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Long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection: a cross-sectional study

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ABSTRACT

Objectives To estimate the prevalence of long COVID symptoms in children with and without a history of SARS-CoV-2 infection and to evaluate factors associated with long COVID.

Design A nationwide cross-sectional study.

Setting Primary care.

Participants 3240 parents of children aged 5–18 with and without SARS-CoV-2 infection completed an online questionnaire (11.9% response rate); 1148 and 2092 with/without a history of infection, respectively.

Primary and secondary outcome measures Primary outcome was the prevalence of long COVID symptoms in children with/without a history of infection. Secondary outcomes were the factors associated with the presence of long COVID symptoms and with failure to return to baseline health status in children with a history of infection including gender, age, time from illness, symptomatic illness and vaccine status.

Results Most long COVID symptoms were more prevalent in children with a history of SARS-CoV-2 infection: headaches (211 (18.4%) vs 114 (5.4%), p<0.001), weakness (173 (15.1%) vs 70 (3.3%), p<0.001), fatigue (141 (12.3%) vs 133 (6.4%), p<0.001) and abdominal pain (109 (9.5%) vs 79 (3.8%), p<0.001). Most long COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group (12–18) compared with the younger age group (5–11). Some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention problems with school malfunctioning (225 (10.8%) vs 98 (8.5%), p=0.05), stress (190 (9.1%) vs 65 (5.7%), p<0.001), social problems (164 (7.8%) vs 32 (2.8%)) and weight changes (143 (6.8%) vs 43 (3.7%), p<0.001).

Conclusion This study suggests that the prevalence of long COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A nationwide coverage of participants.
⇒ A relatively large number of participants with a broad age range (5–18 years old).
⇒ A comparison of children with or without a history of SARS-CoV-2 infection.
⇒ A relatively low response rate (11.9%) which may cause a selection bias.
⇒ The responses were from a proxy (the parent) rather than the child itself.

INTRODUCTION

SARS-CoV-2 has emerged in December 2019 and was declared a pandemic by WHO in March 2020. Evidence emerged slowly but consistently about persistent symptoms following infection and WHO defined the post-COVID-19 condition (also known as long COVID) in October 2021.[1] Reports were first made for adults,[2–4] and later evidence started to emerge regarding the existence of long COVID in children and adolescents; the first scientific report came from Sweden with a case series by Ludvigsson, who followed five children with a potential long COVID syndrome.[5] First reports were primarily descriptive, with relatively small sample sizes and without a control group.[6]

Behnood *et al* performed a meta-analysis of controlled and uncontrolled studies regarding long COVID in children and adolescents.[7] Among all studies, only five were controlled studies.[8–12] They found a higher prevalence of cognitive difficulties, headache, loss of smell, sore throat and sore eyes in test-positive children. However, symptoms like abdominal pain, cough, fatigue, myalgia, insomnia, diarrhoea, fever, dizziness or dyspnoea were not significantly increased in test-positive children in this study. Controversy later emerged when some of the largest

studies about long COVID in children and adolescents reported different results of prevalence of at least one long COVID symptom with ranges varying between 1.8% and 61.9%.[8–11 13 14]

This study aimed to estimate the prevalence of long COVID symptoms in Israeli children with and without a history of SARS-CoV-2 infection and evaluate the factors associated with long COVID and failure to return to baseline health status.

METHODS

Study design and setting

We designed a nationwide cross-sectional study using the centralised database of Maccabi Healthcare Services, the second largest healthcare maintenance organisation in Israel, which covers a quarter of Israel's population (2.6 million citizens). We sent an online questionnaire using text messages to parents of children aged 5–18 years with a positive PCR test for SARS-CoV-2 one to six months before data collection. In addition, we sent the questionnaire to a control group of parents of children with no positive PCR results (with a ratio of 1:2). We asked parents to choose one child per family and answer the questionnaire according to his or her health status. (The questionnaire is available in online supplemental material part A.) The questionnaire did not include questions about other infections. Informed consent was given via the online questionnaire.

Variables

Demographic and medical variables included age, sex, native born, height, weight and the presence of any chronic illness (including diabetes mellitus, asthma, inflammatory disease, oncological disease, anxiety or depression). COVID-19-related variables included details about the acute illness, including the date of illness, presence of any symptoms (without mentioning which ones), whether the child was admitted to a hospital due to COVID-19, and if so, whether oxygen supply was warranted, and vaccination status against COVID-19. The last section included questions regarding the presence of long COVID symptoms (including physical and mental health symptoms, long COVID symptoms were defined as symptoms lasting more than 4 weeks) and asked parents whether the overall health status of their children is worse, the same or better than their baseline health status. We chose to refer to these symptoms as long COVID symptoms in both groups for reasons of clarity, although long COVID does not exist in the control group. The questionnaire was created by the authors of this study related to most symptoms reported in the literature.

Statistical analysis

Sample size calculations—to show a difference of relatively rare symptoms, we assumed a prevalence of 0.5% in children without and 3.5% in children with a history of SARS-CoV-2 infection. To show a significant difference with a power of 80% and alpha of 5% with a 2:1 ratio, we needed at least 275 in children with and 550 in children without a history of SARS-CoV-2 infection. We assumed a prevalence of 5% in children without and 10% in children with a history of SARS-CoV-2 infection for more prevalent symptoms. In the same terms, we needed at least 341 in children with and 682 in children without a history of SARS-CoV-2 infection.

Descriptive statistics were used for all variables, with absolute numbers and percentages for categorical variables and mean and SD for continuous variables. First, we performed a univariate analysis to all long COVID symptoms and compared children with and without a history of SARS-CoV-2 infection using the χ^2 test. We then performed the same analysis with age stratification (ages 5–11 and 12–18). Next, we performed two sets of multivariable tests to examine which factors were associated with having at least one long COVID symptom and which factors were associated with worse health status than baseline health status. Both analyses were made using a logistic regression analysis with two blocks, the first using all variables (the ENTER approach, a statistical approach in logistic regression analysis, where all variables are entered into the model) for baseline characteristics and forward stepwise selection for more elaborated variables. Last, we performed a univariate analysis of the differences between parents of children who did and did not answer the questionnaire. We used the Statistical Package for Social Sciences (SPSS) software V.28 for data analysis.

Patient and public involvement

No patients were involved.

RESULTS

Study population

In December 2021 and January 2022, we sent the online questionnaire to 27240 parents of children (8550 of parents had at least one child with a history of SARS-CoV-2 infection). In Israel, all formal testing (PCR/antigen) are reported and documented in the central database of each health maintenance organization (HMO). Home antigen tests were available in Israel from January 2021; however, to get a formal certificate of recovery, all people had to have a formal test. Thus, most patients with SARS-CoV-2 infection had a formal test.

A total of 3240 parents answered the questionnaire and agreed to participate in the study (11.9% overall response rate, 13.4% in children with and 11.2% in children without a history of infection). Of all the respondents, 1148 children had a history and 2092 children had no history of SARS-CoV-2 infection. The average age of children with and without a history of SARS-CoV-2 infection was 10.8 and 9.5, with 731 (63.7%) and 1282 (61.3%) females, respectively (table 1).

Parents of children who did or did not fill the questionnaire were different in a few aspects (table 2); among the

Table 1 Characteristics of children with and without a history of SARS-CoV-2 infection

	Children with a history of SARS-CoV-2 infection N=1148	Children without a history of SARS-CoV-2 infection N=2092
Age, mean±SD	10.8±0.08	9.5±0.09
Background variables	**n (%)**	**n (%)**
Females	731 (63.7)	1282 (61.3)
Native born	931 (81)	1635 (78.1)
Any regular medications	88 (7.7)	188 (10.6)
Diabetes mellitus	4 (0.35)	4 (0.2)
Asthma	20 (1.7)	21 (1)
Inflammatory/immune disease	6 (0.5)	17 (0.8)
Depression/anxiety	9 (0.8)	18 (0.9)
A history of any oncological disease	2 (0.2)	4 (0.2)
COVID-related variables	**n (%)**	**n (%)**
At least 1 vaccination	172 (15)	1424 (68)
Symptomatic COVID-19	720 (62.7)	
Hospitalisation due to COVID-19	4 (0.3)	
Time since COVID-19 infection (months) Mean±SD Range	4.39±1.5 1–12 months	

Table 2 Characteristics of parents who did or did not respond to the questionnaire

	Respondents (N=3778)	Non-respondents (N=23 469)	
	n (%)	n (%)	P value
Females	2310 (61.1)	12 570 (53.6)	<0.001
Age			
<24	1 (0.03)	9 (0.04)	<0.001
25–34	221 (5.8)	1961 (8.3)	
35–44	1441 (38.1)	9216 (39.3)	
45–54	1749 (46.3)	10 080 (42.9)	
>55	366 (9.7)	2203 (9.4)	
Sector			
Orthodox-Jewish	115 (3)	841 (3.6)	<0.001
Arab	109 (2.9)	1912 (8.1)	
All other	3554 (94.1)	20 716 (88.3)	

respondents, more were females, in higher age groups and non-Arab and non-Orthodox Jews.

Of all the children with a history of SARS-CoV-2 infection, 720 (62.7%) had symptomatic COVID-19, four were hospitalised due to COVID-19 (0.3%) and one needed oxygen supply. The mean duration between infection and answering the questionnaire was 4.4 months. Overall, 696 (33.3%) children without and 502 (43.7%) children with a history of SARS-CoV-2 infection reported at least one symptom (p<0.001) and 89 (4.3%) children without and 114 (9.9%) children with a history of SARS-CoV-2 infection reported at least five symptoms (p<0.001). In addition, 113 (5.4%) children without and 107 (9.3%) children with a history of SARS-CoV-2 infection reported an inability to return to their baseline health status (p<0.001) (table 3).

Long COVID symptoms

The five most prevalent long COVID symptoms reported by parents of children with compared with children without a history of SARS-CoV-2 infection were headaches (211 (18.4%) vs 114 (5.4%), p<0.001), weakness (173 (15.1%) vs 70 (3.3%), p<0.001), fatigue (141 (12.3%) vs 133 (6.4%), p<0.001), abdominal pain (109 (9.5%) vs 79 (3.8%), p<0.001) and cough (101 (8.8%) vs 49 (2.3%), p<0.001) (figure 1). Other more prevalent symptoms in children with a history of SARS-CoV-2 infection were myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnoea and increased heart rate (table 3).

Most long COVID symptoms in children with a history of SARS-CoV-2 infection were more prevalent in the older age group[12–18] compared with the younger age group,[5–11] including headaches (56 (25%) vs 155 (19%), p=0.05), weakness (60 (26.8%) vs 112 (13.7%), p<0.001), fatigue (64 (28.6%) vs 77 (9.4%), p<0.001), taste (32 (14.3%) vs 28 (3.4%), p<0.001), smell (36 (16.1%) vs 31 (3.8%), p<0.001), myalgia (34 (15.2%) vs 65 (8%), p=0.002), decreased mood (29 (12.9%) vs 40 (4.9%), p<0.001) and attention (30 (13.4%) vs 68 (8.3%), p=0.028). None of the symptoms were more prevalent in the younger age group (online supplemental material table 1S part B; figure 2).

Symptoms more prevalent in children without a history of SARS-CoV-2 infection were attention problems with school malfunctioning (225 (10.8%) vs 98 (8.5%), p=0.05), stress or increased worries (190 (9.1%) vs 65 (5.7%), p<0.001), social problems (164 (7.8%) vs 32 (2.8%)), weight changes (143 (6.8%) vs 43 (3.7%), p<0.001) and sleep disturbances (103 (4.9%) vs 34 (3%), p=0.008). All these symptoms were more prevalent in the older age group. However, in the older age group, all these symptoms were not significantly different between children with or without a history of SARS-CoV-2 infection (online supplemental material table 1S part B).

Symptoms which were not found significantly different between children with or without a history of SARS-CoV-2 infection include decreased mood (69 (6%) vs 163 (7.8%), p=0.064), rash (13 (1.1%) vs 18 (0.9%), p=0.455),

Table 3 Univariate comparison of symptoms of patients with and without a history of SARS-CoV-2 infection

	No history of SARS-CoV-2 infection N=2092	With a history of SARS-CoV-2 infection N=1148	
	n (%)	n (%)	P value
No reported symptoms	1396 (66.7)	646 (56.3)	<0.001
≥1 symptom	696 (33.3)	502 (43.7)	
≥5 symptoms	89 (4.3)	114 (9.9)	<0.001
Current health status compared with before illness/pandemic—worse	113 (5.4)	107 (9.3)	<0.001
Symptoms more prevalent in patients with a history of SARS-CoV-2 infection			
Headaches	114 (5.4)	211 (18.4)	<0.001
Weakness	70 (3.3)	173 (15.1)	<0.001
Fatigue	133 (6.4)	141 (12.3)	<0.001
Abdominal pain	79 (3.8)	109 (9.5)	<0.001
Cough	49 (2.3)	101 (8.8)	<0.001
Myalgia	47 (2.2)	99 (8.6)	<0.001
Decreased smell sensation	4 (0.2)	67 (5.8)	<0.001
Decreased taste sensation	2 (0.1)	60 (5.2)	<0.001
Nausea	43 (2.1)	51 (4.4)	<0.001
Memory disturbances	18 (0.9)	51 (4.4)	<0.001
Dizziness	33 (1.6)	46 (4.0)	<0.001
Arthralgia	12 (0.6)	39 (3.4)	<0.001
Chest pain	13 (0.6)	31 (2.7)	<0.001
Dyspnoea	20 (1)	31 (2.7)	<0.001
Increased heart rate	14 (0.7)	23 (2.0)	<0.001
Symptoms more prevalent in patients with no history of SARS-CoV-2 infection			
Attention problems with school malfunctioning	225 (10.8)	98 (8.5)	0.05
Stress or increased worries	190 (9.1)	65 (5.7)	<0.001
Social problems	164 (7.8)	32 (2.8)	<0.001
Weight changes	143 (6.8)	43 (3.7)	<0.001
Sleep disturbance	103 (4.9)	34 (3.0)	0.008
Symptoms with non-significant results			
Decreased mood	163 (7.8)	69 (6)	0.064
Rash	18 (0.9)	13 (1.1)	0.455
Visual disturbance	22 (1.1)	14 (1.2)	0.727
Hearing disturbances	7 (0.3)	0 (0)	0.056

visual disturbances (14 (1.2%) vs 22 (1.1%), p=0.727) and hearing problems (0 (0%) vs 7 (0.3%), p=0.056).

Multivariate analysis

Factors associated with at least one long COVID symptom include older age and a history of symptomatic COVID-19 infection. Each 1 year increment in age increases the risk in 8% (OR=1.08, 95% CI 1.03 to 1.14, p=0.001). The history of symptomatic COVID-19 infection increases the risk substantially (OR=4.41, 95% CI 3.27 to 5.94, p<0.001) (online supplemental material table 2S part B).

Failure (or inability) to return to baseline health status in children with a history of SARS-CoV-2 infection was associated with fatigue (OR=9.71, 95% CI 5.58 to 16.87, p<0.001), weight changes (OR=4.75, 95% CI 1.92 to 11.76, p<0.001), decreased social functioning (OR=4.58, 95% CI 1.64 to 12.77, p=0.004), dyspnoea (OR=3.35, 95% CI 1.16 to 9.63, p=0.025), increased stress (OR=2.97, 95% CI 1.37 to 6.43, p=0.006), dizziness (OR=2.75, 95% CI 1.17 to 6.49, p=0.021), headaches (OR=2.70, 95% CI 1.52 to 4.80, p<0.001) and attention disturbances with malfunction in

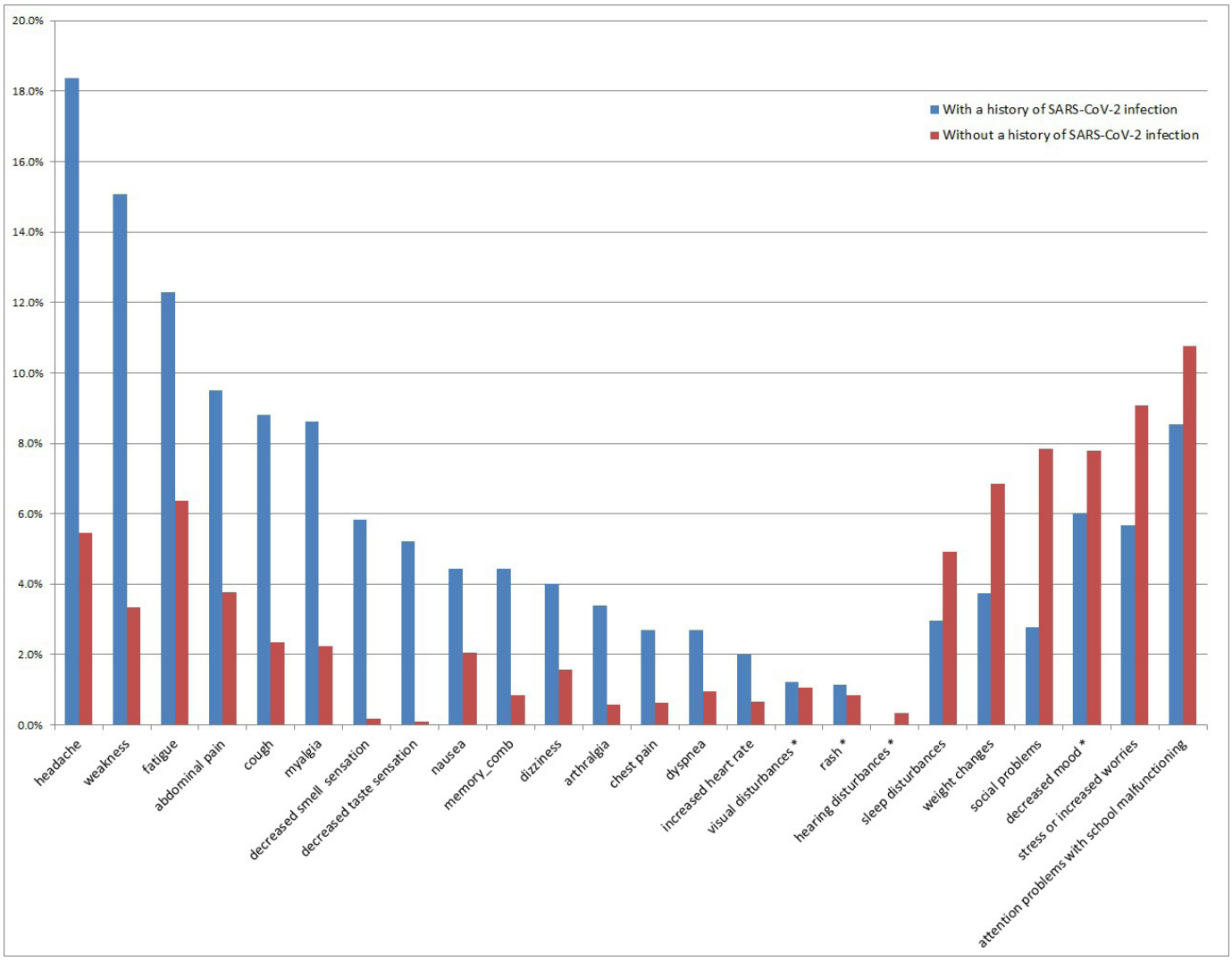

Figure 1 Rates of long COVID symptoms in children with and without a history of SARS-CoV-2 infection. Long COVID symptoms with insignificant differences are marked with an asterisk (*).

school (OR=2.19, 95% CI 1.12 to 4.26, p=0.022) (online supplemental material table 3S part B). Age, gender, time from illness, symptomatic disease and vaccination status were not associated with not returning to baseline health status in test-positive children.

DISCUSSION

Principal findings

We conducted a nationwide cross-sectional study to assess the prevalence of long COVID symptoms reported by the parents of children with or without a history of SARS-CoV-2 infection. In addition, we evaluated the factors associated with the presence of any long COVID symptom and not returning to baseline state of health.

Children with a history of SARS-CoV-2 infection had significantly more physical symptoms, including headaches, weakness, fatigue, abdominal pain, cough, myalgia, decreased smell and taste sensation, nausea, memory disturbances, dizziness, arthralgia, chest pain, dyspnoea and increased heart rate. Children without a history of SARS-CoV-2 infection had significantly more functional symptoms, including attention problems with a malfunction in school, stress or increased worries, social problems, weight changes and sleep disturbances. Almost all symptoms were more prevalent among the older age group than the younger age group.

Factors associated with at least one long COVID symptom were age and symptomatic SARS-CoV-2 infection. Factors associated with not returning to baseline health status were long COVID symptoms, including fatigue, weight changes, decreased social functioning, dyspnoea, increased stress, dizziness, headache and attention disturbances with malfunction at school.

Strengths and limitations

The strengths of this study are its nationwide coverage, the relatively large number of participants, the comparison of children with or without a history of SARS-CoV-2 infection and the broad age range (5–18 years old).

This study has several limitations. First, its relatively low response rate (11.9%) and the cross-sectional design

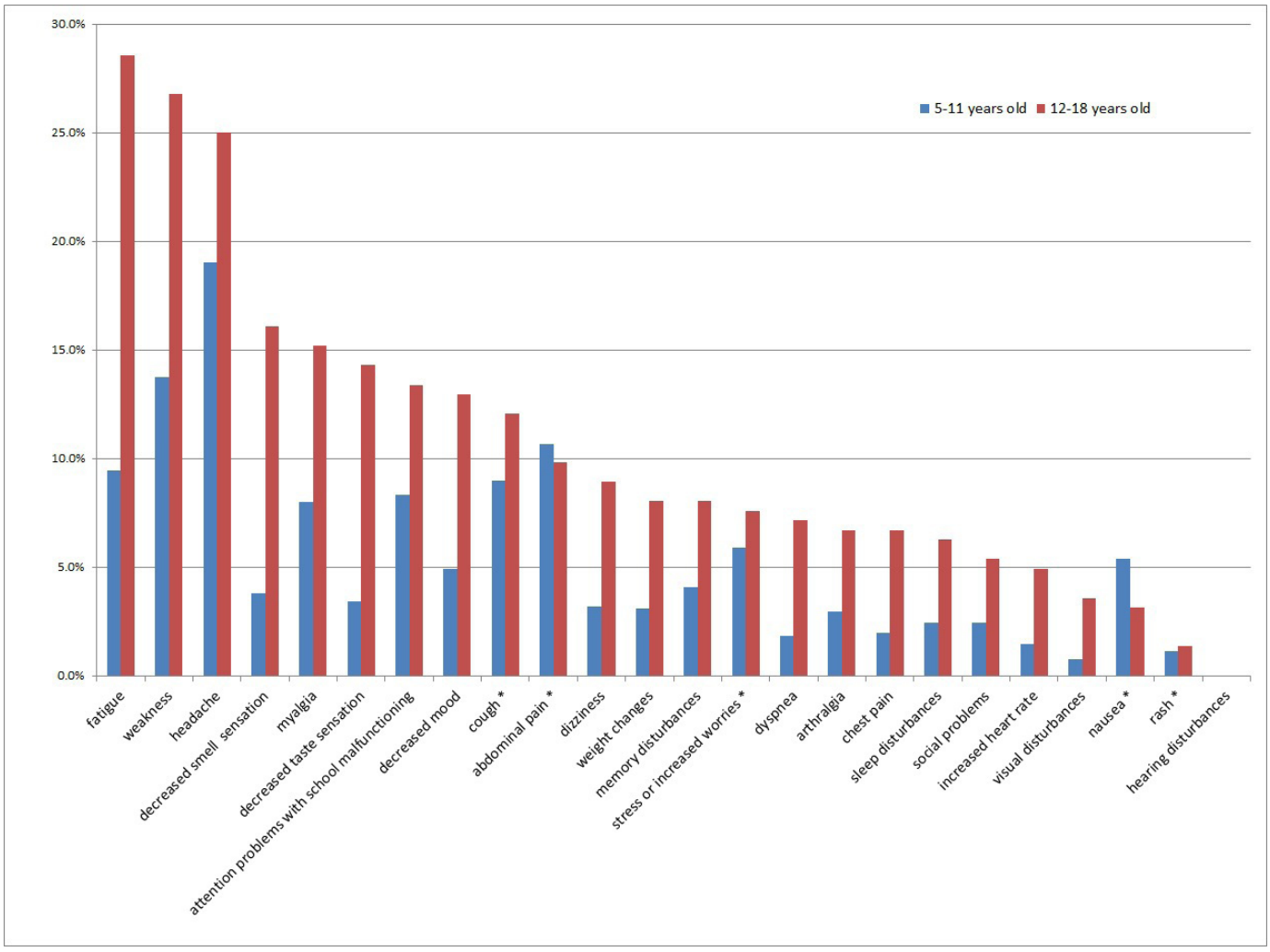

Figure 2 Rates of long COVID symptoms in children with a history of SARS-CoV-2 infection—a comparison between children aged 5–11 and adolescents aged 12–18. Long COVID symptoms with insignificant differences between age groups are marked with an asterisk (*).

may cause a selection bias. Parents of children with more symptoms might respond more than other parents. Since parents could choose which child they report in the questionnaire, they might have chosen the child with the most symptoms. Second, the responses from a proxy (a parent) rather than the child and the potential for differential misclassification bias as parents to children with a history of SARS-CoV-2 infection may report more symptoms than children without a history of SARS-CoV-2 infection. These factors combined might have caused the reported prevalence of long COVID symptoms to be higher than it is. Third, this study represents only long symptoms related to the Delta and Omicron variants. Different variants might not have the same long-term influence on children. Fourth, children without a history of SARS-CoV-2 infection might actually have an asymptomatic infection they were unaware of. This, however, gives us a conservative estimation of the difference between the groups. Fifth, the questionnaire was built by the authors of this study and is not validated. This might also affect the results. In order to overcome some of the above-mentioned limitations, especially the possible selection bias, we have compared the parents who did and did not respond to our survey to reduce this possible selection bias.

Interpretation

We report a high rate of at least one long COVID symptom in both children with or without a history of SARS-CoV-2 infection (43.7% vs 33.3%). This is in line with other studies that found similar rates of long COVID symptoms, including 35.4% vs 8.3% in the CLOCK study and 61.9% vs 57% in the LongCOVIDKidsDK.[9 13] However, other studies reported much lower rates of having at least one long COVID symptom, including Molteni *et al* with only 4.4% after 28 days and 1.8% at 56 days, Radtke *et al* with 4% vs 2% and Zavala *et al* with 6.7% vs 4.2%.[8 10 12] In Borch *et al*'s study, the prevalence of long COVID symptoms was 28%. However, the residual difference was only 0.8%, implicating a very low prevalence of long COVID in children attributable to the infection itself.[14] These differences were addressed by Molteni herself and explained by some possible reasons: different study design, different

response rates (and thus a better or worse representation of the entire paediatric population), gender imbalance, recall bias and the higher awareness for this syndrome due to extensive media coverage.[15]

The presence of at least five symptoms in our study is 9.9% vs 4.3%, lower than the rate reported by the CLOCK study (23.7% vs 3.8%). The age differences in both studies can explain this. The CLOCK focused mainly on adolescents, whereas our study age range was 5–18, with a median age of 10.8 and 9.5 in test-positive and test-negative children, respectively.

The five most prevalent long COVID symptoms reported by parents of children with versus without a history of SARS-CoV-2 infection were headaches, weakness, fatigue, abdominal pain and cough. In Behnood *et al*'s meta-analysis, headache, loss of smell, sore throat and sore eyes were more prevalent in test-positive than test-negative children.[7] However, abdominal pain, cough, fatigue, myalgia, insomnia, diarrhoea, fever, dizziness and dyspnoea were similarly prevalent in both groups. It is important to note that the LongCOVIDKidsDK was not included in this meta-analysis. In this study, the most prevalent symptoms were dyspnoea, cough, sore throat, dizziness and chest pain.[13] Borch *et al* reported that fatigue, loss of smell and taste, muscle weakness, chest pain, dizziness and respiratory problems were the most reported symptoms.[14] The symptoms in children are similar to the symptoms most commonly reported by adults. These include weakness, general malaise, fatigue, dyspnoea, arthralgia and headache.[16–19]

Interestingly, our study found that some symptoms were more prevalent in children without a history of SARS-CoV-2 infection, including attention with malfunction in school, stress or increased worries, social problems, weight changes and sleep disturbances. These are all functional complaints that may reflect life's impact during the pandemic on children. Notably, no significant difference in these symptoms existed in the older age group in adolescents with or without a history of SARS-CoV-2 infection. This is in line with the results of Blankenburg *et al*, which reported a lack of differences in neurocognitive, general pain and most mood symptoms with a very high rate of reported symptoms (at least 35%) regardless of serostatus.[11] It is also in line with Borch *et al*'s study that reported concentration problems to be more prevalent in children without a history of infection.[14] This highlights the impact of the pandemic itself, rather than being infected, as a significant source of stress, decreased mood and poor quality of life for children and adolescents.[20–23]

We found that the presence of any long COVID symptom was associated with older age and a history of a symptomatic disease but not with gender. Older age and female gender were associated with long COVID symptoms in children and adolescents in most studies.[7 9–11] In adults, risk factors for long COVID symptoms include age, female gender and the history of symptomatic disease.[24–26]

CONCLUSION

This study suggests that the prevalence of long COVID symptoms in children with a history of SARS-CoV-2 infection might be higher and more prevalent in adolescents than in young children. Some of the symptoms, mainly somatic symptoms, were more prevalent in children without a history of SARS-CoV-2 infection, highlighting the impact of the pandemic itself rather than the infection.

Contributors LA is the guarantor for this study. LA conceptualised and designed the study, designed the data collection instruments, carried out the initial analysis, drafted the initial manuscript and reviewed and revised the manuscript. MI designed the data collection instruments, collected the data and reviewed and revised the manuscript. IY, JA, RH, AS and MMR conceptualised and designed the study and reviewed and revised the manuscript. ZG conceptualised and designed the study, designed the data collection instruments and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by the Maccabi Healthcare Services Institutional Review Board (ID 0169-20-MHS). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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