Received: 3 January 2023 | Revised: 11 August 2023 | Accepted: 29 August 2023

DOI: 10.1111/apa.16966

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

ORIGINAL ARTICLE

Comparative study showed that children faced a 78% higher risk of new-onset conditions after they had COVID-19

Costanza Di Chiara[1,2] | Elisa Barbieri[1,2] | Yu Xi Chen[3] | Elisa Visonà[1] | Sara Cavagnis[1] | Giulia Sturniolo[1] | Agnese Parca[3] | Cecilia Liberati[1] | Luigi Cantarutti[4] | Angela Lupattelli[5] | Marthe Le Prevost[6] | Giovanni Corrao[3] | Carlo Giaquinto[1,2,4] | Daniele Donà[1,2] | Anna Cantarutti[3]

[1]Division of Paediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Padua, Italy

[2]Penta–Child Health Research, Padua, Italy

[3]Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy

[4]Società Servizi Telematici-Pedianet, Padua, Italy

[5]PharmacoEpidemiology and Drug Safety Research Group, Department of Pharmacy, and PharmaTox Strategic Research Initiative, University of Oslo, Oslo, Norway

[6]MRC Clinical Trials Unit at University College London, London, UK

Correspondence
Costanza Di Chiara, Division of Paediatric Infectious Diseases, Department for Women's and Children's Health, University of Padua, Via Giustiniani 3, Padua, Italy.
Email: costanza.dichiara@phd.unipd.it

Funding information
European Union's Horizon 2020 research and innovation programme, Grant/Award Number: 101016167

Abstract

Aim: Children have largely been unaffected by severe COVID-19 compared to adults, but data suggest that they may have experienced new conditions after developing the disease. We compared outcomes in children who had experienced COVID-19 and healthy controls.

Methods: A retrospective nested cohort study assessed the incidence rate of new-onset conditions after COVID-19 in children aged 0–14 years. Data were retrieved from an Italian paediatric primary care database linked to Veneto Region registries. Exposed children with a positive nasopharyngeal swab were matched 1:1 with unexposed children who had tested negative. Conditional Cox regression was fitted to estimate the adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for the exposure and outcome associations after adjusting for covariates.

Results: We compared 1656 exposed and 1656 unexposed children from 1 February 2020 to 30 November 2021. The overall excess risk for new-onset conditions after COVID-19 was 78% higher in the exposed than unexposed children. We found significantly higher risks for some new conditions in exposed children, including mental health issues (aHR 1.8, 95% CI 1.1–3.0) and neurological problems (aHR 2.4, 95% CI 1.4–4.1).

Conclusion: Exposed children had a 78% higher risk of developing new conditions of interest after COVID-19 than unexposed children.

KEYWORDS
COVID-19, new-onset conditions, paediatric patients, population-based study, real-world evidence

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; IR, incidence rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Daniele Donà and Anna Cantarutti contributed as co-last authors

1 | BACKGROUND

The aftermath of the COVID-19 pandemic continues to affect public health systems worldwide. During the first waves of the pandemic, the main focus was on understanding the clinical features of the acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. More recently, attention has focused on evaluating the emerging sequelae known as long COVID.[1]

Several long-term clinical follow-up studies on adults who recovered from COVID-19 have shown that a notable proportion developed persistent symptoms that affected every organ system. These lasted for weeks or months, regardless of the COVID-19 disease severity.[2–4]

Although the clinical and immunological features of COVID-19 differ in children and adults,[5–9] it has been shown that post-acute sequelae of the SARS-CoV-2 infection may also occur in the paediatric population. It has been reported that children have presented with neurological and psychological symptoms, as well as loss of smell, fatigue and dyspnoea.[10–12] However, evidence on the incidence of the onset of new conditions after COVID-19 in children and adolescents is still limited. One of the main reasons is the marked heterogeneity between studies, leading to difficulties in interpreting the findings.[9,13–15] Furthermore, attributing persistent symptoms to the SARS-CoV-2 infection or pandemic-associated social restrictions is still difficult. The reasons include a lack of studies with control groups who did not get the SARS-CoV-2 infection.[16] Therefore, the disease burden in children after COVID-19 remains uncertain and difficult to define.

The aim of this study was to evaluate the incidence and risk of the onset of new conditions after COVID-19 in Italian children and adolescents using a large paediatric primary care database. The study comprised subjects with and without a laboratory-confirmed SARS-CoV-2 infection.

Key Notes

- We compared new-onset conditions in children aged 0–14 years after they had tested positive for the virus that causes COVID-19 and in a non-affected control group.
- An Italian paediatric database was used to evaluate 1656 exposed and 1656 unexposed children from 1 February 2020 to 30 November 2021.
- Overall, children were 78% more likely to develop conditions of interest after COVID-19, including mental health issues and neurological problems.

2 | MATERIALS AND METHODS

2.1 | Setting

We conducted a retrospective nested-cohort study on data that 44 family paediatricians had supplied to the Italian Pedianet database (Società Servizi Telematici Srl). Pedianet uses Junior Bit software (Sosepe Srl) and comprises data from around 400 primary care family paediatricians. The network covers around 3% of the Italian paediatric population and has previously been described in detail.[17]

Pedianet records several types of patient-level information, including demographic data, health status, clinical symptoms, and outcomes. The database is linked to the Italian hospitalisation registry, which records all diagnoses when patients are discharged from public or private hospitals. It is also linked to the COVID-19 registry, which records details of all nasopharyngeal swabs carried out in the Veneto Region.

When children are born, the Italian National Healthcare System automatically assigns them to family paediatricians. They provide them and their families with free healthcare, regardless of income, nationality, and pre-existing health conditions. The first dataset records tend to start with their first paediatric visit and continue until their 14th or 16th birthday. The parents decide when the visits stop. Inclusion in the Pedianet database is voluntary, and less than 5% of parents or guardians refuse consent for their children's anonymised data to be used for research purposes. This means that the dataset is representative of the Veneto regional population.[17]

2.2 | Study design

The data were extracted on 30 November 2021. Data from national and regional registries showed that, up until 11 December 2021, 96% of infections in the Veneto region were caused by the Parental and Delta variants.[18] That means that this analysis covered the period before the Omicron wave (Table S1).

We identified all children aged between birth and 14 who were enrolled in Pedianet and had at least one positive or negative SARS-CoV-2 nasopharyngeal swab reported between 1 February 2020 and 30 November 2021. We only included children who attended regular well-child visits with their family paediatrician, in line with previous studies and as defined in Table S2.[19] We adopted this approach because children could also be followed up by a private paediatrician outside the National Healthcare System. This ensured that we had complete data on exposure, outcomes, and covariates.

2.3 | Exposure

Patients were classified as exposed if they had a positive SARS-CoV-2 nasopharyngeal swab. One unexposed child was randomly selected from the Pedianet Veneto cohort for each exposed child. They were both registered with the same family paediatrician and were the same sex and age at cohort entry. The controls had not

been infected at the time of the selection process or only had negative swabs noted in their records. Children classified as unexposed could be selected for matching more than once and could contribute to both the unexposed and exposed data if they had a positive SARS-CoV-2 swab at a later date. This happened in 84/3312 (2.5%) cases.

The index date was the first positive nasopharyngeal swab in the exposed child, and the period of interest started 28 days later. We identified three periods of interest (Figure S1). Short-term was 4 months after a positive test: up to 90 days after day 28. The medium term was 7 months after a positive test: 91–180 days after day 28. Long-term was more than 7 months after a positive test: 181 days to the end of follow-up after day 28. All the children contributed to the short-term period, but they only contributed to the medium and long-term periods of interest if data were available.

2.4 | Outcomes

The risk of the onset of new medical conditions after COVID-19 disease was assessed among exposed and unexposed children. We considered eight clinical outcomes of interest: cardiovascular, respiratory, gastrointestinal, neurological, mental health, musculoskeletal, metabolic, and others. The other categories mostly included smell and taste alterations and skin rashes. Signs, symptoms, and diagnoses of interest were selected based on the existing literature on post COVID-19 conditions (Table S3). Diagnoses and symptoms were extracted from specialist outpatient visits, hospital, and emergency room admissions. We also examined any medical observations recorded in the free text sections of the medical notes during visits to family paediatricians. To avoid misclassifying and overestimating outcomes, each diagnosis was reviewed and validated by two paediatricians with expertise in paediatric infectious diseases (CD and GS). They were both blinded to which exposed or unexposed group the subject belonged to. The records were verified by a third blinded paediatrician (DD) if there were any disagreements about the classification. Outcomes were not recorded if the data were not considered acceptable, for example, if the diagnosis was unclear or information was missing or conflicting. We also looked at any diagnoses or symptoms during the pre-COVID-19 time period from 1 January 2018 to 1 February 2020 and excluded any subjects with the conditions of interest during this period.

2.5 | Covariates

Information on the covariates used to adjust for confounding was obtained from the Pedianet dataset. The earliest date considered was 1 January 2018 so that we had at least 2 years' worth of data before the pandemic. The latest date was the index date, which was when the case had a positive result for SARS-CoV-2. These included the year the child was born, the preterm birth, number of medical evaluations by family paediatricians, outpatient and specialist visits, and prescribed antibiotic therapies. Preterm birth was used as a proxy for the intensity of healthcare support required by the child, and we also included delivery characteristics not related to preterm birth.

2.6 | Statistical analysis

Descriptive statistics were used to summarise the baseline characteristics of the exposed and unexposed children, including year of birth, evaluations by family paediatricians, outpatient and specialistic visits, prescriptions for antibiotic therapies, and preterm birth. The Mantel-Haenszel test was used to assess differences between categorical covariates.

Incidence rates (IR) of the onset of new conditions of interest after the child had COVID-19 were expressed as the number of cases per 100 000 person-months, with 95% confidence intervals (CI). They were stratified by short, medium, and long-term COVID-19 disease. The Cochran-Armitage trend test analysed the trend over time of the post-COVID-19 conditions.

Conditional Cox proportional hazard regression estimated the hazard ratios (HRs) and 95% CIs for the association between exposure to COVID-19 and the subsequent onset of new conditions for each category of interest. HRs were adjusted for all covariates, and adjusted HRs (aHRs) are presented. The results were corrected using the Benjamini-Hochberg false discovery rate method.[20]

The participants accumulated person-months of follow-up from the index date until the date of the onset of the condition of interest. They were censored by whatever came first: 30 November 2021 or when they died, moved to a different family paediatrician or general practitioner, or left the Veneto region.

COVID-19 vaccinations for children aged 12–18 years began in Italy in July 2021 and a sensitivity analysis was carried out that added vaccination to the censored events.

SAS software, version 9.4 (SAS Institute) was used for the analyses[21] and two-tailed p values of less than 0.05 were considered significant for all hypotheses.

2.7 | Ethics

Pedianet's Internal Scientific Committee provided ethical approval for the study and access to the database. The study protocol and access to the data were approved by the Pedianet Institutional Review Board in Padova. No additional ethical consent was required due to the retrospective nature of the study and the use of aggregated and anonymised data.

3 | RESULTS

3.1 | Study population characteristics

Of the 36,270 children who met the inclusion criteria, 5208 (14.4%) had experienced COVID-19, and 2789 were successfully matched with an unexposed child (Figure 1). We excluded 1133 pairs because

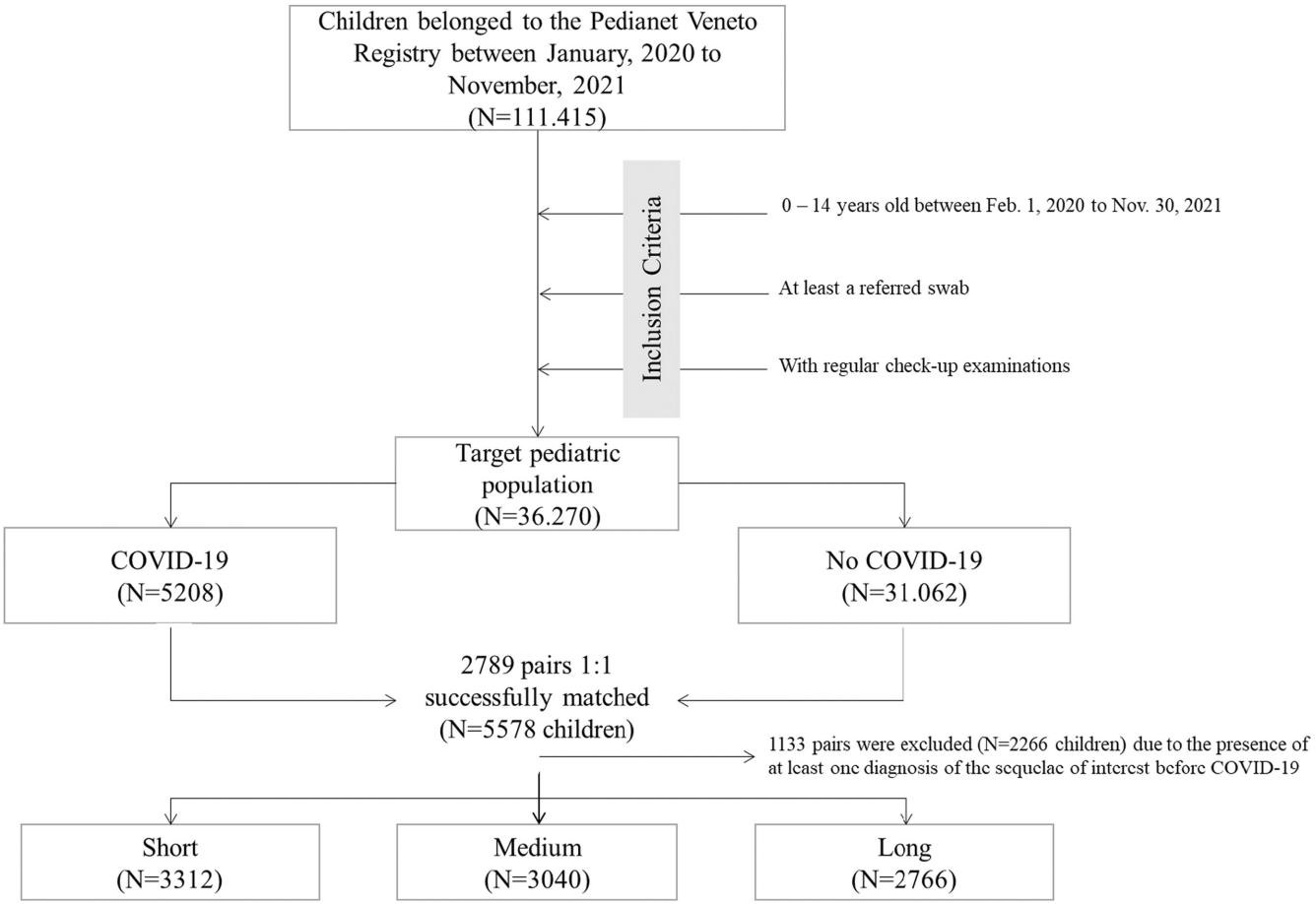

FIGURE 1 Flow-chart of the study cohort. Pedianet Veneto data 2020–2021.

the cases had been exposed to at least one diagnosis of a condition of interest before they had COVID-19. The final cohort comprised 3312 children: 1656 exposed (34 758 person-months) and 1656 unexposed (34 330 person-months).

The sociodemographic and clinical variables of the study population at the index date are detailed in Table 1. This shows that about one-third of the children who were included were born between 2007 and 2010, 2011 and 2015, and 2016 and 2021. At the index date, no differences were observed between the number of outpatient and specialistic visits or the number of previous courses of antibiotic therapy between exposed and unexposed participants.

3.2 | Disease burden after COVID-19

The study assessed the incidence of the onset of new conditions in children who had COVID-19 up to a maximum of 21 months after they tested positive for the virus. This showed that 158/1656 (9.5%) exposed children had at least one new diagnosis after COVID-19 (IR 10.6×100 person-months, 95% CI 9.0–12.3), compared to 98/1656 (5.9%) unexposed children (IR 6.5×1000 person-months, 95% CI 5.2–7.7) (p value < 0.0001).

There was an overall decreasing trend in the IR of new-onset conditions after COVID-19 over time. The IR for neurological conditions was highest among the exposed children, ranging from 7.0 (95% CI 5.0–9.1) for the short-term period to 2.9 (95% CI 2.0–3.8) for the long-term period (Figure 2, Table S4). A high IR was also observed in this group for mental health conditions, ranging from 6.5 (95% CI 4.6–8.5) to 2.8 (95% CI 2–3.7) in the short-term and long-term periods, respectively (Figure 2, Table S4). The lowest IRs varied between the two groups. The IRs for metabolic conditions ranged from 0.9 (95% CI 0.2–1.7) to 0.4 (95% CI 0.1–0.7) for short-term and long-term periods in exposed children. In contrast, the IRs for musculoskeletal conditions ranged from 1.1 (95% CI 0.3–1.9) to 0.5 (95% CI 0.1–0.8) for the short-term and long-term periods in unexposed children (Figure 2, Table S4). No statistically significant trends were observed.

We found that 256/3312 (8%) *rounded up* of the exposed and unexposed children had at least one new onset condition of interest. Overall, 22% of the children only had a mental health disorder, 22% had a neurological disorder, and 13% had a disorder that belonged to the other category, which mostly included taste and smell alterations and skin rashes. This was followed by conditions of the respiratory (9%), cardiovascular, musculoskeletal, gastrointestinal (7%), and metabolic (5%) systems. Only 2% of the children had two disorders at the same time (Table S5).

In general, the excess risk of new-onset conditions after COVID-19 was 78% higher in the exposed children when we compared them to the unexposed cohort, with an aHR of 1.7 (95% CI

TABLE 1 Sociodemographic and clinical characteristics of the study population.

Sociodemographic and clinical characteristics	Exposed (SARS-CoV-2 positive) (*N* = 1656)		Unexposed (SARS-CoV-2 negative) (N = 1656)		*p* Value
	N	(%)	*N*	(%)	
Year of birth					
2007–2010	500	(30.19)	498	(30.07)	MV
2011–2015	550	(33.21)	556	(33.57)	
2016–2021	606	(36.59)	602	(36.35)	
Sex					
Female	797	(48.13)	797	(48.13)	MV
Male	859	(51.87)	859	(51.87)	
Number of outpatient visits					
0–12	716	(43.24)	717	(43.3)	0.9556
13–32	534	(32.25)	527	(31.82)	
≥33	406	(24.52)	412	(24.88)	
Number of specialistic visits					
0	998	(60.27)	1040	(62.8)	0.2397
1–2	464	(28.02)	422	(25.48)	
≥3	194	(11.71)	194	(11.71)	
Number of antibiotic therapies					
0–1	828	(50)	828	(50)	0.7611
2–5	435	(26.27)	450	(27.17)	
≥6	393	(23.73)	378	(22.83)	
Preterm birth					
No	1617	(97.64)	1603	(96.8)	0.1388
Yes	39	(2.36)	53	(3.2)	

Note: Pedianet Veneto data 2020–2021.

Abbreviation: MV, matching variables.

1.4–2.3) (data not shown). The risk was significantly increased after COVID-19 for mental health disorders (aHR 1.8, 95% CI 1.1–3.0), neurological diseases (aHR 2.4, 95% CI 1.4–4.1), and other conditions, including skin rashes and taste and smell alterations (aHR 2.0, 95% CI 1.0–3.8) (Table 2). These relationships were consistent after the p values were corrected with a false discovery rate. No differences were found in the sensitivity analysis, including data censored for COVID-19 vaccinations (Table S6).

It was interesting that there were no differences in the prevalence of outcomes between male and female participants. However, cardiovascular and neurological diseases appeared to be more prevalent in older children than younger children, while respiratory and mental disorders followed the opposite trend and were more prevalent in younger children (Table 3).

3.3 | Discussion

This study compared 1656 children aged 0–14 years old who were diagnosed with COVID-19 from February 2020 to November 2021 with 1656 unexposed matched children. We evaluated the IR and excess risks for the onset of new medical conditions up to 21 months after the SARS-CoV-2 infection using clinical data from the Pedianet database of the Veneto Region of Italy. To the best of our knowledge, this study was one of the largest cohorts of children with both exposed and unexposed participants.

In general, the excess risk of new-onset conditions after COVID-19 was 78% higher in the exposed children when we compared them to the unexposed subjects.

Our results suggest that children are at risk of developing new conditions after SARS-CoV-2 infections. In particular, we found a significantly increased risk of mental health disorders (aHR 1.8), neurological disease (aHR 2.4) and other conditions (aHR 2.0) among exposed children compared to unexposed children. Furthermore, a decreasing trend in IRs over short, medium, and long-term periods was observed for all the clinical outcome domains of interest in exposed and unexposed children.

The size and richness of data in our cohort allowed us to carry out a comprehensive evaluation of the risk of several conditions after COVID-19 in children by exploring the onset of new pathologies. Being able to include a comparison group of children allowed us to estimate the true burden of new conditions after COVID-19 disease. This was

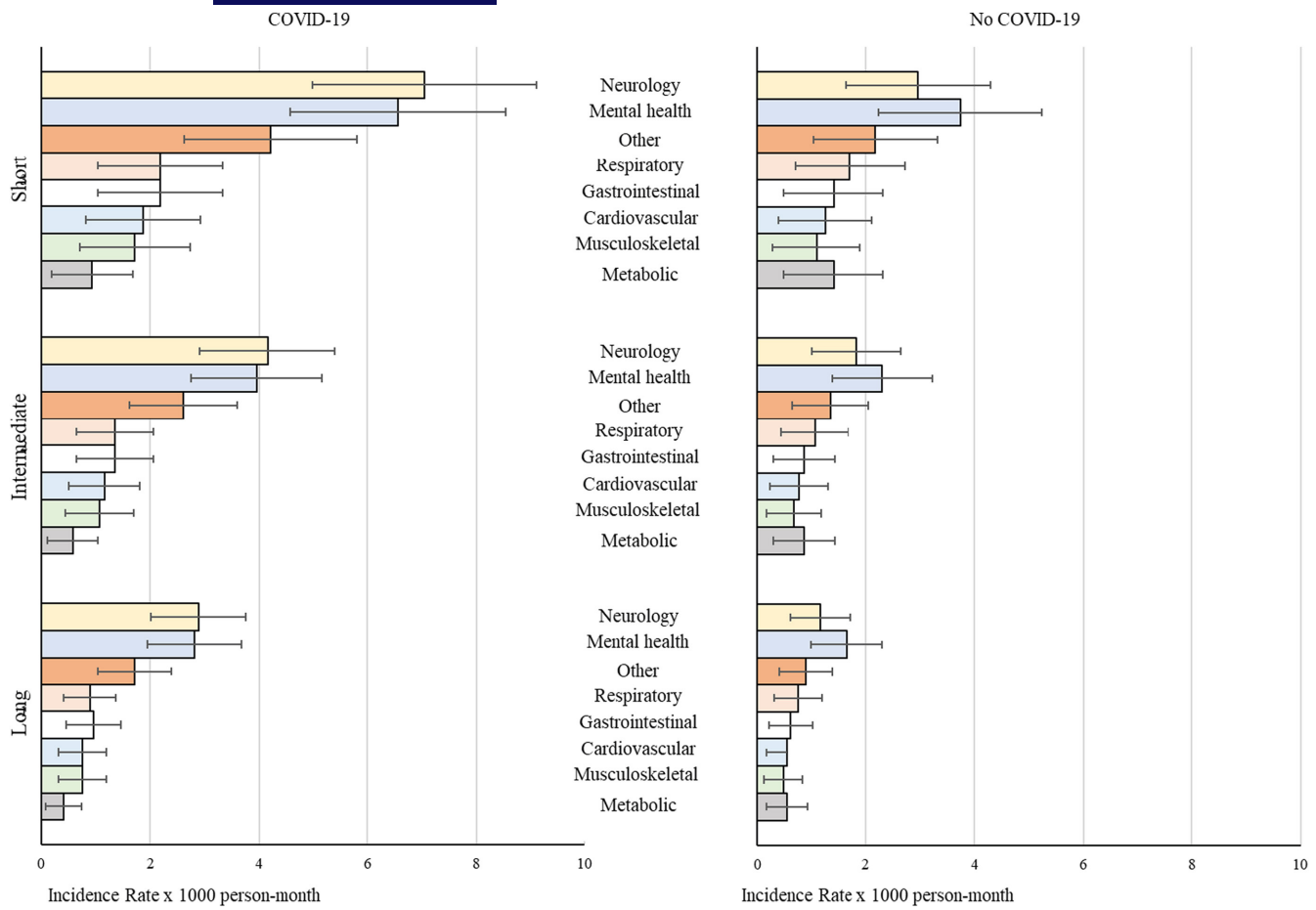

FIGURE 2 Incidence rate and 95% confidence intervals of selected categories of conditions in the short, intermediate, and long-term time after the COVID-19 period of interest, according to children exposed to SARS-CoV-2 infection compared to unexposed children. Pedianet Veneto data 2020–2021. IR, incidence rate; CI, confidence interval.

TABLE 2 Results of adjusted Cox proportional hazard regression comparing the onset of new conditions after COVID-19 in children exposed and unexposed to the SARS-CoV-2 infection.

	Number with the outcome		Number of person days			
Disease category	Unexposed	Exposed	Unexposed	Exposed	aHR	(95% CI)
Cardiovascular	8	12	477 934	476 217	1.62	(0.66–3.97)
Respiratory	11	14	478 099	475 395	1.26	(0.57–2.79)
Gastrointestinal	9	14	477 767	475 063	1.65	(0.72–3.83)
Neurological	19	45	475 186	469 233	2.38	(1.39–4.07)
Mental health	24	42	474 444	471 707	1.81	(1.10–2.99)
Musculoskeletal	7	11	478 112	476 715	1.65	(0.64–4.28)
Metabolic	9	6	477 820	477 230	0.72	(0.25–2.02)
Others	14	27	476 707	473 311	1.99	(1.04–3.79)

Note: Pedianet Veneto data 2020–2021. The hazard ratio and 95% confidence intervals were estimated with conditional Cox-proportional hazard model regression. Estimates were adjusted for the year of birth, the number of outpatient and specialist visits, prescriptions of antibiotic therapies, and preterm births between exposed and unexposed children.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

because we were able to reduce the risk of overestimation due to sequelae related to lockdown and social restrictions. Furthermore, the longitudinal nature of Pedianet made it possible to identify and exclude children with pre-existing pathologies of interest before the pandemic. This minimised the potential risk of overestimating these sequelae. Evidence on the onset of new diseases after COVID-19 in children has been limited and mainly based on studies that did not include unexposed controls. Systematic literature reviews have found

TABLE 3 Prevalence of new-onset conditions of interest after COVID-19 disease in exposed children, stratified by sex and year of birth. Pedianet Veneto data 2020–2021.

	Cardiovascular		Respiratory		Gastrointestinal		Neurological		Mental disorders		Musculoskeletal		Metabolic		Others[a]	
	(N = 18)		(N = 24)		(N = 21)		(N = 64)		(N = 66)		(N = 18)		(N = 14)		(N = 41)	
Sex																
Female, N (%)	8	(0.5)	13	(0.8)	12	(0.8)	35	(2.2)	28	(1.8)	11	(0.7)	3	(0.2)	22	(1.4)
Male, N (%)	10	(0.6)	11	(0.6)	9	(0.5)	29	(1.7)	38	(2.2)	7	(0.4)	11	(0.6)	19	(1.1)
p Value[b]	0.75		0.55		0.41		0.29		0.35		0.27		0.04		0.47	
Year of birth																
2007–2010, N (%)	12	(1.2)	4	(0.4)	7	(0.7)	30	(3.0)	15	(1.5)	9	(0.9)	5	(0.5)	18	(1.8)
2011–2015, N (%)	1	(0.1)	7	(0.6)	8	(0.7)	24	(2.2)	17	(1.5)	8	(0.7)	4	(0.4)	6	(0.5)
2016–2021, N (%)	5	(0.4)	13	(1.1)	6	(0.5)	10	(0.8)	34	(2.8)	1	(0.1)	5	(0.4)	17	(1.4)
p Value[b]	0.02		0.06		0.5		<0.01		0.02		0.01		0.77		0.49	

[a]Others included smell and taste alterations and skin rashes.

[b]Chi-square test or Cochran-Armitage Trend Test as appropriate.

high variations in the reported prevalence of the onset of new pathologies after COVID-19 in children, ranging from 2% to 70%.[10–12]

Buonsenso et al. published one of the first preliminary studies to evaluate the onset of new diseases after COVID-19 in July 2021. The authors observed that at least one symptom persisted in more than half of the 129 enrolled children.[13] However, there was no comparison group, and some children did not have a medical examination due to COVID-19 restrictions and were followed up on the phone.

Subsequent studies, which included comparison groups, observed a lower incidence of the onset of new diseases after COVID-19.[16,22] Kikkenborg Berg et al. used data from the Denmark national healthcare record database and conducted a cross-sectional study with 10997 cases and 33016 controls.[16] They found higher odds of persistent symptoms in children who tested positive, rather than negative, for SARS-CoV-2.

Our findings agree with previous studies that reported that neurological and mental health symptoms were the most common issues in children after they had COVID-19.[10–12] A systematic review and meta-analysis by Benhood et al. documented significantly higher proportions of cognitive difficulties and neurological diseases in children who had tested positive for the SARS-CoV-2 infection.[11]

Our study examined the IRs for several conditions over short, medium, and long-term periods in children with and without a positive SARS-CoV-2 result. Overall, we found higher IRs for each condition in the short-term period, which decreased over time. Several papers have observed that pathologies after COVID-19 may be driven by long-term tissue damage and inflammation, both in adults and children, regardless of the severity of the acute infection.[23–25] Echocardiographic alterations in myocardial deformation indexes have been described in children and adults after SARS-CoV-2 infections, suggesting possible tissue alterations.[26,27] In addition, one study investigated immunological profiles in children during and after COVID-19. It was observed that the immune system had less ability to switch from an innate to adaptive response in patients with persistent symptoms than in those who fully recovered. This indicated that long-term activation of the immune system was related to the onset of new syndromes after COVID-19.[28]

Our study showed a lower incidence of respiratory symptoms during the long-term period after infections. This was in line with the findings from a small cohort of 61 children with a previous diagnosis of asymptomatic or mild COVID-19, who underwent spirometry at a median of 10 months after a positive SARS-CoV-2 result.[29] The study observed that there were no chronic respiratory symptoms or lung function impairments after an asymptomatic or mild SARS-CoV-2 infection.[29]

3.4 | Strengths and limitations

Our study had a number of strengths. Firstly, the matched-cohort study design increased confidence that the pathologies were new-onset conditions after COVID-19 disease rather than the consequences of pandemic lockdowns. In addition, the rigorous methods we used reduced the risk of misclassification and improved the

specificity of data extraction. These included comprehensive access to a range of linked healthcare databases and ensuring two to three blinded paediatricians reviewed all outcomes.

However, our study also had several limitations. First, we used an electronic healthcare record database that included data from the Veneto region, but this only yielded a small study sample. The prevalence of the onset of new conditions after COVID-19 ranged from 0.002 to 0.007 in the unexposed group. With a study power of 80% and a first-type error of 0.05%, the minimum detectable hazard ratio for these parameters ranged from 5 to 2.71, respectively, for the prevalence data above. When we considered the minimum detectable risk for specific symptoms or diagnoses, we were interested to observe that improving the study cohort size would have allowed us to achieve statistical power to find significant differences in outcomes.

In addition, exposure misclassification might have affected the study. Some children who had the SARS-CoV-2 infection might not have been traced, and some children with asymptomatic infections might not have undergone testing. However, this misclassification could have reduced the differences between the two groups. The incidence of new conditions after COVID-19 may also have been low in our study because it predated the Omicron variant, which had a much greater impact on children. Furthermore, the lack of information on parental socioeconomic status could have led to residual confounding. We were not able to directly assess the impact of new symptoms on children's daily lives. However, the presence of new symptoms, including neurological and mental health conditions, and the need for specialistic visits could be considered an indirect sign of impaired everyday functioning. The potential impact of respiratory viral co-infections on the onset of new conditions after the COVID-19 period was not evaluated. This was due to the absence of multiple testing for other respiratory viruses. However, this study went up to the end of November 2021, before seasonal respiratory viruses normally emerge. Lastly, our study could not evaluate the role that social restriction measures played in the burden of new-onset diagnoses after COVID-19 disease. This was due to the lack of a comparison group of children who were not exposed to lockdown.

We need larger studies to further understand the epidemiological and clinical features of the onset of new conditions after COVID-19 in children. These should include patients who were infected with the Omicron variant and those who received COVID-19 vaccinations. That would be interesting because the Omicron variant had a large number of mutations, which resulted in higher transmissibility but lower severity than previous variants. In addition, vaccination appeared to protect young adults against the onset of post-COVID-19 syndromes, and it would be interesting to see if this happened in children.[30]

4 | CONCLUSION

Our study provides evidence of the increased risk of new conditions after COVID-19 disease in children. Further population-based studies are needed to better describe the incidence of these new conditions. This is very important, as we need to provide healthcare services to tackle these issues and prevent debilitating consequences. We also need to weigh up the pros and cons of the strict lockdown measures that were put in place to reduce the spread of SARS-CoV-2.

ACKNOWLEDGEMENTS

We would like to thank project manager Dr. Federica D'Ambrosio from Fondazione Penta Onlus, Torre di Ricerca Paediatrica in Padua, and data curator Antonio Scamarcia from the Società Servizi Telematici srl in Padua for their assistance with this study. Also, the Pedianet family paediatricians who are listed in Appendix S1.

FUNDING INFORMATION

This study received funding from the European Union's Horizon 2020 research and innovation programme (H2020-RIA GA number 101016167).

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ORCID

Costanza Di Chiara https://orcid.org/0000-0002-3586-0612

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Di Chiara C, Barbieri E, Chen YX, Visonà E, Cavagnis S, Sturniolo G, et al. Comparative study showed that children faced a 78% higher risk of new-onset conditions after they had COVID-19. Acta Paediatr. 2023;112:2563–2571. https://doi.org/10.1111/apa.16966