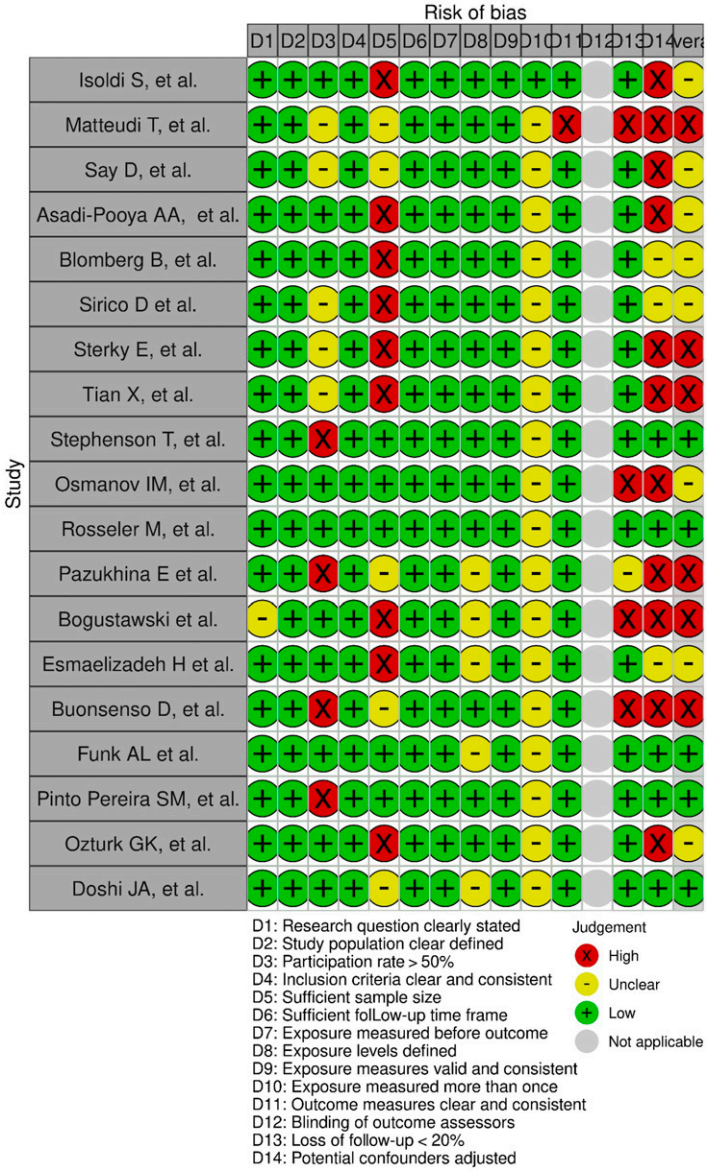
Supplemental Information

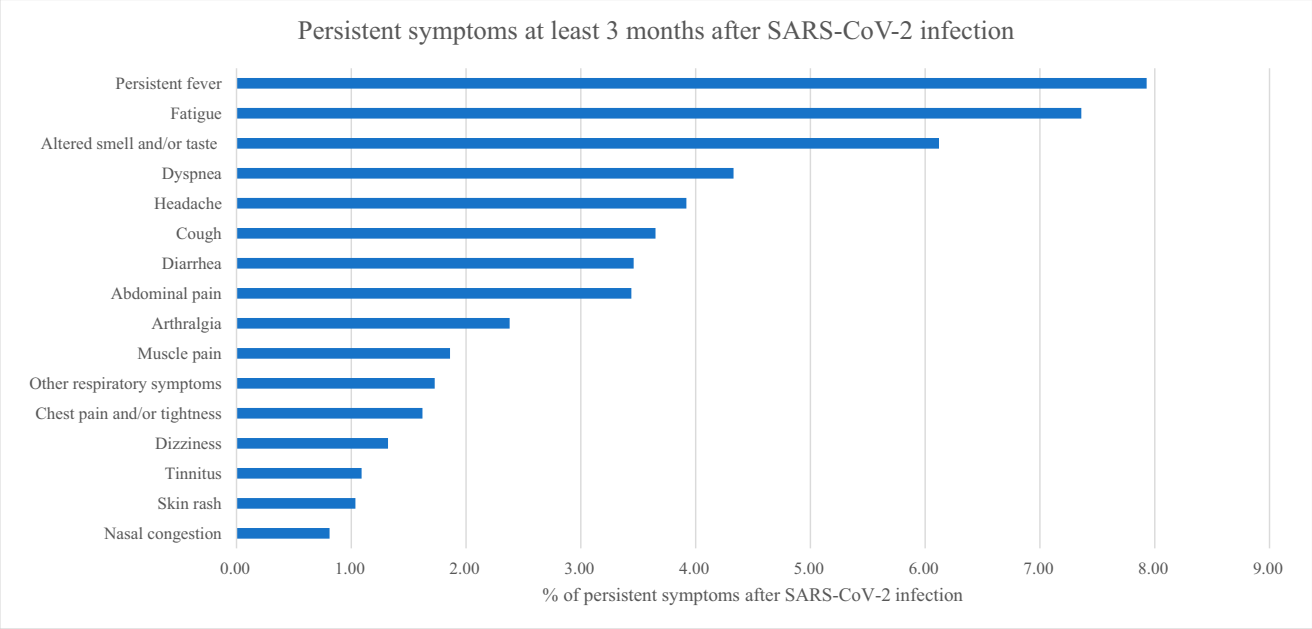
Research Question:

What are the prevalence and characteristics of the long-term outcomes of SARS-CoV-2 infection in children and adolescents?

- Population: the general neonates, children and adolescents population
- Intervention (exposure): SARS-CoV-2 infection
- Comparison: neonates, children, and adolescents not infected with SARS-CoV
- Outcome: new, persistent, recurring symptoms after acute SARS-CoV-2 infection



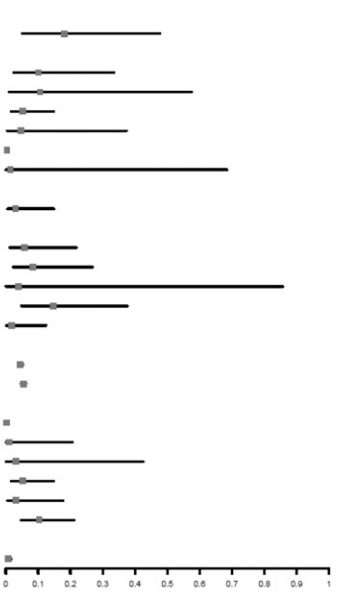
SUPPLEMENTAL FIGURE 4
Risk of bias of included prospective cohort studies ($N = 19$).



SUPPLEMENTAL FIGURE 5
Pooled proportion of persistent symptoms of COVID-19 (at least 3 months after acute SARS-CoV-2 infection) in neonates, children, and adolescents (0–19y)—Sensitivity analysis.

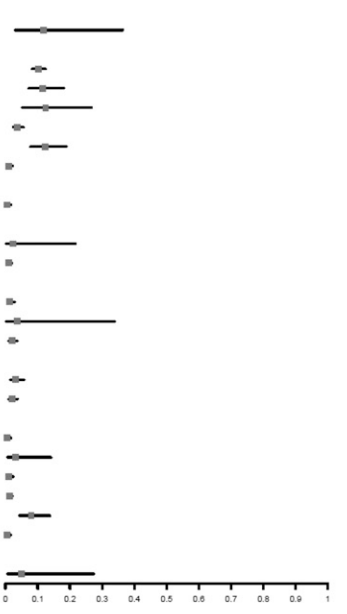
A

Followed–symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	4	1232	5158	99.3499
Systemic symptoms				
Fatigue	5	750	5199	98.3498
Persistent fever	3	582	4990	98.8078
Sleep disturbance	1	3	58	0.0000
Headache	4	819	5048	98.1086
Weight loss	1	7	1884	0.0000
Dizziness	2	464	4949	98.0795
Cardiac symptoms				
Chest pain and/or tightness	4	289	5040	94.1622
Respiratory symptoms				
Dyspnea	4	379	5057	97.1930
Cough	6	529	5249	97.5182
Nasal congestion	2	20	1925	98.9357
Sore throat	2	690	3106	78.5186
Other respiratory symptoms	2	15	1942	90.5031
Gastrointestinal symptoms				
Abdominal pain	1	138	3065	0.0000
Diarrhea	1	166	3065	0.0000
Neurologic and musculoskeletal symptoms				
Depression	1	6	1884	0.0000
Tinnitus	2	159	4949	97.5185
Altered smell and/or taste	3	641	4990	98.6211
Arthralgia	1	3	58	0.0000
Muscle pain	4	348	5048	95.5336
Muscle weakness	1	6	58	0.0000
Skin manifestations				
Skin rash	2	45	4949	78.2976



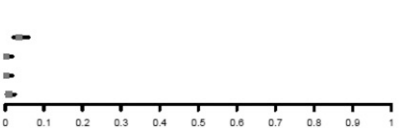
B

Followed–symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	3	136	668	91.0333
Systemic symptoms				
Fatigue	2	87	856	0.0000
Persistent fever	1	16	138	0.0000
Sleep disturbance	2	67	639	91.9293
Headache	2	23	624	0.0000
Weight loss	1	17	138	0.0000
Dizziness	2	5	622	0.0000
Neurocognitive symptoms				
Difficulty in concentration	1	2	486	0.0000
Cardiac symptoms				
Chest pain and/or tightness	2	13	625	93.0978
Palpitation	3	9	969	0.0000
Respiratory symptoms				
Dyspnea	1	7	503	0.0000
Cough	2	22	641	96.1349
Nasal congestion	1	10	505	0.0000
Gastrointestinal symptoms				
Abdominal pain	3	17	653	33.4286
Diarrhea	1	10	499	0.0000
Neurologic and musculoskeletal symptoms				
Paresthesia	1	2	472	0.0000
Altered smell and/or taste	4	50	982	87.1615
Arthralgia	2	6	630	0.0000
Muscle pain	3	10	988	0.0000
Muscle weakness	1	11	138	0.0000
Tremor	2	3	638	0.0000
Skin manifestations				
Skin rash	2	26	635	95.6282



C

Followed–symptoms	Number of studies	Cases	Sample size	I^2
Fatigue	1	13	360	0.0000
Palpitation	1	1	360	0.0000
Arthralgia	1	1	360	0.0000
Muscle pain	1	3	360	0.0000

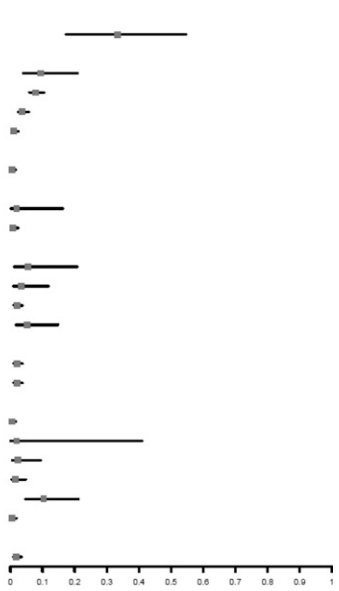


SUPPLEMENTAL FIGURE 6

Pooled proportion of persistent symptoms of COVID-19 (at least 3 months after acute SARS-CoV-2 infection) in neonates, children, and adolescents (0–19y)—subgroup analysis by follow-up duration. (A) Three to 6 months of follow-up. (B) Six to 12 months of follow-up. (C) >12 months of follow-up.

A Up-middle income countries

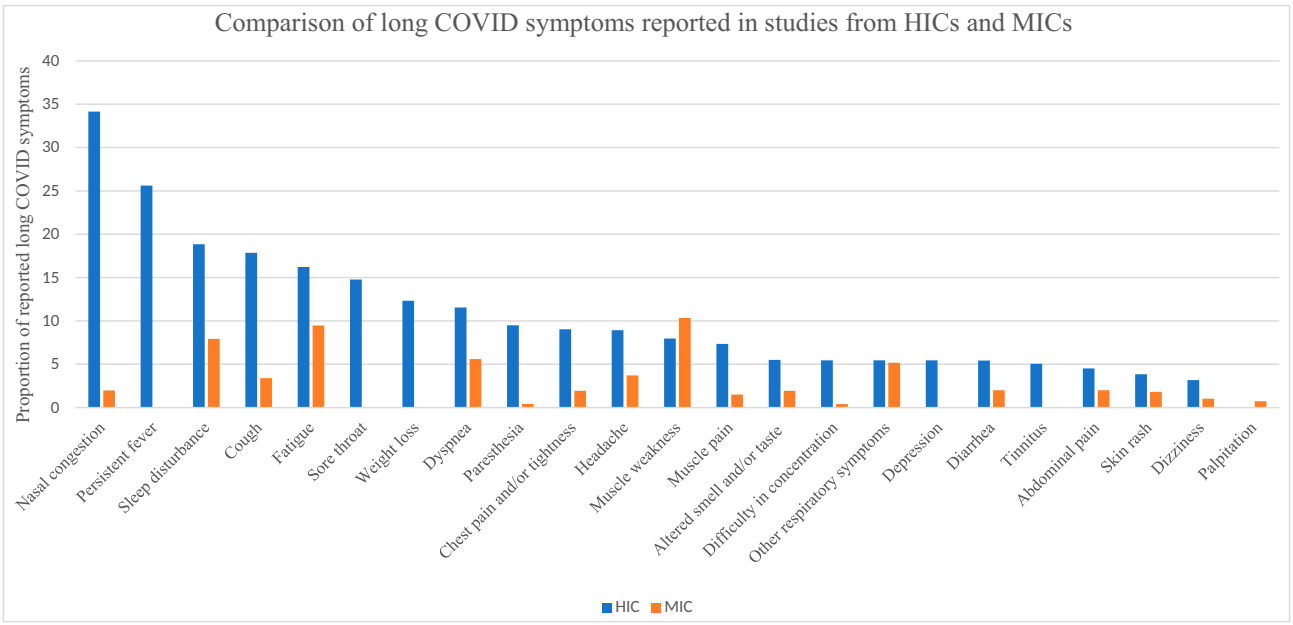
Followed−symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	2	154	572	90.0245
Systemic symptoms				
Fatigue	3	78	914	90.8858
Sleep disturbance	2	44	559	0.0000
Headache	2	20	544	0.0000
Dizziness	1	5	484	0.0000
Neurocognitive symptoms				
Difficulty in concentration	1	2	486	0.0000
Cardiac symptoms				
Chest pain and/or tightness	2	6	537	87.3112
Palpitation	2	6	831	33.7460
Respiratory symptoms				
Dyspnea	3	19	611	90.0618
Cough	3	12	611	81.0979
Nasal congestion	1	10	505	0.0000
Other respiratory symptoms	1	3	58	0.0000
Gastrointestinal symptoms				
Abdominal pain	1	10	499	0.0000
Diarrhea	1	10	499	0.0000
Neurologic and musculoskeletal symptoms				
Paresthesia	1	2	472	0.0000
Altered smell and/or taste	2	46	828	92.2571
Arthralgia	2	9	550	76.4319
Muscle pain	3	10	908	72.0289
Muscle weakness	1	6	58	0.0000
Tremor	1	3	500	0.0000
Skin manifestations				
Skin rash	1	9	497	0.0000



B High-income countries

Followed−symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	6	1139	3562	94.7059
Systemic symptoms				
Fatigue	4	725	3312	90.5527
Persistent fever	3	589	3244	95.1482
Sleep disturbance	1	26	138	0.0000
Headache	4	823	3381	94.2701
Weight loss	1	17	138	0.0000
Dizziness	2	462	3203	86.7537
Neurocognitive symptoms				
Difficulty in concentration	1	3	55	0.0000
Cardiac symptoms				
Chest pain and/or tightness	3	293	3244	0.0000
Respiratory symptoms				
Dyspnea	1	354	3065	0.0000
Cough	4	526	3395	95.0504
Nasal congestion	1	14	41	0.0000
Sore throat	2	690	3106	78.5186
Other respiratory symptoms	3	3	55	0.0000
Gastrointestinal symptoms				
Abdominal pain	3	145	3219	0.0000
Diarrhea	1	166	3065	0.0000
Neurologic and musculoskeletal symptoms				
Depression	1	3	55	0.0000
Paresthesia	1	13	137	0.0000
Tinnitus	1	155	3065	0.0000
Altered smell and/or taste	5	636	3315	81.8603
Muscle pain	4	345	3299	59.9989
Muscle weakness	1	11	138	0.0000
Skin manifestations				
Skin rash	2	52	3203	98.4622

SUPPLEMENTAL FIGURE 7
Pooled proportion of persistent symptoms of COVID-19 (at least 3 months after acute SARS-CoV-2 infection) in neonates, children, and adolescents (0–19y)—subgroup analysis by country's income level. (A) Upper-middle income countries. (B) High-income countries.



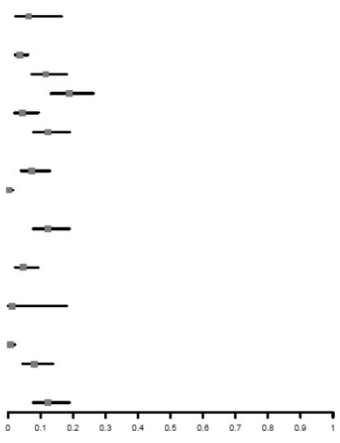
SUPPLEMENTAL FIGURE 8
Comparison of the prevalence of long COVID symptoms reported in prospective cohort studies from HICs and MICs.

A

Followed−symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	7	1395	5864	98.7375
Systemic symptoms				
Fatigue	7	811	5750	97.7769
Persistent fever	3	582	4990	98.8078
Sleep disturbance	2	44	559	0.0000
Headache	6	844	5671	98.0534
Weight loss	1	7	1884	0.0000
Dizziness	3	469	5433	97.7922
Neurocognitive symptoms				
Difficulty in concentration	2	5	541	87.7034
Cardiac symptoms				
Chest pain and/or tightness	5	292	5527	94.5495
Palpitation	1	5	471	0.0000
Respiratory symptoms				
Dyspnea	5	386	5560	97.0808
Cough	7	534	5752	97.5055
Nasal congestion	3	30	2430	98.0614
Sore throat	2	690	3106	78.5186
Other respiratory symptoms	3	18	1997	88.9558
Gastrointestinal symptoms				
Abdominal pain	2	148	3564	84.2870
Diarrhea	2	176	3564	89.7739
Neurologic and musculoskeletal symptoms				
Depression	2	9	1939	93.7922
Paresthesia	2	15	609	94.2817
Tinnitus	2	159	4949	97.5185
Altered smell and/or taste	5	688	5513	97.7314
Arthralgia	2	9	550	76.4319
Muscle pain	6	356	5593	94.7432
Muscle weakness	1	6	58	0.0000
Tremor	1	3	500	0.0000
Skin manifestations				
Skin rash	3	54	5446	73.7920

B

Followed−symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	2	8	154	43.1362
Systemic symptoms				
Fatigue	1	13	360	0
Persistent fever	1	16	138	0
Sleep disturbance	1	26	138	0
Headache	1	6	138	0
Weight loss	1	17	138	0
Cardiac symptoms				
Chest pain and/or tightness	1	10	138	0
Palpitation	2	1	498	0
Respiratory symptoms				
Cough	1	17	138	0
Gastrointestinal symptoms				
Abdominal pain	2	7	154	0
Neurologic and musculoskeletal symptoms				
Altered smell and/or taste	3	3	514	83.3069
Arthralgia	0			
Muscle pain	2	3	498	0
Muscle weakness	1	11	138	0
Skin manifestations				
Skin rash	1	17	138	0



SUPPLEMENTAL FIGURE 9

Pooled proportion of persistent symptoms of COVID-19 (at least 3 months after acute SARS-CoV-2 infection) in neonates, children, and adolescents (0–19y)—subgroup analysis by study population. (A) Recruiting a pediatric population only. (B) Recruiting a mixed adult and pediatric population, with pediatric data reported separately.

SUPPLEMENTAL TABLE 4 Search Strategy for PubMed (Dec 31, 2022)			
Search Number	**Search Terms**	**Results**	**Comments**
Search set 1	COVID-19 Terms		
1	SARS-CoV-2[MeSH] OR COVID-19[MeSH] OR "SARS Coronavirus 2"[tiab] OR "Coronavirus 2, SARS"[tiab] OR 2019 Novel Coronavirus*[tiab] OR "Coronavirus, 2019 Novel"[tiab] OR "Novel Coronavirus, 2019" OR "Wuhan Seafood Market Pneumonia virus"[tiab] OR SARS-CoV-2 [tiab] OR "SARS CoV 2"[tiab] OR "2019-nCoV"[tiab] OR COVID-19 [tiab] OR "COVID 19"[tiab] OR "virus, COVID-19"[tiab] OR "Wuhan Coronavirus"[tiab] OR COVID19 [tiab] OR virus*, COVID19[tiab] OR "severe acute respiratory syndrome coronavirus 2"[tiab] OR "coronavirus disease 2019"[tiab] OR "disease 2019, coronavirus"[tiab] OR "coronavirus disease 19"[tiab] OR "coronavirus disease-19"[tiab] OR "infection, SARS-CoV-2"[tiab] OR "disease, 2019-nCoV" OR "virus infection, COVID-19"[tiab] OR "disease, COVID-19 virus"[tiab] OR "viral disease, COVID-19" [tiab] OR "infection, 2019-nCoV"[tiab] OR "pandemic, COVID-19"[tiab]	322 794	
Search set 2	Pediatric		
2	"infant, newborn" [Mesh] OR "infants, newborn" [tiab] OR newborn infant*[tiab] OR newborn* [tiab] OR neonate* [tiab]	767 895	
3	child [Mesh] OR children [tiab]	2 457 610	
4	adolescent [Mesh] OR adolescents [tiab] OR adolescence [tiab] OR teen* [tiab] OR teenager* [tiab] OR youth*[tiab]	2 291 862	
5	2 OR 3 OR 4	4 169 272	
Search set 3	Long-term symptoms and outcomes		
6	long[tiab] OR "long-term"[tiab] OR "long term" [tiab] OR "persistent" [tiab] OR prolong* [tiab] OR "post-acute"[tiab] OR "post acute"[tiab] OR "chronic"[tiab]	3 523 405	
7	Symptom* [tiab] OR infect*[tiab] OR complication*[tiab] OR syndrome*[tiab] OR illness* [tiab] OR sequelae*[tiab] OR outcome*[tiab] OR duration*[tiab] OR "follow up"[tiab] OR "follow-up"[tiab] OR followup [tiab] OR recover* [tiab]	8 113 765	
8	6 AND 7	1 579 008	
Search set 4	Long COVID		
9	"Post-acute COVID-19 syndrome"[tiab] OR "long-COVID"[tiab] OR "long COVID"[tiab] OR "long-haul COVID"[tiab] OR "post-acute COVID syndrome"[tiab] OR "post-acute COVID19 syndrome"[tiab] OR "persistent COVID-19"[tiab] OR "long hauler COVID"[tiab] OR "post-acute sequelae of SARS-CoV-2 infection"[tiab] OR "long haul COVID"[tiab] OR "chronic COVID syndrome"[tiab]	2740	
Final search			
10	1 AND 8	28 561	
11	9 OR 10	28 970	
12	5 AND 11	3328	

SUPPLEMENTAL TABLE 5 Search Strategy for Embase (Dec 31, 2022)			
Search Number	**Search Terms**	**Results**	**Comments**
Search set 1	COVID-19 terms		
1	exp coronavirus disease 2019/	315 581	
2	SARS-CoV-2.mp. or exp severe acute respiratory syndrome coronavirus 2/	158 855	
3	(new or novel or 19 or 2019 or Wuhan or China or Chinese or Huanan) adj3 (coronavirus* or corona virus* or CoV or HCoV or betacoronavirus* or COVID).mp.	385 202	
4	1 or 2 or 3	402 568	
Search set 2	Long term symptoms		
5	(long or prolong* or long-term or longterm or "long term" or chronic or persist* or post-acute or "post acute" or postacute or longlasting or "long lasting" or long-lasting).mp.	5 721 697	
6	(symptom* or infect* or complication* or syndrome* or illness* or outcome* or sequelae* or duration* or followup or "follow up" or follow-up or recover*).mp.	14 483 510	
7	5 adj3 6	688 890	
Search set 3	Long COVID		
8	(long covid or chronic covid or persistent covid or persisting covid or postacute covid or post-acute covid or post acute covid).mp.	4618	
Search set 4	Pediatric		
9	exp newborn/	680 817	
10	exp infant/	1 288 884	
11	exp pediatrics/	137 503	
12	exp child/ or exp school child/ or exp preschool child/	3 430 438	
13	exp adolescent/	1 865 054	
14	exp young adult/	488 037	
15	(infant* or newborn* or neonate* or child* or teen* or adolescen* or youth* or school age*).mp.	5 171 270	
16	9 or 10 or 11 or 12 or 13 or 14 or 15	5 513 142	
Joint term			
17	4 and 7	10 889	
18	8 or 17	12 936	
19	16 and 18	1974	
20	limit 19 to yr="2019 - 2022"	1863	

SUPPLEMENTAL TABLE 6 Search Strategy for Web of Science (Dec 31, 2022)		
Search Number	**Search Terms**	**Results**
Search set 1	COVID-19 terms	
1	**Topic:** "SARS-CoV-2"OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "2019 Novel Coronaviruses" OR "Coronavirus, 2019 Novel" OR "Novel Coronavirus, 2019" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2 Virus" OR "SARS CoV 2 Virus" OR "SARS-CoV-2 Viruses" OR "Virus, SARS-CoV-2" OR "2019-nCoV" OR "COVID-19 Virus" OR "COVID 19 Virus" OR "COVID-19 Viruses" OR "Virus, COVID-19" OR "Wuhan Coronavirus" OR "Coronavirus, Wuhan" OR "SARS Coronavirus 2" OR "Coronavirus 2, SARS" OR "Severe Acute Respiratory Syndrome Coronavirus 2"	283 133
Search set 2	Long term symptoms	
2	**Topic:** long or prolong* or long-term or longterm or "long term" or chronic or persist* or post-acute or "post acute" or postacute or longlasting or "long lasting" or long-lasting	12 299 417
3	**Topic:** symptom* or infect* or complication* or syndrome* or illness* or outcome* or sequelae* or duration* or followup or "follow up" or follow-up or recover*	20 077 234
4	2 AND 3	3 674 933
Search set 3	Long COVID terms	
5	"long covid" or "chronic covid" or "persistent covid" or "persisting covid" or "postacute covid" or "post-acute covid" or "post acute covid"	4113
Search set 4	Pediatric	
6	adolescen* OR child* OR infant* OR neonat* OR newborn* OR pediatric* OR pre-school* OR preschool* OR school* OR teen* OR toddler* OR youth*	8 192 044
Joint term		
7	1 and 4	38 516
8	5 or 7	40 037
9	6 and 8	6088
10	Limit 19= "2019 to 2022"	5943

Search Strategy for medRxiv

for title "adolescen*,child*,infant*, neonat*,newborn*, p?ediatric*, pre-school*, preschool*, school*,teen*, toddler, youth, young adult" (match any words) and abstract or title "long, prolonged, long lasting, chronic, postacute, symptom*, sequelae*, follow up, infect*, illness, complication, outcome" (match any words) and full text or abstract or title "long covid, chronic covid, persistent covid, postacute covid, post-acute covid, post acute covid, long lasting covid" (match whole any) and posted between "01 Dec, 2019 and 31 Dec, 2022"

Results: 420

SUPPLEMENTAL TABLE 7 Meta Regression Results Between Developing Long COVID Symptoms and Male Proportion

Symptom	Numbers of Study	Coefficient Estimate (95% CI)	*P*
Total number of children with persistent symptoms	9	−1.28 (−10.73 to 8.16)	.79
Fatigue	8	−11.18 (−23.95 to 1.58)	.09
Dyspnea	5	−7.02 (−22.46 to 8.41)	.37
persistent fever	4	−21.07 (−46.09 to 3.96)	.10
Sleep disturbance	3	−10.99 (−16.73 to −5.26)	<.01
Chest pain and or tightness	6	−13.43 (−27.66 to 0.79)	.06
Headache	7	−18.25 (−29.03 to −7.46)	<.01
Altered smell and or taste	8	−6.92 (−25.38 to 11.53)	.46
Abdominal pain	4	−7.25 (−13 to −1.51)	.01
Dizziness	4	−22.43 (−44 to −0.85)	.04
Muscle pain	8	−2.89 (−19.62 to 13.85)	.74
Cough	8	−13.52 (−28.51 to 1.47)	.08
Other respiratory symptoms	3	2.25 (−30.33 to 34.82)	.89
Nasal congestion	3	−56.95 (−76.31 to −37.59)	<.01
Palpitation	3	20.29 (−37.42 to 78)	.49
Skin rash	4	−10.57 (−25.42 to 4.28)	.16

SUPPLEMENTAL TABLE 8 Quality assessment tool for observational cohort and cross-sectional studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

*CD, cannot determine; NA, not applicable; NR, not reported.