey Cohort) (n = 9507)*	SARS-CoV-2 survey & antibody testing (Antibody Cohort)† (n = 6665)†
N	9507	6665
Age (y), median (IQR)	36.0 (22.0)	37.0 (21.0)
Age (y), min-max	18-94	18-94
Female sex, frequency (%)	3777 (39.7)	3068 (46.0)
Household size, median (IQR)	5 (4)	5 (4)
Household size, min, max	1, 15	1, 15
Household sick contact, frequency (%)	4870 (60.6)	3636 (61.4)
Household sick contact, median (IQR, max)	2 (2, 15)	2 (2, 15)
Any symptoms, frequency (%)	5828 (61.3)	4112 (61.7)
Fever, frequency (%)	2685 (46.1)	1886 (45.9)
Peak temperature (°F), mean ± SD	101.0 ± 1.2	101.0 ± 1.2
Peak temperature (°F), min-max	99.0-106.0	99-106
Duration (d), mean ± SD	1.7 ± 2.6	1.7 ± 2.6
Duration (d), min-max	<1-10	<1-10
Cough, frequency (%)	3210 (56.2)	2319 (56.6)
Muscle ache, frequency (%)	3800 (66.5)	2722 (66.4)
Anosmia, frequency (%)	2726 (47.7)	1966 (48.0)
Dysgeusia, frequency (%)	2543 (44.5)	1829 (44.6)
Headache, frequency (%)	3558 (62.4)	2540 (62.0)
Diarrhea, frequency (%)	1601 (28.1)	1140 (27.8)
Vomiting, frequency (%)	274 (4.8)	189 (4.6)
Stomach ache, frequency (%)	1041 (18.3)	735 (17.9)
Rash, frequency (%)	180 (3.2)	115 (2.8)
Positive PCR, frequency (%)	603 (6.6)	422 (6.4)
Required oxygen therapy, frequency (%)	48 (0.5)	36 (0.5)
Emergency department visit, frequency (%)	117 (1.3)	90 (1.4)
Inpatient hospitalization, frequency (%)	55 (0.6)	41 (0.6)

IQR, Interquartile range; *min*, minimum; *max*, maximum.

Similar rates of survey completion were observed across different age groups (97.4% for age 18-49 y, 98.3% for 50-69 y, and 97.8% for 70+ y).

*Within the cohort of patients who completed the SARS-CoV-2 survey, missing data were encountered in 1475 (15.5%) for age, 1424 (15.0%) for sex, 0 (0.0%) for presence of symptoms, 9 (0.09%) for any fever, peak fever, or fever length, 117-132 (1.2%-1.4%) for other symptoms, 319 (3.4%) for PCR testing, 176 (1.9%) for requirement of oxygen therapy, 187 (2.0%) for emergency department visits, and 187 (2.0%) for inpatient hospitalizations.

†Within the cohort of patients who completed the SARS-CoV-2 survey and had antibody testing, missing data were encountered in 19 (0.3%) for age, 0 (0.0%) for sex, 27 (0.4%) for household size, 743 (11.4%) for household sick contacts, 0 (0.0%) for presence of symptoms, 1 (0.01%) for any fever and peak fever, 2 (0.02%) for duration of fever, 1 for duration of fever (1.7%), 12-16 (0.3%-0.4%) for other symptoms, 27 (0.4%) for PCR testing, 21 (0.3%) for requirement of oxygen therapy, 21 (0.3%) for emergency department visits, and 21 (0.3%) for inpatient hospitalizations.

TABLE E2. Associations of symptomatic vs asymptomatic disease among adults with positive SARS-CoV-2 IgG antibodies

	Any symptoms					
	No (n = 178)	Yes (n = 1817)				
Variable	Frequency (%)	Frequency (%)	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age (y)						
18-49	122 (8.9)	1257 (91.2)	1.00 (reference)	—	1.00 (reference)	—
50-69	42 (8.1)	478 (91.9)	1.11 (0.77-1.59)	.59	**1.74 (1.06-2.85)**	**.03**
≥70	12 (13.5)	77 (86.5)	0.62 (0.33-1.18)	.14	0.94 (0.30-2.99)	.92
Sex						
Male	62 (8.3)	689 (91.7)	1.00 (reference)	—	1.00 (reference)	—
Female	116 (9.3)	1128 (90.7)	1.14 (0.83-1.58)	.42	0.81 (0.55-1.20)	.30
Household size						
1-5	93 (11.4)	722 (88.6)	1.00 (reference)	—	1.00 (reference)	—
≥6	85 (7.3)	1074 (92.7)	**1.63 (1.20-2.22)**	**.002**	1.21 (0.82-1.79)	.34
Household sick contact						
No	79 (23.2)	261 (76.8)	1.00 (reference)	—	1.00 (reference)	—
Yes	63 (4.6)	1352 (95.65)	**6.50 (4.55-9.28)**	**<.0001**	**6.06 (4.13-8.88)**	**<.0001**
COVID test result by nasal swab						
Negative	172 (10.2)	1511 (89.8)	1.00 (reference)	—	1.00 (reference)	—
Positive	6 (2.1)	285 (97.9)	**5.41 (2.37-12.32)**	**<.0001**	**4.77 (1.89-12.08)**	**.001**

Analyses were limited to adults with *positive* SARS-CoV-2 IgG test results. Bivariable logistic regression models were constructed with any SARS-CoV-2 symptoms (yes vs no) as the dependent variable and age, sex, household size, household sick contacts, and self-report of a positive SARS-CoV-2 nasal swab test result as the independent variables. Crude ORs and 95% CI were estimated. Multivariable regression models included all variables from the bivariable models, and state of residence. Adjusted ORs and 95% CI were estimated. Bold indicates statistical significance ($P < .05$).

TABLE E3. Associations of number of self-reported SARS-CoV-2 symptoms

	No. of SARS-CoV-2 symptoms				
Variable	Mean ± SD	Crude RR (95% CI)	*P* value	Adjusted RR (95% CI)	*P* value
Age (y)					
18-49	4.1 ± 2.0	0.00 (reference)	—	0.00 (reference)	—
50-69	3.9 ± 2.0	−0.05 (−0.10 to −0.004)	.07	−0.02 (−0.08 to 0.04)	.48
≥70	3.1 ± 1.9	**−0.28 (−0.40 to −0.16)**	**<.0001**	**−0.30 (−0.46 to −0.13)**	**<.0001**
Sex					
Male	3.9 ± 2.0	0.00 (reference)	—	0.00 (reference)	—
Female	4.1 ± 2.0	**0.05 (0.004 to 0.09)**	**.03**	0.03 (−0.02 to 0.08)	.27
Household size					
1-5	3.9 ± 2.1	0.00 (reference)	—	0.00 (reference)	—
≥6	4.2 ± 1.9	**0.08 (0.04 to 0.13)**	**<.0001**	0.03 (−0.03 to 0.08)	.33
Household sick contact					
No	3.2 ± 2.2	0.00 (reference)	—	0.00 (reference)	—
Yes	4.3 ± 1.9	**0.28 (0.22 to 0.34)**	**<.0001**	**0.26 (0.20 to 0.33)**	**<.0001**
Positive COVID test result by nasal swab					
No	3.9 ± 2.0	0.00 (reference)	—	0.00 (reference)	—
Yes	4.7 ± 1.8	**0.18 (0.12 to 0.24)**	**<.0001**	**0.19 (0.12 to 0.26)**	**<.0001**

RR, Relative risk.

Analyses were limited to adults with positive SARS-CoV-2 IgG test results. Bivariable Poisson regression models were constructed with number of self-report of any SARS-CoV-2 symptoms as the continuous dependent variable and age, sex, household size, and household sick contacts as the independent variables. Crude RR and 95% CI were estimated. Multivariable models included all variables from the bivariable models, and state of residence. Adjusted RR and 95% CI were estimated. Bold indicates statistical significance ($P < .05$).