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TESI DI LAUREA

Long-term sequelae of COVID-19 in children: a retrospective cohort study

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SUMMARY

ABSTRACT

Background. Despite children are largely spared from severe COVID-19 compared to adults, recent data shown that they may also suffer from long-term consequences following SARS-CoV-2 infection.

Aims. To determine the association between COVID-19 and the persistence or onset of new symptoms after infection in children.

Methods. A retrospective cohort study was conducted on clinical data of children aged 0-14 years with a SARS-CoV-2 positive nasopharyngeal swab, retrieved from Pedianet, a paediatric primary care database linked to the Veneto region's hospitalization database.

Results. Among a total of 2.285 COVID-19 cases evaluated from 01/02/2020 to 30/11/2021, we observed a significantly higher prescriptions rate of cardiology, pneumology and neurology visits in COVID-19 cases compared to controls during the immediately short-term post-infection follow-up. Assessing symptoms or specific diagnosis associated to the prescriptions, no significant differences were found.

Conclusion. In our retrospective cohort study, we observed an increased number of prescriptions for specialistic visits after SARS-CoV-2 infection in children, suggesting a possible clinical consequence related to COVID-19 in the pediatric population.

ABSTRACT (ITALIAN VERSION)

Background. Al contrario degli adulti, i bambini raramente presentano infezione severa da SARS-CoV-2. Recentemente è stato dimostrato che possono comunque soffrire di conseguenze a lungo termine dopo la COVID-19.

Scopo dello studio. Determinare nei bambini l'associazione tra COVID-19 e la persistenza o l'insorgenza di nuovi sintomi dopo l'infezione.

Metodi. Uno studio retrospettivo di coorte è stato condotto basandosi su dati clinici di bambini di età compresa tra 0 e 14 anni con un tampone nasofaringeo positivo per SARS-CoV-2. I dati sono stati derivati da Pedianet, un database di cure pediatriche primarie collegato al database delle ospedalizzazioni della regione Veneto.

Risultati. Sono stati valutati 2.285 casi di COVID-19 dal 01/02/2020 al 30/11/2021. Abbiamo osservato un tasso significativamente elevato di prescrizioni cardiologiche, pneumologiche e neurologiche tra i casi di COVID-19 in confronto ai controlli durante il follow-up a breve termine post-infezione. Quando sono stati valutati i sintomi o le diagnosi specifiche associate alle prescrizioni, non sono state trovate differenze significative.

Conclusione. Nel nostro studio retrospettivo di coorte, è stato osservato un aumento di prescrizioni per visite specialistiche dopo l'infezione da SARS-CoV-2 nei bambini, che suggerisce delle possibili conseguenze cliniche correlate alla COVID-19 nella popolazione pediatrica.

1. INTRODUCTION

Coronaviruses are an important class of animal and human pathogens, in which they cause mild to moderate respiratory infections. They were identified for the first time in the 1960s and are part of Nidovirales order. They are enveloped, positive-stranded RNA viruses and their virion has a crown-like appearance. (1)

In December 2019, in the Wuhan's district in China, a cluster of "viral polmonitis" was noticed. Outside China, the first laboratory confirmed cases were in Thailand (13^{th} of January), then in Japan (15^{th} of January) and in the USA (20^{th} of January). On March 11, 2020, the WHO declared COVID-19 a pandemic because of the global spread and severity of the outbreak. On March 13, 2020, Europe became the centre of the pandemic, with a number of cases and deaths secondary only to the Republic of China. Italy was one of the country most affected: since the 23^{rd} of February the country was in lockdown. The first vaccine started to be tested in March 2020 and 2 billion of doses were ensured by COVAX in the beginning of 2021. (2–4)

Globally, as of June 10, 2022, there have been 532.201.219 confirmed cases of COVID-19, including 6.305.358 deaths. As of June 7, 2022, a total of 11.854.673.610 vaccine doses have been administered. (5) The number of new weekly cases has continually declined since a peak in January 2022. (6)

The long-lasting impact of the pandemic on individuals' mental and physical health is yet to be fully measured, with the effects of the virus, whether it be the lingering COVID-19 symptoms or long-COVID many people are experiencing, or the impact of social restrictions, still being investigated both in child and adults.

1.1 COVID-19 IN CHILDREN

1.1.1 EPIDEMIOLOGY

In the beginning of the pandemic children were overlooked by the scientifical community, even though paediatric infection was a substantial number; incidence increases with age. As of May 31, 2022, paediatric infections in Italy are distributed as follows (a similar distribution was found in other countries, such as in the USA):

(7,8)

- Age 0 through 5 years – 16 %
- Age 5 through 11 years – 36 %
- Age 12 through 19 years – 47 %

One of the first overview on paediatric patients was conducted in Italy in 2020 by Bellino et al., in which data of the Italian integrated COVID-19 surveillance system were analysed. As of May 8, 2020, the paediatric population accounted for 1,8% of all COVID-19 cases at a national level. (9) The Chinese Center for Disease Control and Prevention found a similar prevalence on a large case series in mainland China: as of February 11, 2020, 1% of infected was aged 9 years or younger and 1% was aged 10-19 years. (10) In the first pandemic peak in England (between 16 January 2020 and 3 May 2020), children represented 1.1% of SARS-CoV-2 positive cases, despite they were largely tested: of 35,200 tests performed, only 4% were positive. (11) Therefore, a relative low burden of paediatric disease was found in most of the countries in the early stages of the pandemic; differences in age distribution and prevalence may be attributed to different testing policy and case definition among nations. (9) Since most children are asymptomatic or paucisymptomatic, the true prevalence may have been underestimated due to the low rate of testing, as suggested by serological studies. In fact, in studies where children were tested regardless the presence of symptoms, the rates of infection were similar to those in adults. (12) Moreover, in the first waves of the pandemic they had less opportunities for exposure due school, day-care, and activity closures. (13,14)

Since then, the number of infected children has spiked significantly, shifting infection prevalence towards younger age groups. As of May 26, 2022, the American Academy of Paediatrics reported almost 13.4 million children infected with SARS-CoV-2 since the onset of the pandemic, accounting for 18,9% of all available cases; 376,000 of these cases were added in the 4 weeks before (**Fig. 1**). In the week from 19 to 26 May 2022, children accounted for 16,2% of cases, with a 2% increase in the cumulated number of paediatric patients. Infections in children had increased dramatically during the spreading of the Omicron variant. However, cumulative hospitalizations and mortality remain low, with only 0.1%-1.5% of all child COVID-19 cases resulted in hospitalization and 0.00%-0.02% of all child COVID-19 cases resulted in death. (15)

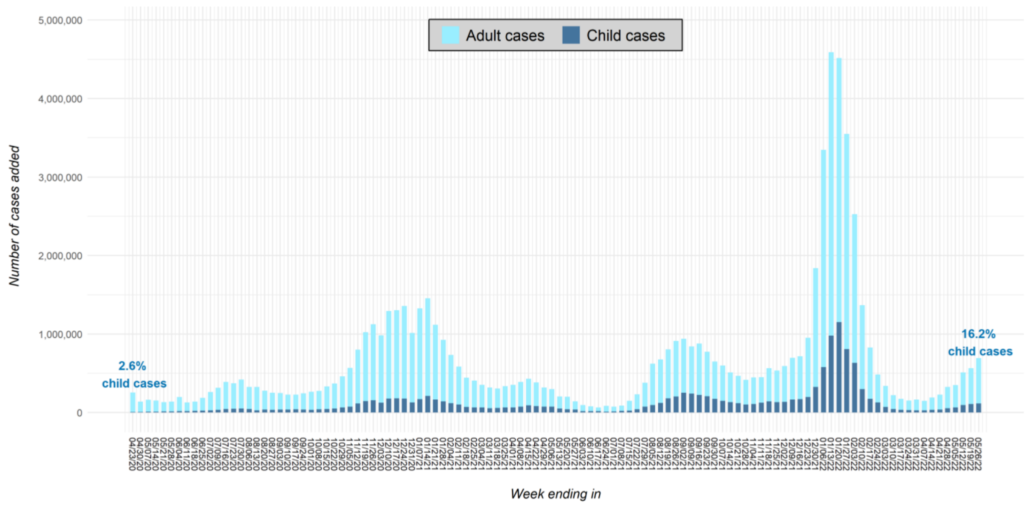

Figure 1 - United States: number of COVID-19 cases added in the past week for children and adults. Version: 5/26/2022. Source: Children and COVID-19: State-Level Data Report. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

In Italy, as of May 25, 2022, since the beginning of the pandemic there were 3.905.569 cases in the population aged 0-19 years, among which 18.636 were hospitalized, 413 admitted to ICU and 57 dead. (8)

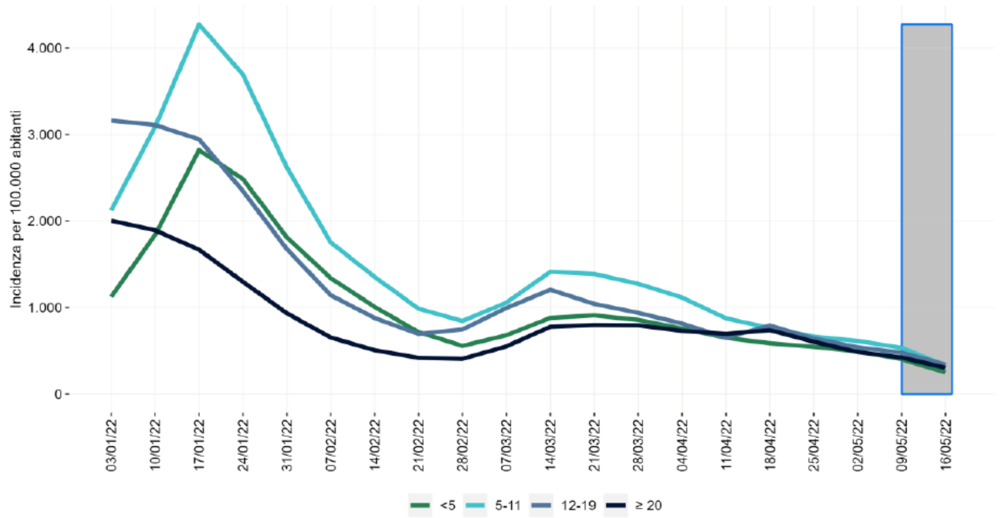

Figure 2 - Age distribution of weekly incidence rates of COVID-19 cases among children aged 0-19 years. Version: 5/25/2022. Source: REPORT ESTESO ISS. Available from: https://www.iss.it/cov19-cosa-fa-iss-varianti

Classe di età (in anni)	N. casi	N. ospedalizzazioni	N. ricoveri in TI	N. deceduti
<5	599.225	9.072	131	20
5-11	1.554.550	3.800	87	15
12-15	868.736	2.360	84	11
16-19	883.058	3.404	111	11
Totale	**3.905.569**	**18.636**	**413**	**57**

Figure 3 - Age distribution of cases and deaths reported in children aged 0-19 in Italy since the beginning of the pandemic. Version: 5/25/2022. Source: REPORT ESTESO ISS. Available from: https://www.iss.it/cov19-cosa-fa-iss-varianti

As of May 30, 2022, in the last 30 days paediatric patients accounted for 17,7 % of COVID-19 cases, with most of them (44%) aged 12-19 years (**fig. 2-3**). Also, in the last 30 days, infection's severity in children and adolescents ranged from asymptomatic to mild, with a small percentage of severely ill patients between 0-1 years old (**fig.4**). (16)

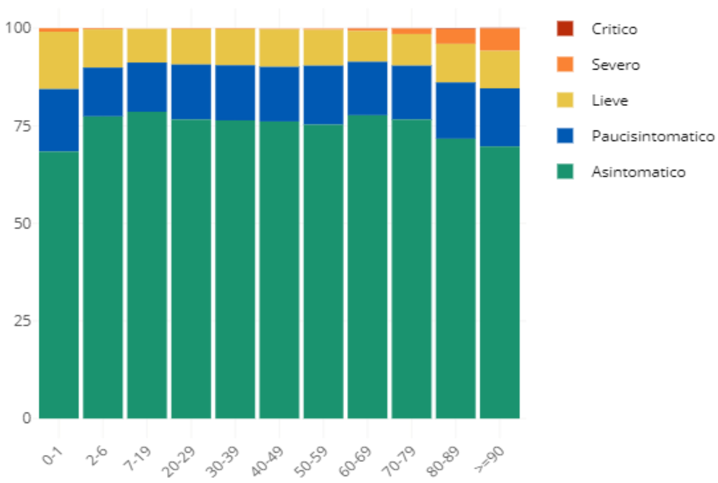

Figure 4 – Distribution for age and severity of COVID-19 cases in Italy in the last 30 days. Version: 30/05/2022. Source: Infografica web - Dati della Sorveglianza integrata COVID-19 in Italia. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard

The increase in the prevalence of paediatric cases may be attributed to changes in testing criteria, high vaccination rate in adults, high household attack rates with Delta and following variants. (13,17) In fact, usually children acquire SARS-CoV-2 from an adult contact: a household member, visitors to the home or in the context of social gatherings. School attendance is associated with SARS-CoV-2 infections only when there is inconsistent use of masks at school. (12) Outbreaks in school were predominantly among adult staff and adolescents rather than children. (17) On the contrary, transmission of infection from children to household contacts occurs with the ancestral strain of SARS-CoV-2 but did not contribute significantly to the pandemic spread. With the emergence of more transmissible variants, household transmission rates has become higher but adult transmission remains higher than in children. (12,17)

Paediatric infections increased significantly with the predominance of the Omicron variant: in the USA, as of February 2022, approximately 75% of children and adolescents had serologic evidence of previous infection with SARS-CoV-2, with approximately one third becoming newly seropositive since December 2021. The greatest increase in seroprevalence was among the groups with less vaccination coverage. (18) However, a pre-print study by Wang et al. found that in children aged < 5 years, first-time SARS-CoV-2 infection with Omicron was associated with significantly less severe outcomes than first-time infection with Delta. (19)

1.2.2. CLINICAL ASPECTS

Most of children infected with SARS-CoV-2 are asymptomatic or paucisymptomatic and are at lower risk of hospitalization and life-threatening complications. (12,13,20) The proportion of asymptomatic infections ranges from 15 up to 50%. (12,21)

The reason why COVID-19 is milder in children than in adults is still debated; hypothesis include: age differences in the expression of SARS-CoV-2 binding receptors, pre-existing immunity to other seasonal coronaviruses, lower prevalence of co-morbidities, infection mainly with variants with a decreased pathogenicity, stronger innate immune system, trained immunity, and effects of containment strategies. (13,21,22)

Infection is identified mostly in school-aged children and, although no significant sex difference was found, there is a slight male predisposition. (8,20)

The clinical spectrum of paediatric COVID-19 is heterogenous. (20,21) In a large meta-analysis of 129 studies conducted in 31 different nations, including 9335 children between 0 and 19 years, the most common presenting symptoms were: fever (63.3%), cough (33.7%) followed by nausea or vomiting (20.0%) and diarrhoea (19.6%). Other symptoms included: dyspnoea, nasal-symptoms, rashes, Kawasaki-like symptoms, conjunctivitis, fatigue, abdominal pain, and neurological symptoms. Clinical features were similar in the three age groups: ≤5 years, >5 to ≤10 years, >10 years. (20) Other studies found that adolescents present predominantly with respiratory symptoms, whereas infants often have fever, feeding difficulties, lethargy, but less respiratory symptoms. (12,20,21)

In terms of clinical syndromes, children may present with acute respiratory infection, influenza-like illness, fever without an obvious source, gastroenteritis, or asthma exacerbations. (13)

Cardiovascular abnormalities have been reported in small case series; even though cardiac involvement is predominant in children with MIS-C. Myocarditis is associated with paediatric COVID-19, but the absolute risk is low. (21,23)

Gastrointestinal manifestations may also occur without respiratory symptoms; the most common ones include diarrhoea, vomiting, and abdominal pain. (24–26) Acute cholestasis, pancreatitis and hepatitis have also been reported. (27–29)

Neurologic manifestations are more common in hospitalized children and in those with pre-existing disorders. The most common ones include headache, acute encephalopathy, seizures, and weakness. (30) Anosmia and ageusia are not common in children but are strong predictors of a positive SARS-CoV-2 test. (31)

Dermatological manifestations include maculopapular, urticarial, and vesicular eruptions, transient livedo reticularis, acral peeling and “COVID-toes” (red-purple nodules similar to chilblains). (32,33)

Clinical thrombotic events are rare in children compared to adults. Kidney disfunction may occur in severely ill children. (34,35)

The most common laboratory findings are increased C-Reactive Protein, lactate dehydrogenase and D-dimer. Other abnormalities are elevated erythrocyte sedimentation rate (ESR), lymphopenia, procalcitonin and biomarkers for organ injury such as elevated BNP, troponin, CKMB. Moreover, 44,1% cases have radiological abnormalities, among which ground glass opacity is the most common one. (20)

Severe and critical cases among children are less frequent than in adults. Severe disease in children is defined as “child with clinical signs of pneumonia (cough or difficulty in breathing + fast breathing or chest wall indrawing) with at least one of the following: 1) SpO2 < 90%; 2) Very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger sign (inability to breastfeed or drink, lethargy or unconsciousness, or convulsions)”. Critical cases include children presenting with ARDS, septic shock, sepsis, acute thrombosis, and MIS-C. (36)

In a retrospective study conducted during the beginning of the pandemic in China, severe and critical cases in children were distributed as follows: (37)

- Age 0 through 1 year – 10.6%
- Age 1 through 5 years – 7.3%
- Age 6 through 10 years – 4.2%
- Age 11 through 15 years – 4.1%
- ≥16 years – 3.0%

In the USA, the annual COVID-19-associated hospitalization rate among children <18 years is 48.2 per 100’000 overall but varies with age: 66.8 per 100’000 children aged 0 to 4 years, 25 per 100’000 children aged 5 to 11 years, and 59.9 per 100,000 children aged 12 to 17 years. (38) With the circulation of Omicron variant, during December 2022, hospitalizations between 0-17 years increased rapidly, especially among children who were not eligible for vaccination (0 to 4 years). Moreover, monthly hospitalization rate among unvaccinated adolescents aged 12 to 17 years was six times higher that among fully vaccinated adolescents. Among children aged 5 to 11 years, who became eligible for vaccination in November 2021, hospitalization rates were approximately twice as high in unvaccinated than in vaccinated children. (39)

Despite increased rates of hospitalization with Delta and Omicron variants (**fig. 5**), the proportion of children requiring intensive care or invasive mechanical ventilation was lower with Omicron and similar with Delta and earlier circulating strains. (39,40) However, hospitalization rates may have been overestimated due to universal testing for SARS-CoV-2 before admission to hospitals; some cases may have been incidental in children who were admitted for other reasons. (41,42)

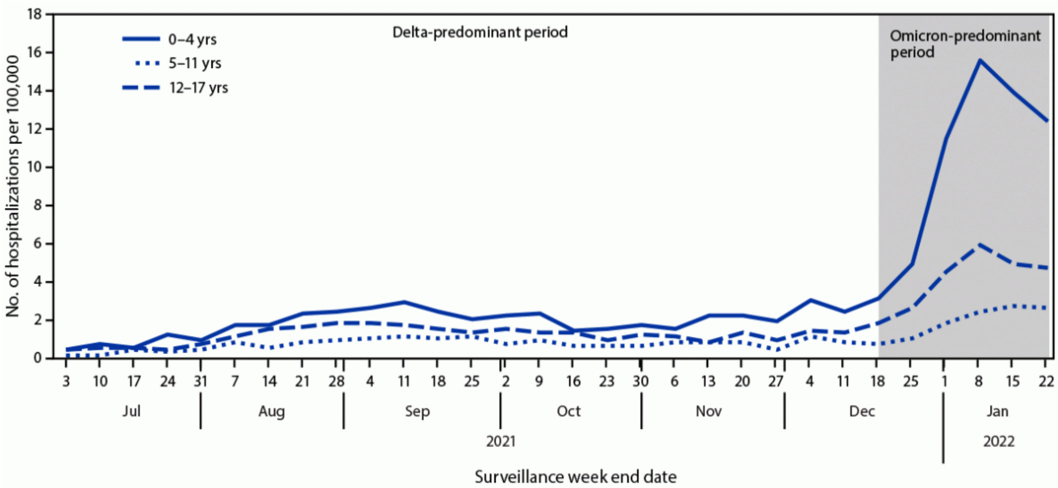

Figure 5 - Weekly COVID-19–associated hospitalization rates among children and adolescents aged 0–17 years, by age group. Source: Marks KJ, Whitaker M, Anglin O, Milucky J, Patel K, Pham H, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, July 2021–January 2022. MMWR Morbidity and Mortality Weekly Report 2022.

SARS-CoV-2 related deaths are rare in children and adolescents. CDC (Centre for Disease Control and prevention) reports 0.00%-0.02% of all child COVID-19 cases resulted in death in the USA. (15) In the first Italian report, only 4 children died but mostly due to deterioration of an already compromised situation. (9) In a systematic review by Irfan et al., deaths were found only among severe cases. (20)

Reported risk factors for severe disease include age, viral load, and comorbidities. (20) In a large cohort of US paediatric patients, 7% met the criteria for severe illness. Overall, 8 out of 135’794 died and 6 of them had pre-existing comorbidities. Among hospitalized children, 42% had one or more underlying condition. (43)

Comorbidities associated with severe disease in children are (43–46):

- Medical complexity
- Genetic conditions

- Neurologic conditions
- Metabolic conditions
- Congenital heart disease/cardiovascular disease
- Obesity (BMI >95th percentile for age and sex)
- Diabetes mellitus
- Chronic pulmonary disease; however, the evidence for asthma is inconsistent
- Sickle cell disease and thalassemia
- Immunosuppression
- Substance use disorder
- Age < 1 year was associated with severe disease in some studies, but this finding is inconsistent.

However, whether comorbidities are associated with increased risk of severe disease or with a lower threshold for hospitalization is still unclear. (47)

1.2.3 INDIRECT IMPACTS ON CHILDREN'S HEALTH

COVID-19 pandemic and consequent public health responses have had an important impact on children's health. Here we provide an overview of some of the consequences recognized to date.

Impact on other infectious diseases: although non-pharmaceutical interventions taken to mitigate the pandemic had reduced respiratory viruses and travel-related infections (48), routine immunization of children and adolescents has decreased. (49–51) Disruption of immunization may lead to vaccine-preventable diseases outbreaks. Consequently, the WHO has declared immunization a core service and has prepared guidelines for public health authorities. (52)

Impact on physical health: health-seeking behaviours have been altered during the pandemic. Paediatric Emergency Department have been underused during the first stages of the pandemic, most likely because parents were afraid of risk of SARS-CoV-2 infection, and, even later, none had returned to their baseline. (53,54)

Moreover, children with pre-existing health conditions or disabilities suffered from reduced healthcare access: Save the Children's survey reports that, respectively, 45% and 59% of children with chronic diseases or disabilities were unable to access regular health or rehabilitation services. (55) Since comorbidities are a risk factor for severe COVID-19, these patients and their household were advised to be cautious; unfortunately, this also caused an excessive sense of fear and anxiety. (56)

Finally, COVID-19 pandemic exacerbated many risk factors for children's obesity: increased out-of-school time, reduced opportunities for physical activities, increased screen-time, over-consumption of ultra-processed and high calories food are examples of obesogenic behaviours associated with lockdown measures. (57,58) There was also the issue of malnourishment since many children rely on school meals. UNICEF data report that as many as 370 million children may have missed nutritious school meals, with increased food insecurities causing long term psychological effects. (59)

Impact on mental health: many factors unique in this pandemic had an important effect on children's emotional and behavioural health. **Fig. 6** shows all stressors that could have impacted children during the pandemic; length of lockdown being one of the most significant. (56) Different responses to pandemic stress may be attributed also to environmental context, personal biobehavioural reactivity and loss of a caregiver. (60)

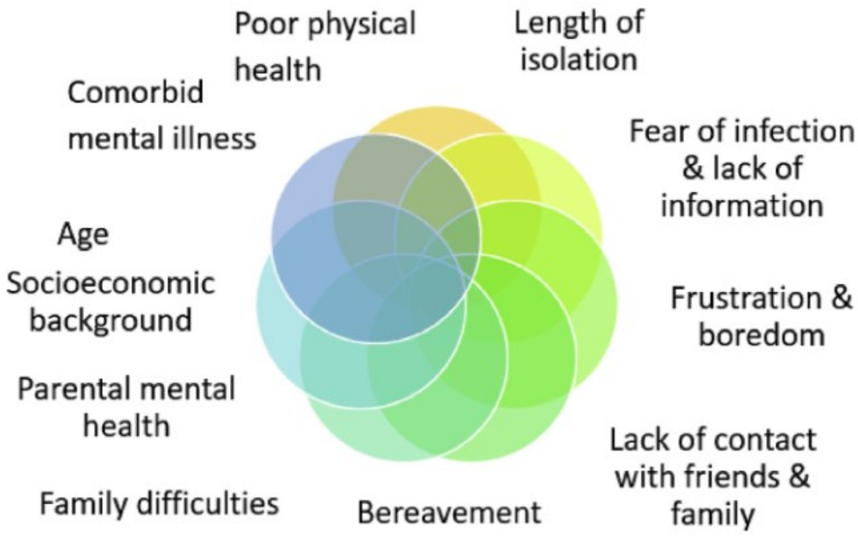

Figure 6 - Stressors that could impact the mental health of children and young people. Source: Interim Guidance on Supporting the Emotional and Behavioral Health Needs of Children, Adolescents, and Families During the COVID-19 Pandemic.

A large metanalysis estimates that globally, after one year of pandemic, 1 in 4 youth is experiencing high levels of depression symptoms and 1 in 5 is experiencing anxiety symptoms, with depression being higher in older children while anxiety among girls. (61)

Infants and young children have a lower threshold to stress; they manifest distress through disruption of physiologic functions, such as sleep. (60) Children between 3 and 6 years are more likely to manifest clinginess and fear of family members being infected. Children of all age groups revealed increased irritability, inattention, clinging behaviour, feelings of uncertainty and isolation, disturbed sleep, poor appetite, agitation. (62) Closure of schools had disrupted education, physical activities, interactions with peers and mentors, opportunities for socializations. During 2020, 188 countries have imposed school closure, affecting more than 1,5 billion children and youth. (63) Consequently, children showed impaired daily routine, boredom, lack of innovative ideas, increased dependence on their parents. Remote learning was also associated with increased symptoms of depression, no-suicidal self-injury, suicidality, anxiety, disordered eating, and insomnia. (64–66) Furthermore, there was an increased risk of domestic violence and decreased referral to child protective services, which were also suspended during the pandemic. (59,67–70) Children with special needs, such as neurodevelopmental disorders and previous mental health conditions, were particularly affected because of disruption of their routine and interruption of services they depend on. (71)

Even though strict public health measures such as quarantine and social isolation are starting to ease, new challenges are to be faced: return to in-person school attendance, consequences of remote schooling, increased use of social communication, vaccine refusal, the general loss of hope. The impact of COVID-19 on children’s health, development and education is yet to be realized. (60)

1.2 POST-COVID SYNDROMES

Globally, as of June 1, 2022, about 504 million people have recovered from COVID-19. (72) Growing evidence shows that patients infected with COVID-19 manifest prolonged multisystemic symptoms. “Post COVID conditions” is an umbrella term that includes all physical and mental consequences presenting in some patients starting 4 weeks from recovering, regardless of the severity of the primary infection. Since COVID-19 is an emerging illness, its consequences and clinical course are still under investigation. (73,74) Likewise, long term consequences were observed in patients who had healed from SARS and MERS. (75)

Persistence of symptoms after primary infection is well documented in adults but data regarding children are still scarce. Between 2 and 6 weeks after infection children could suffer from MIS-C (Multisystem Inflammatory Syndrome in Children), an hyperinflammatory syndrome that, unlike long-COVID, is well described in its symptoms, definition, and physiopathology. (76)

On September 2020 the WHO added, by request of the State members, “post-COVID condition” and “Multisystem inflammatory syndrome associated with COVID-19” in the International Classification of Disease (ICD) for the purposes of recognition, data analysis, health service planning and delivery. The term “post-COVID” does not underline any specific etiopathogenesis, so it could be used to link any condition following an acute COVID disease. (77)

1.2.1 MIS-C

A small proportion of children develop an acute hyperinflammatory condition 2 to 6 weeks after SARS-CoV-2 infection, called Multisystem Inflammatory Syndrome (MIS-C). It resembles Kawasaki disease or toxic shock syndrome, and it may happen in any paediatric patient, regardless of the severity of SARS-CoV-2 infection. (78,79)

The incidence is uncertain but apparently it is a rare complication, happening in <1% of children with confirmed SARS-CoV-2 infection. (80) Most cases occur in older children and adolescents (median age 8 years) previously asymptomatic. Risk factors are unclear, but male, black, and Hispanic children appear to be unequally affected. Obesity is the most common comorbidity associated with MIS-C. (81)

It is unclear if MIS-C develops because of the direct effect of the virus and ongoing viral replication, post-infective immune dysregulation, or a combination of both mechanisms; but, since it responds well to immunomodulatory and anti-inflammatory therapies, inappropriate immune system activation is more likely involved. (81)

Children with MIS-C present with fever, gastrointestinal symptoms, lymphadenitis, Kawasaki and/or toxic shock syndrome-like features, cardiovascular, dermatologic, neurologic and mucocutaneous involvement. (82) Common laboratory findings include abnormal blood cell counts, markedly elevated inflammatory markers (apparently related with severity of illness), and elevated cardiac markers. (80) Given cardiac involvement is common, echocardiogram and electrocardiogram are usually performed. Common findings include depressed LV function, coronary artery abnormalities, including dilation or aneurysm, mitral regurgitation, pericardial effusion. Other tests should be performed according to signs and symptoms.

Currently, there are three different case definitions of MIS-C: (**tab. I**) (36,82)

Table I. Case definitions of MIS-C

Criteria	**RCPCR** **(Royal College of Paediatrics and Child Health)**	**CDC**	**WHO**
Age	All children (age not defined)	< 21 years	0-19 years
Fever	Persistent fever ≥ 38,5°	≥ 38°C for ≥ 24 hours OR Subjective fever ≥ 24 hours	Fever ≥ 3 days
Clinical symptoms	Single or multi-organ dysfunction AND Additional features (Abdominal pain, confusion, conjunctivitis, cough, diarrhoea, headache, lymphadenopathy, mucus membrane changes, neck swelling, rash, respiratory symptoms, sore throat, swollen hand and feet, syncope, vomiting)	Severe illness (hospitalized) AND ≥ 2 organ system involved	2 of the following: 1. Rash, bilateral non purulent conjunctivitis, mucocutaneous inflammation 2. Hypotension or shock 3. Cardiac involvement: features of myocardial dysfunction, pericarditis, valvulitis, or coronary artery abnormalities (including ECHO findings or elevated TnI/NT-pro-BNP) 4. Coagulopathy

			5. Acute GI symptoms
Inflammation	Neutrophilia AND ↑ CRP AND Lymphopenia	Laboratory evidence of inflammation not limited to 1 or more of the following: • ↑ CRP • ↑ ESR • ↑ Fibrinogen • ↑ PCT • ↑ D-dimer • ↑ Ferritin • ↑ LDH • ↑ IL-6 • ↑ Neutrophils • ↓ Lymphocytes • ↓ Albumin	Elevated inflammatory markers such as: ↑ ESR ↑ CRP ↑ PCT
Link to SARS-CoV-2	PCR +/-	Current or recent: PCR+, Serology+, Antigen test + OR COVID-19 exposure within prior 4 weeks	Evidence of COVID-19 with any of the following: 1. PCR + 2. Antigen test + 3. Serology + 4. Likely COVID-19 contact
Exclusion	Exclusion of other infections	No alternative diagnosis	No obvious microbial cause of inflammation

MIS-C should be distinguished from Kawasaki disease, severe acute COVID-19, bacterial sepsis, toxic shock syndrome, appendicitis, vasculitis, SLE, other infections. (80)

Treatment requires a multidisciplinary approach to stabilize life-threatening conditions and prevent long-term sequelae. Thus, supportive care and treatment directed against the inflammatory process are essential. The former includes fluid resuscitation, inotropic and/or respiratory support, ECMO in rare cases. IVIG and corticosteroids are administered as anti-inflammatory measures. Thrombotic prophylaxis is often used given the hypercoagulable state associated with MIS-C. Aspirin may be administered due to coronary artery involvement. Antibiotic therapy may be useful to prevent sepsis while waiting for culture results, on the other hand antiviral therapy is rarely administered. (81,83,84)

Up to date, the prognosis of MIS-C is positive: even though the disease course is often severe, with many children requiring hospitalization or intensive care, the vast majority survives. (85,86) More long-term follow-up studies are needed, but so far it appears that most children had recovered at 6-months: LEVF improves, coronary artery aneurisms regress and there is no inflammation or cardiac scarring. (87)

1.2.2 LONG COVID

1.2.2.1 DEFINITION

In the beginning of the pandemic, the term "long-COVID" was first introduced by long symptomatic patients on Twitter and other social media. (88) In literature, it is also called "long haulers," or "post-acute COVID" or "chronic COVID syndrome" or "late sequela COVID" or "persistent COVID", but currently international recognised definition and diagnostic criteria are still lacking. (89,90)

For example, the NICE (National Institute for health and Care Excellence) guidelines define long-COVID as "signs and symptoms that continue or develop after acute COVID-19 and could not be explained by another diagnosis, including both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)". This is the most common definition, also used by the ISS (National Institute of Heath in Italy). (76,91) Another definition is "not recovering several weeks or months following the start of symptoms that were suggestive of COVID-19, regardless individuals were tested or not". (92) Fernández de las Peñas et al. propose an integrative definition based on time, influencing factors and whether a patient was hospitalized or not. (93)

It could be generally described as a clinical condition in which a patient previously infected with SARS-CoV-2 does not return to the same health condition showed before the acute infection. (76)

The CDC underlines the difficulties in distinguish between symptoms that are part of the syndrome and the ones occurred for other reasons, for example pre-existing health conditions unmasked by infection, reinfection or symptoms related to social isolation. Moreover, it is also possible that patients were not tested during the acute phase, or they had an inaccurate test. (90)

Fig. 7 shows all current definitions. In October 2021 the WHO summarized all of them and proposed the following definition of "post-COVID condition":

"Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time." (94)

It is also underlined that a different definition could be applied to children, although a recent consensus from SIP (Italian Society of Paediatrics) applies the same definition to children. (94,95)

Source	Text
Wellcome	Symptoms persisting beyond 4 weeks after symptom onset suggestive of COVID-19 *(33)*.
Lancet	Multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients. They range from cough and shortness of breath, to fatigue, headache, palpitations, chest pain, joint pain, physical limitations, depression, and insomnia, and affect people of varying ages. At the Lancet–Chinese Academy of Medical Sciences conference on 23 November 2020, Bin Cao presented data (in press at the Lancet) on the long-term consequences of COVID-19 for patients in Wuhan, and warned that dysfunctions and complications could persist in some discharged patients for at least 6 months. So-called long COVID is a burgeoning health concern and action is needed now to address it *(34)*.
NICE	Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis *(35)*.
Scientific American	Individuals whose symptoms persist or develop outside the initial viral infection, but the duration and pathogenesis are unknown *(36)*.
Royal Society	The onset of persistent or recurrent episodes of one or more of the following symptoms, within x* weeks of infection with SARS-CoV-2 and continuing for y* weeks or more: severe fatigue, reduced exercise capacity, chest pain or heaviness, fever, palpitations, cogintive impairment, anosomia or ageusia, vertigo and tinnitus, headache, peripheral neuropathy, metallic or bitter taste, skin rash joint pain or swelling *(3)*. * Maximum period between acquisition of the infection (if known) and the onset of symptoms, and the minimum duration of symptoms, should be specified in the definition.
Haute Autorité de santé, France	Three criteria: Having presented with a symptomatic form of COVID-19; presenting with one or more initial symptoms 4 weeks after the start of the disease; and none of these symptoms can be explained by another diagnosis *(37)*.
CDC	Long COVID: While most persons with COVID-19 recover and return to normal health, some patients can have symptoms that can last for weeks or even months after recovery from acute illness. Even people who are not hospitalized and who have mild illness can experience persistent or late symptoms *(38)*.
Wikipedia	Condition characterized by long-term sequelae – persisting after the typical convalescence period – of coronavirus disease 2019 (COVID-19) *(39)*.
Nature	Post-acute COVID-19 as persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms *(40)*.

Figure 7 - Repository of published and available definitions of post COVID-19 condition. Source: A clinical case definition of post COVID-19 condition by a Delphi consensus. 2021.

1.2.2.2 EPIDEMIOLOGY

A significant number of adults suffers from long-COVID: data on prevalence are various but a recent summarising document of the WHO estimates that about 1 in 4 patients has continuing symptoms 4-5 weeks after infection and 1 in 10 after 12 weeks. (96) Prevalence is higher between women, people aged 35-69, people living in the most deprived areas, those working in health or social care, and those with another activity-limiting health condition or disability. (100)

Data on children are even more scant: one of the first study on 129 children in Italy showed that 42.6% of people aged less than 18 experienced at least one symptom >60 days after infection. (97) In contrast, a prospective cohort study in Norway found out that long-COVID affects mostly young adults (16-30 years) than children (0-15 years): in the first group 52% patients suffered persistent symptoms, whereas in the second one only 13%. (98) The largest data set comes from the Office of National Statistics (ONS) and show that 14% of patients still have symptoms 5 weeks after infection and 11,7% after 12 weeks; 12.9% of children aged 2-11 and 14.5% of children aged 12-16 also reported symptoms after 5 weeks. Thus, apparently adolescents have a higher risk than younger children. (99)

Overall, prevalence of long-COVID in children and young people with laboratory-confirmed or suspected COVID-19 ranges from 1% to 51%. Smaller studies report higher prevalence rates. Heterogeneity in the prevalence could be attributed to the lack of a common definition, different sample size, different median age of the included population, duration, and modalities of follow-up. Moreover, it should be noticed that many studies are based on self or parent-reported symptoms, without a proper clinical evaluation, and most of them recruited people online. Lastly, often there is selection bias of cases without an appropriate control group. (101,102) As suggested by Amin-Chowdhury Z et al., the best control group would be the general population, because many of the self-reported symptoms are nonspecific and common also among general population and because symptoms could be relapsing or appear even months after primary infection. (103) Different prevalence was found according to the moment of symptoms assessment. Generally, it was low short after acute SARS-CoV-2 infection and high after 12 weeks from infection. Probably, other mechanisms different from organ damage play a role in the long-term. However, regardless of the moment of assessment, prevalence was lower than in adults. (94)

To date, apparently post-COVID conditions are less common in children and adolescents than in adults, but long-term effects after COVID-19 do occur also in this age group.

1.2.2.3 PATOPHYSIOLOGY

SARS-CoV-2 infection has a multiorgan and multisystemic impact, and so does long-COVID syndrome. Pathogenesis is still poorly understood, but it probably involves inflammation, cytokine storm, a dysregulated immunological response and incomplete eradication of the virus. (104) The wide expression of ACE2 receptor in the body, as demonstrated during previously SARS-CoV pandemic, could explain the variety of long-COVID symptoms. (102)

In a recent review of A. Umesh et al. published in April 2022, three mechanisms are proposed:

1. Direct cell damage caused by virus entry through ACE2 receptors
2. Immune system activation and inflammation
3. Counter response by the host mediated by non-specific activation of the immune system, counter-regulatory hormones, and cytokines.

These mechanisms combine differently in each organ or tissue and cause specific damage. (105) In **fig. 8**, specific pathophysiology mechanisms are shown for each organ; as it could be seen, pathological processes are complex and interrelated.

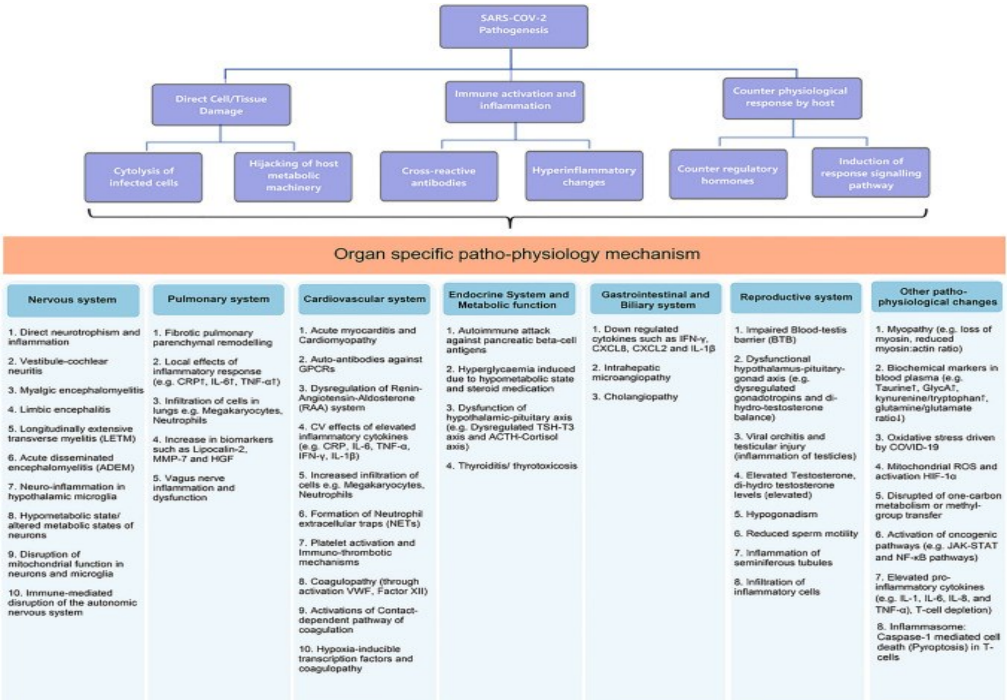

Figure 8 - Pathophysiological mechanisms in long-COVID or post-COVID syndrome. Source: Umesh A, Pranay K, Pandey RC, Gupta MK. Evidence mapping and review of long-COVID and its underlying pathophysiological mechanism. Infection, 2022 Apr 30.

Another mechanism hypothesized is the persistence of a viral reservoir in some tissues, supported by evidence of improved symptoms after administration of anti-SARS-CoV-2 vaccines in people with post-COVID syndrome and detection of viral RNA in stool samples. Prothrombotic state is a crucial damage mechanism during acute infection, but its duration and extension to post-COVID syndrome is unclear. (106)

Specific research on the pathophysiology of long-COVID in children is scarce, but many mechanisms appear to be similar. (102) Only a pre-print study and a case report investigate children with PASC (post-acute sequelae of SARS-CoV-2 infection). In the pre-print study of Di Sante et al., immunological differences between children that completely recovered from infection and those with PASC were found. The latter showed higher levels of plasmablasts, switched IgM-IgD-B cells, IL-6 and IL1β, meaning that chronic inflammation and immune dysregulation play a role in the syndrome. (107) The case report of a 14-year-old girl diagnosed with mild COVID-19 and then with persistent PASC after 7 months shows similar findings. Her immunological assessment found high expression of IL-6, IL-1 and TNF-α as well as unusual B-cell and regulatory T-cell patterns, suggesting a proinflammatory background. She also had high levels of IgA and IgG anti-SARS-CoV-2. Moreover, cardiopulmonary exercise testing (CPET) showed organ damage, with mild pulmonary hypertension. (108)

To better understand the physiopathology, it will be important to distinguish between lingering symptoms of acute disease and new symptoms related to long-COVID and to eliminate all confounding variants, mostly related to neuropsychiatric conditions. Linking pathophysiological damage to clinical symptoms will help to better describe the syndrome. (106)

1.2.2.4 CLINICAL PRESENTATION

Clinical manifestations of long-COVID in adults are various and to date there is no consensus on their characteristics. In a large international cohort study, participants interviewed described more than 200 self-reported symptoms in 10 organ systems; in another review more than 100 symptoms were recorded. (109,110) They may persist after the infection or may be of new onset; they may also relapse or fluctuate. (95)

Symptoms are independently associated with severity of initial illness, increased convalescent antibody titres and pre-existing chronic lung disease. (98) Several studies found that patients with more severe acute COVID-19 are at higher risk of post-COVID symptoms, (111) but symptoms may also present in patient with mild acute disease; given the high prevalence of this group, long-COVID could become a problem of public health. (112)

Consequences can be divided into general manifestations and organ specific. (76) The most common manifestations are systemic, neuropsychiatric, cardiac, and respiratory. (106) The most common symptoms include fatigue, shortness of breath, muscle pain, weakness, difficult concentrating, insomnia, depression and anxiety, loss of smell. (93,104,111,113). **Fig. 9** shows the variety and prevalence of long-COVID symptoms. (76,91,114)

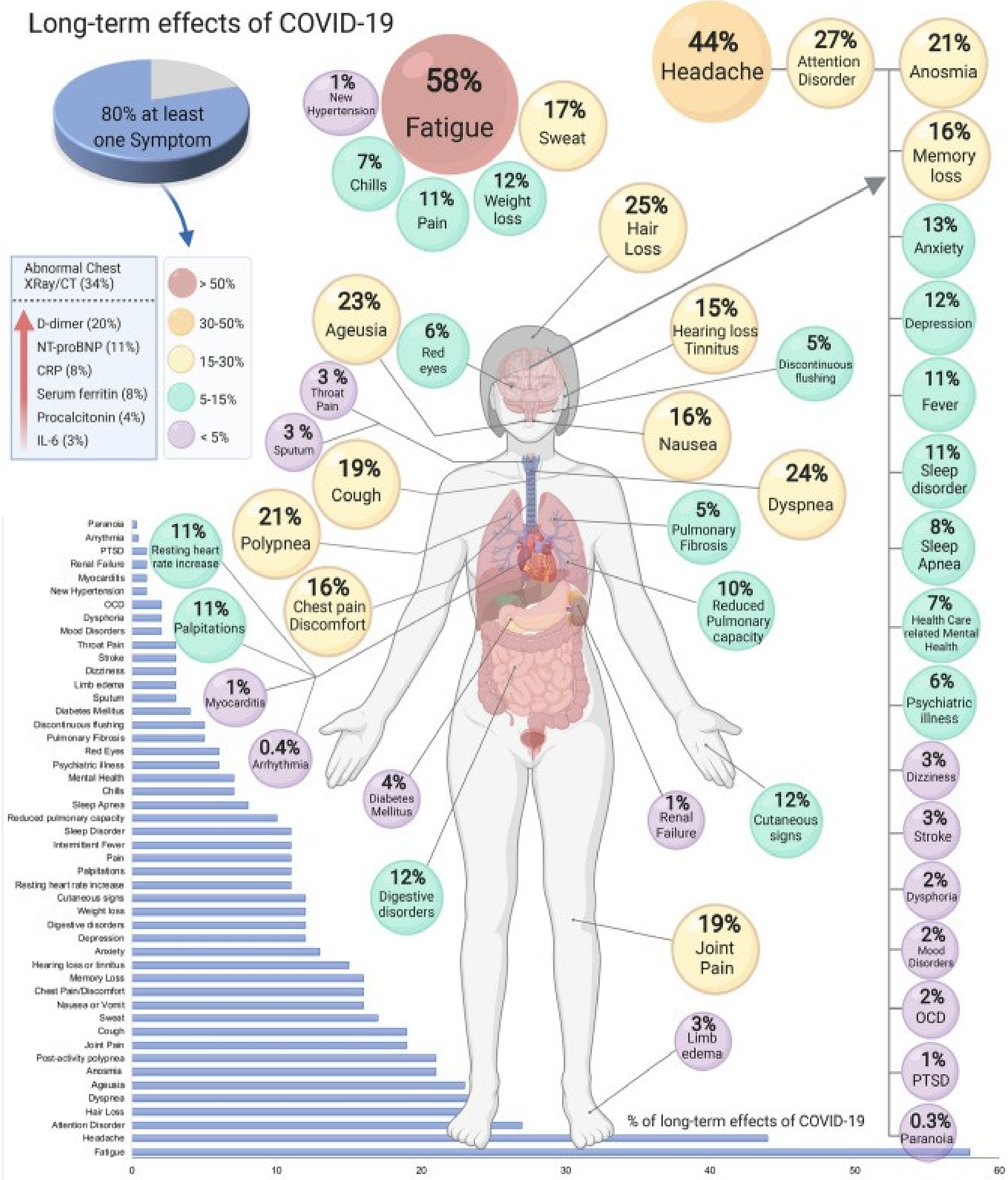

Figure 9 - Prevalence of long-term effects of COVID-19. Source: Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Scientific Reports 2021 11:1. 2021 Aug 9;11(1):1–12.

General manifestations include:

- Fatigue: usually persistent, in several studies it is the most common symptom both in the post-acute phase and long-term. Patients affirm their day-to-day activities had been limited "a lot", meaning long-COVID may also have a social impact because it restricts the ability to work. (96,112,113) Its pathophysiology is still under investigation, the most likely hypothesis is the coexistence of central, peripheral, and psychological factors; moreover, chronic neuroinflammation and neuromuscular damage also play an important part. (102)

- Fever: studies are contradicting about fever-like symptoms. A case description described patients with fluctuating fever and others who were sometimes soaked with sweat. Another study reports that among patients who had fever during acute infection, the symptom had resolved in 97% of cases during follow-up. (112)
- Worsening of previous health condition
- Weight loss and reduced appetite

Cardiovascular manifestations: the impact of COVID-19 may be acute, long-lasting, or persistent. During acute infection hypoxia, hypotension or shock may cause myocardial injury that further leads to long-term complications. (105) Myocardial injury was found independently form previous conditions, also in young athletes (115,116). Symptoms include:

- Chest pain / chest tightness
- Palpitations / tachycardia
- Arrythmias
- Blood pressure variations

Pulmonary manifestations:

- Dyspnoea
- Persistent cough
- Prolonged oxygen requirement related to baseline pulmonary status
- Laboratory findings include abnormal lung function and persistent radiological abnormalities such as ground glass opacity, signs of reticulations or pulmonary fibrosis; they are related to COVID-19 severity. (106)

Neurological manifestations: changes in brain structure and function after COVID-19 are an area of investigation. Up to date, neural changes in the limbic and other brain areas were found, together with reduction in functional connectivity and structural domains. (117) Symptoms include:

- Headache: it is the most common neurological consequence; usually it is bilateral, moderate to severe, throbbing, or persistent and does not respond to common analgesic therapy. It can be of new onset or a worsening of pre-existing migraine. (76,118)
- Cognitive impairment: commonly called ‘brain fog’, it includes loss

of concentration and memory issues.

- Dizziness: due to orthostatic hypotension, postural tachycardia, or vertigo.
- Sleep disturbances
- Anosmia / dysgeusia
- Peripheral neuropathy symptoms (pins and needles and numbness)
- Visual disturbance
- Mobility impairment

Psychiatric manifestations: the relationship with COVID-19 is likely bidirectional. A diagnosis of COVID-19 is associated with a higher risk of a first psychiatric diagnosis, especially anxiety or depression; meanwhile, a psychiatric diagnosis is a risk factor for being diagnosed with COVID-19. All these psychiatric sequelae may also be caused indirectly by the pandemic state, as a consequence of social isolation, living in a persistent state of stress and uncertainty for the future; many of the studies do not include a comparison group, so it is difficult to fully differentiate the aetiology. Symptoms include: (96,119)

- Depression and anxiety: the most common symptoms found in several studies. (119)
- PTSD (post-traumatic stress disorder): severity of COVID-19 is a risk factor; the highest prevalence of PTSD is reported in ICU patients. (119)
- Obsessive-compulsive disorder
- Psychosis
- Delirium in older population

Gastrointestinal manifestations: prevalence of each symptom is not high, but they have a high impact on survivors' quality of life. Studies have confirmed that SARS-CoV-2 persists in the GI tract several weeks after a negative throat swab, although the exact pathophysiology of long-lasting symptoms is still unknown. Hypotheses include direct invasion of SARS-CoV-2 into GI epithelial cells resulting in intestinal inflammation, perturbance of intestinal flora's homeostasis, interrelation between GI system and other systems damaged by the virus (disturbance of gut-brain, gut-lung, or gut-liver axis) and, finally, COVID-19 drug induced symptoms. (120–122) Symptoms include:

- Abdominal pain
- Nausea and vomiting
- Dyspepsia
- Oesophageal reflux
- Diarrhoea

Ear, nose, and throat manifestations:

- Otalgia
- Tinnitus
- Sore throat
- Dysphagia
- Dysphonia
- Nasal congestion

Dermatological manifestations: dermatological manifestations are common in acute COVID-19 and could persist even after the acute phase. A study of Devon E. et al based on an international registry found the following symptoms (123):

- Pernio-like lesion: the most common one, lasting for more than 60 days in long-haulers. (123)
- Measles-like rash and urticaria: these manifestations are more ephemeral, with a maximum duration of 28 days. (123)
- Alopecia: the most common form is telogen effluvium, usually acute and self-limiting in maximum 6 months. (76)

Musculoskeletal manifestations: include joint pain and myalgia. These symptoms were found almost widespread in a study on hospitalized patients. Joint pain was mostly in the knee, foot–ankle, and shoulder, and myalgia was mostly in the lower leg, arm, and shoulder girdle. (124) Arthromyalgia was one of the most common symptoms found even after one year of follow-up in a metanalysis. (125)

Haematological manifestations: thromboembolic events are well recognized during acute COVID-19. The rate of venous thromboembolism in post-acute COVID syndrome is considered to be lower than 5%, so thromboprophylaxis is not recommended. However, these data are probably inadequate and assessment of hypercoagulability state during long-COVID needs further studies. (106)

Renal symptoms: includes proteinuria and haematuria; renal injury could happen also in those with normal renal function during acute COVID-19. (76)

Endocrinological symptoms: ACE2 receptors are expressed in the hypothalamus, pituitary, adrenal gland, thyroid, testes, and pancreatic islets leading to the involvement of the endocrine system during and after the recovery from the disease. (126)

- New onset diabetes: there is a bidirectional relationship between the two conditions. (127)
- Subacute thyroiditis: data on the acute and long-term effects of SARS-CoV-2 on thyroid functioning are still scarce and insufficient, but there is evidence that the thyroid axis is involved. (126)
- Other effects on the endocrine system are showed in **fig. 10**. (126)

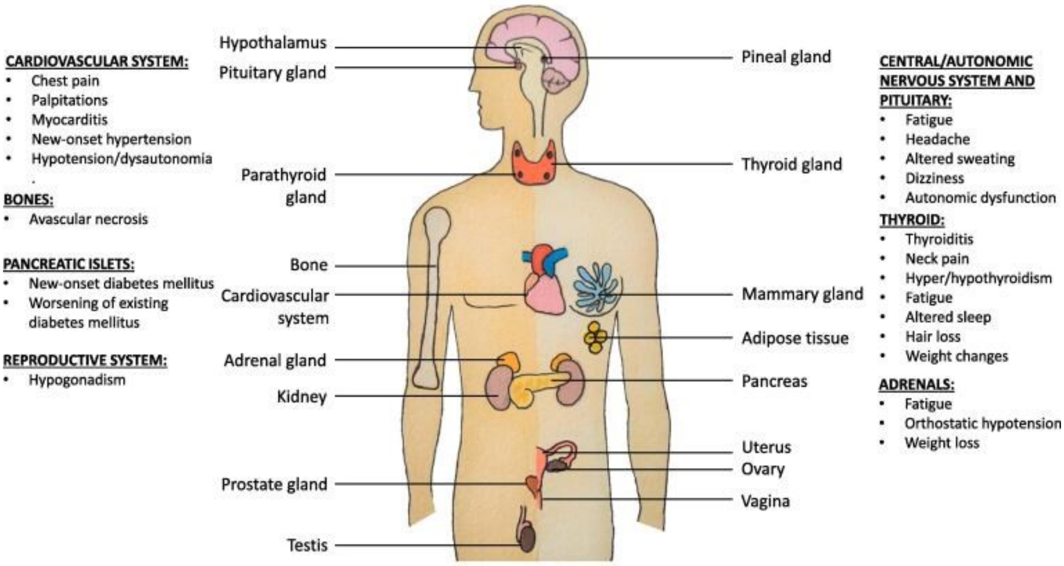

Figure 10 - Manifestations of long-COVID on the endocrine system. Source: Bansal R, Gubbi S, Koch CA. COVID-19 and chronic fatigue syndrome: An endocrine perspective. Journal of Clinical & Translational Endocrinology

Natural history and clinical course of long-COVID is still unknown; as of the 6 of May 2022, the ONS Infection survey shows 21% of people with self-reported long COVID still have symptoms after 12 weeks, 44% after one year and 13% after two years. (113) Some symptoms resolve more quickly than others. For example, fevers, chills, anosmia and ageusia typically resolve within two to four weeks, while fatigue, dyspnoea, chest tightness, cognitive deficits, and psychological effects may last for months. A longer recovery time is expected in patients with hospital admission in the acute phase, with pre-existing comorbidities, older people and with longer ICU admissions. (128)

It is important to note that many studies evaluating persistent post-COVID-19 symptoms have significant methodologic limitations. (128)

1.2.2.5 CLINICAL ASPECTS OF LONG-COVID IN CHILDREN

As in adults, there is heterogeneity in long-COVID symptoms, duration, and intensity; symptoms can be relapsing, persistent or transient and may appear combined in various presentations. Long-COVID seems to affect more children with symptomatic or severe acute infections, but it is described also in asymptomatic or paucisymptomatic patients. (102)

Cardiovascular	**Neurological/Neuropsychiatric**
Chest tightness or pain (1–31%)	Brain fog
Palpitations (4–18%)	Concentration difficulties (2–81%)
Dermatological	Sleep disturbance (2–63%)
Skin rashes (2–52%)	Dizziness (3–20%)
Gastrointestinal	Irritability and mood changes (5–24%)
Stomachache (5–70%)	Headache (3–80%)
Abdominal pain (1–76%)	Memory loss
Diarrhea (2–24%)	Smell disorder (12–70%)
Vomiting (2–24%)	Taste disorder (20–70%)
General	Nocturnal sweating
Fatigue (3–87%)	**Respiratory**
Persistent fever (2–40%)	Cough (1–30%)
Loss of appetite or weight (2–50%)	Dyspnea (40–50%)
Muscular	**Upper Airway**
Myalgia or arthralgia (1–61%)	Nasal congestion or rhinorrhea (1–12%)
	Sore throat (4–70%)

Figure 111 - Prevalence of clinical manifestations in children with long COVID. Source: Fainardi V, Meoli A, Chiopris G, Motta M, Skenderaj K, Grandinetti R, et al. Long COVID in Children and Adolescents. Life 2022, Vol 12, Page 285. 2022 Feb 14;12(2):285.

Fig. 11 summarizes long-COVID symptoms in children and their prevalence reported up to date. (102)

NICE guidelines state that cardiac and respiratory symptoms are less commonly found in children and young people than in adults, especially the following ones: shortness of breath, persistent cough, pain on breathing, palpitations, variations in heart rate and chest pain. On the contrary, evidence from 6 studies found that the most common ongoing symptoms in children included tiredness, weakness, and fatigue (reported by 87% of patients); headaches;

abdominal pain; muscle aches and pain; shortness of breath; loss of smell; lack of concentration or delirium; dizziness or light headedness; skipped meals and skin rash or red welts. (91,102)

The first report about persistent symptoms in five children (four or which were females) after SARS-CoV-2 infection was published by Jonas F. Ludvigsson in November 2021: symptoms lasted for 6-8 months. All of them suffered from fatigue, dyspnoea, heart palpitations or chest pain; four had headaches, difficulties concentrating, muscle weakness, dizziness, and sore throat. Two of them underwent a cardiac examination and two had a psycological evaluation. They all suffered from fatigue and couldn't fully return to school, even when other symptoms had improved. (129)

Soon after, an Italian study assessed 129 children with laboratory-confirmed SARS-CoV-2 infection through phone calls or in an outpatient setting. Symptoms were still present after 120 days in 43.6% of them and the median age of the affected children was 11.4, in line with Ludvigsson's report. The most frequent symptoms were insomnia (18.6%), respiratory symptoms (14.7%), nasal congestion (12.4%), fatigue (10.8%), muscle (10.1%) and joint pain (6.9%), and concentration difficulties (10.1%), particularly in those assessed after 60 days. (130)

The most relevant problem with the studies regarding paediatric long-COVID is that only 6 included a negative control group and most have a small sample size. (131)

One study with a control group was made in Switzerland by Radtke et al.; in this country school were closed only during the 6-week nationwide lockdown (from March 16 to May 10, 2020), so lockdown may had contributed less on the aetiopathogenesis of symptoms. The prevalence of reported symptoms was lower compared to other studies, with only 4% of seropositive children having symptoms after 12 weeks versus 2% of seronegative ones; the most common were tiredness, difficulty concentrating and increased need for sleep. (132)

In another large cohort study, Molteni et al. also found a small proportion (4.4%) of children aged 5-17 with persistent parents-reported symptoms after infection. The most common were fatigue, headache, and anosmia. After 28 days the symptom burden was low compared to the first week of illness; only 1,8% of patients still had symptoms after 56 days, meaning long-COVID improves over time. Interestingly, neuropsychological symptoms were reported rarely but the authors recognize that mental health problems could not be proxy-reported and data regarding school attendance were not collected. (133) However, this study was criticized because it underestimates long-COVID due to some limitations: the small number of symptoms assessed, investigation of only persistent symptoms, excluding the relapsing-remittent nature of the syndrome, drop off by parents. (134)

A cohort study, conducted by Roge et al. at the Children's Clinical University Hospital in Latvia, compared children previously infected with SARS-CoV-2 and children with other community-acquired infections. Differently from other reports, in this study only 30% of people had returned to the previous health state; 52% of them had multiple symptoms. Cognitive sequelae were significatively higher than in the control group, including persistent fatigue and cognitive impairment inclusive of irritability, mood changes and impaired attention; these were also more common in school-aged children, instead respiratory symptoms were more common in pre-schoolers and infants. Also, general sequelae showed a significant difference. The control group helped justify the attention given to this syndrome, since up to now not many other infections have demonstrated to cause such persistent symptoms. (38)

The CLoCK study, by Stephenson et al, investigated self-reported symptoms of many positive-tested children between 11 and 17 years old compared to negative-tested children at baseline and after three months. Interestingly, after testing children could not be distinguished by the type of symptoms but by the number of them, meaning multiple symptoms are a characteristic of long-COVID. The prevalence of physical symptoms was higher in cases, but mental symptoms did not show any difference in the two groups, so the pandemic may have had an impact in their burden. They also state that mental and physical symptoms are linked, since stressed individuals could present with somatic symptoms, so they should both be considered when assessing long-COVID syndrome. The authors conclude that long-COVID in children is different than in adults and a common case definition is needed to improve further studies, cases recognition and decision making on policy and services. (135)

A brief report of Ashkenazi et al., based on patients that underwent a clinical examination in a long-COVID clinic, showed a various range of symptoms. Blood tests, electrocardiograph and a chest radiograph were also performed. A pulmonary function test (for children older than 6 years), echocardiography and further testing, such as bronchodilator response testing and cardiac magnetic resonance imaging (MRI), were performed following abnormal findings on the initial evaluation. The median number of reported symptoms was 4; among them the most common were fatigue, dyspnoea, and myalgia. Additional persistent symptoms included sleep disturbances, chest pain, paraesthesia, headache, hair loss, anosmia-ageusia or parosmia/euosmia, gastrointestinal symptoms, dizziness, weight loss, memory impairment, vasomotor complaints, arthralgia, tremor, cough, palpitations, difficulty in concentration, tic exacerbation and tinnitus, recurrent febrile episodes, developmental regression, and obstructive sleep apnoea. The investigators found mild radiologic and spirometry abnormalities, but no abnormal findings on echocardiography. (136)

Adolescents have a higher risk than younger children. Female sex, allergic disease, and other pre-existing conditions, including mental health issues, were recognized as risk factors. (131,135)

Overall, as in adults, the prevailing symptom is fatigue. In a pre-print Italian study based on parent's survey, only 10% of children had returned to their previous activity level. (137) In Ashkenazi et al. study, 58.9% of subjects reported impairment in daily activities due to symptoms. (136) Whether also lockdown and school closure had contributed to children's loss of energy or not is still to determine.

The other predominating category of symptoms are neuropsychiatric ones. In the first Italian study by Buonsenso et al., insomnia and lack of concentration were among the most common symptoms. (130) Ludvigsson's report also found headache, lack of concentration and dizziness between the complaints. (129) In a pre-print by Buonsenso et al, parents of 510 previously infected children were interviewed through an online questionnaire. A high prevalence of neuropsychiatric symptoms was reported, including lack of concentration, difficulty in remembering and processing information, difficulty in doing everyday tasks, short term memory issues. 54.5% of them had at least three mental symptoms. (137) Blankenburg et al., on the contrary, did not find any difference between seropositive and seronegative children but did find a high prevalence of neurocognitive, mood and pain disorders. They interviewed with a questionnaire 1560 students with a median age of 15 years. Each symptom was documented in about 35% of the students without difference between the two groups; the most common among them were unhappiness (98.7%), tenseness (86.4%), listlessness (80.7%) and difficulties in concentrating (79.3%). (138) Brackel et al. article based on experience of Dutch paediatricians found a high proportion of neurocognitive disfunction, with as many as 45% reporting concentrating difficulties, 13% reporting memory loss, and a further 2% describing brain fog; 38% suffered from headaches. (139)

As stated in Blankenburg et al. study, distinguish between long-COVID and "long-pandemic" syndrome is crucial because the management is opposite. While strict lock-down measures prevent SARS-CoV-2 transmissions in this age group and thereby prevent long-term complications, they also further restrict social contact, education and development and thereby amplify lockdown associated symptoms. (138) It is also important to remember that physical symptoms could hide a mental distress, so they should not be assessed separately. (135) Moreover, it is difficult to find mental health problems when asking parents or proxy. Worse achievement or absenteeism at school may be evidences of mental health problems, but they are sometimes erroneously attributed to other causes, leading to poor recognition and under-referral. (91)

This short resume on current knowledge shows that data on long-COVID in children are heterogenous and somehow conflicting. This could partially be attributed to the lack of an international recognized definition in children, but also to differences in the protocols of studies. Many were conducted without a control group, without a physical examination of affected children, or only by interviewing parents. Another reason is that prevalence and severity of COVID-19 in children was significantly lower than in adults, especially in the first waves of the pandemic.

Further studies with more subjects and with a negative control group are needed to assess the real impact of SARS-CoV-2 infection on children's life, since also lockdown, social isolation and school closures may result in physical and mental symptoms. In fact, children's health may profoundly be influenced by changes in health styles, family income, unemployment, education, and health service access issues with high risk of domestic violence and neglect. Thus, the impact of pandemic and the risk of infection should be balanced when determining public health measures.

1.2.2.6 DIAGNOSIS

Long-COVID syndrome is a clinical diagnosis, based on history of COVID-19 and failure to fully recover, with the presence of symptoms among the ones listed in the previous chapter. The diagnosis should be made by exclusion of other health conditions that could explain the symptoms. During the examination, history of acute COVID-19 (suspected or confirmed), the nature and severity of previous and current symptoms, their timing and duration since the start of acute COVID-19, history of other health conditions and their exacerbations should be assessed. A positive swab or antibody test are helpful but not needed, since availability of tests, especially in early stages of pandemic, was limited. Moreover, PCR tests are not 100% sensitive and antibody titres decline after some months. (76,91,96)

A clinical case definition in adults was determined by WHO, but there is not for children and adolescents. (94) Worse achievement or absenteeism at school, training or in other fields may be used as "red flags" for children. (91)

Differential diagnosis include post-intensive care syndrome (PICS) and MIS-C. The former is characterized by chronically impaired pulmonary function, neuromuscular weakness, long-term psychological impact, and reduced quality of life; it is common among people with severe acute infections who have spent long periods on ventilators. (96) Also children discharged from PICU (pediatric intensive care unit) have functional impairment, neurocognitive disorders resulting in poorer academical results, and mental health issues such as PTSD, anxiety, depression. All of them impact on their quality of life and on the psychological wellbeing of the family. (140) PICS and long-COVID syndrome have common symptoms and they may coexist. (96) Some symptoms of long-COVID also resemble those of post viral chronic fatigue syndrome (CSF), but long-COVID seems to present as a broader spectrum of symptoms. (76)

1.2.2.7 MANAGEMENT AND FOLLOW-UP

Since data are still scarce, it is difficult to determine the best healthcare approach. Guidelines regarding the management in adults were published by NICE, by Catalonia health department, by ISS; they all contain references to management in children, but dedicated and detailed guidelines for paediatricians are still missing. (76,91,141) A small guidance and recommendations were recently published by SIP and APA (American Academic of Paediatrics). (95,142)

Patients with long-COVID report they were often not taken seriously; despite this, national health systems have organized different response approaches. (96) Also in children long-COVID must be early recognized and correctly referred due to the consequences it may have on the cognitive and mental health in the mid-long term. Since also in children long-COVID has a multiorgan involvement, a multidisciplinary approach is needed.

Information, proper management, and access to healthcare services are the three keywords to manage long-COVID in children, as suggested by ISS. (76)

Firstly, giving correct information to parents is crucial so they can recognize early symptoms. Paediatricians must inform the child and its parents about the natural course of the disease, the fact that symptoms normally disappear within some days, but they could persist up to 4 weeks or, if disappeared, may reappear with the same or with other characteristics. They must also inform about signs and symptoms of MIS-C since it progresses rapidly and needs urgent care. (76,95,142)

Secondly, SIP recommends that primary care paediatricians visit all previously infected subjects after 4 weeks, regardless of the severity and manifestations of acute infection. A questionnaire containing all common symptoms of paediatric long-COVID may be helpful to capture the person's symptoms but must be used in combination with clinical assessment. (91) Examples of questionnaires are the COVID-19 Yorkshire rehabilitation questionnaire, recommended by NHS (National Health Service) England, and the modified International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) global paediatric COVID-19 follow-up questionnaire. (143,144) SIP recommends suspecting long-COVID when the following symptoms are present: persistent headache and fatigue, sleep disturbances, difficulty in concentrating, abdominal pain, myalgia, or arthralgia. Persistent chest pain, stomach pain, diarrhoea, heart palpitations, and skin lesions should be considered as possible symptoms of long-COVID. (95)

Children without clinical manifestations should be discharged with the recommendation of a new visit if new symptoms appear. Further evaluation of symptomatic subjects should be tailored on the complaint; the type and severity of manifestations should determine the depth of investigations. (95) For example, children with persistent respiratory symptoms may undergo pulmonary assessment, including lung function tests and others depending on history and clinical examinations. (102)

On the contrary, mental problems that are severe and persists beyond 12 weeks must be referred to a psychological support. (95) ISS recommend promoting monitoring programs for children at risk of psychological problems. (76)

In any case, a new visit after 3 months should be scheduled to assess new problems or to confirm normality. (95) Regardless persisting symptoms, the paediatrician should also discuss COVID-19 vaccination and return to daily living; subjects with ongoing symptoms may require additional support. (142) Regarding physical activity, APA suggests an extensive evaluation for children who had moderate or severe symptoms before returning to sports. (145)

Fig. 12 sums up all the steps in monitoring long-COVID.

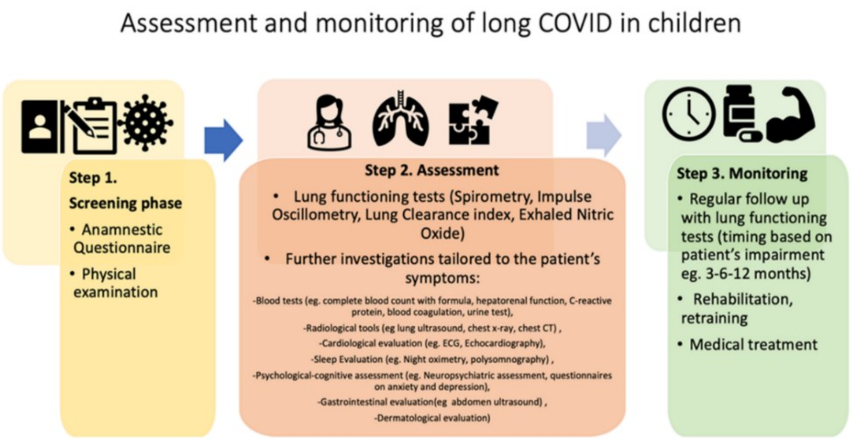

Figure 12 -Screening, assessment and monitoring of children infected by COVID-19. Source: Fainardi V, Meoli A, Chiopris G, Motta M, Skenderaj K, Grandinetti R, et al. Long COVID in Children and Adolescents. Life 2022, Vol 12, Page 285. 2022 Feb

Experience with a multidisciplinary rehabilitation clinic was published by Morrow et al. Their management strategies were based on other chronic conditions with overlapping symptoms, considering all medical, physical, behavioural, environmental, and educational interventions that may be helpful. For example, fatigue was treated by improving sleep hygiene, cognitive behavioural therapy, and graded exercise therapy. (146)

Long-term consequences of long-COVID are still unknown. For example, data on pulmonary impairment are conflicting. Moreover, most of the current knowledge and recommendations are based on the effects of wild SARS-CoV-2, but the role of variants is to be evaluated. (95,102)

More knowledge on the characteristics of paediatric long-COVID is needed to assure a more effective approach to the individual patient. In the meanwhile, general paediatricians are the key to detect all suspect cases of long-COVID.

2. PURPOSE OF THE STUDY

Children could be infected with SARS-CoV-2 as adults, but the disease course is usually asymptomatic or mild. Even though severe disease is rare in children, several studies show that they could suffer from long-COVID. To date, data on incidence, clinical characteristics and outcomes in the paediatric population are scarce and conflicting. The experiences children have during childhood are crucial for their development. Long-term effects in children must be studied carefully by the scientific community to better understand the phenomenon and to reduce future debilitating consequences.

For these reasons in our study, we set two primary objectives: first, to estimate the onset of any pathology signals of long-COVID in children aged 0-14 years in the Veneto region, Italy, between February 2020 and November 2021 by assessing specialistic prescriptions of family paediatricians.

Secondly, to characterize in the same population the association between SARS-CoV-2 infection and the onset of specific pathology, by searching the outpatient and inpatient diagnosis, clinical diaries, and discharge letters fields. Specifically, the association between SARS-CoV-2 infection and signal and consequent diagnosis of the following categories is evaluated: cardiology, neurology, pneumology, dermatology, endocrinology, gastroenterology, and rheumatology.

This study is conducted in collaboration with the University of Milano-Bicocca with the aim of clarifying some aspects of long-COVID in children

We expect to determine which symptoms characterize long-COVID in the paediatric population and to differentiate them from lingering symptoms of acute disease. The control group will allow to distinguish them from those caused by lockdown measures.

3. METHODS

3.1 STUDY DESIGN AND DATA SOURCE

This was a retrospective, nested cohort study, estimating the risk of developing long-COVID symptoms in children 0-14 years old with a laboratory-confirmed diagnosis of COVID-19, compared to children who did not have a positive test.

The data were obtained from the Pedianet database, a paediatric primary care database. Italy has a primary care system specifically devoted to children up to 14 years of age, with around 6000 family paediatricians (FPs) who provide free care; around 400 of these participate in Pedianet, representing around 6% of Italian paediatrician's population. At the time of the writing, the dataset contained information on more than 300,000 patients aged 0-14 years. Generally, the child enters in the dataset at its first paediatric visit and exits between its 14th or 16th birthday, so length of follow-up for each patient is around 14 years.

The data is generated from computer records that the FPs fill during their daily practice; such data, generated using common software (JuniorBit®), are then collected anonymously in a centralized database in Padua. Parents or legal guardians have provided informed consent for the data to be used for research purposes.

The database includes patient demographic and clinical characteristics, including diagnoses (free text or coded diagnoses using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) system), drug prescriptions (recorded according to the Anatomical Therapeutic Chemical (ATC) codes), healthcare co-payment exemptions, specialist visits, diagnostic procedures, hospital admissions, growth parameters (repeated measures of height and weight according to national indications), and free text where symptoms or other medical observations related to the visit are reported. Moreover, as of 2017, through an anonymous individual patient link was possible to link the Veneto Pedianet database with the healthcare registry of the Veneto Region, more specific the Covid-19 registry, which collected all Covid-19 swab referred (i.e., date and results of Covid-19 swabs), and the hospitalization database, which collected all diagnoses at discharge from public or private hospitals.

Ethical approval of the study and access to the database was approved by the Internal Scientific Committee of So.Se.Te. Srl, the legal owner of Pedianet.

3.2 STUDY POPULATION AND OUTCOMES

We included in the study all 0-14 years old children of Veneto region registered in Pedianet who had a nasopharyngeal swab between 01/02/2020 and 30/11/2021.

Some children might be registered with a FP but, in reality, underuse appropriate medical services, being follow by a private doctor. To exclude these patients from the analysis, we excluded patients who did not have the required "well-child visits" at the FP, a regular checkup examination for preventive medicine purposes at specific time points in the life of the child (see **Table II** for the specific well-child visits required).

Tab. II. Well-child visits inclusion criteria

Well-child visits required	i) Two visits during the first year of life 6 months apart; ii) one visit between 2 and 4 years old; iii) one visit between 5 and 7 years old; iv) one visit between 10 and 14 years old.
Inclusion criteria for children whose first healthcare access was within 6 months (153 days) after birth	• if the end of follow-up is > 1st year, two visits 6 months apart are required; • if the end of follow-up is > 4th year, a visit between 2 and 4 years old and (i) are required. • if the end of follow-up is > 10 years, a visit between 5 and 7 years old and (i), (ii) are required; • if the end of follow-up is > 14th year, a visit between 10 and 14 years old and (i), (ii), (iii) are required.
Inclusion criteria for children whose first healthcare access was between 6 months and 2 years after birth	• if the end of follow-up is > 4th year, a visit between 2 and 4 years old is required; • if the end of follow-up is > 10th year, a visit between 5 and 7 years old and (i) are required; • if the end of follow-up is > 14th year, a visit between 10 and 14 years old and (i), (ii) are required;
Inclusion criteria for children whose first healthcare access was	• if the end of follow-up is > 10th year, a visit between 5 and 7 years old is required; • if the end of follow-up is > 14th year, a visit between 10 and

between 2 to 5 years after birth	14 years old and (i) are required;
Inclusion criteria for children whose first healthcare access was between 5 to 10 years after birth	• if the end of follow-up is > 14th year, a visit between 10 and 14 years old is required.
Others	Children who do not cover the necessary timeframe to observe well child visits are included regardless of the above criteria. For example, a child begins the follow-up after his 153rd day after birth and ends it before his 4^{th} birthday.

Patients were classified as "exposed" when they had a laboratory-confirmed diagnosis of COVID-19. These patients were matched up to 1:1 with unexposed children, by age, sex, length of follow-up, and paediatrician. According to the nested design of the study, the same individual can be selected more than once as a control and can contribute as both exposed and unexposed to the study cohort (since children initially classified as unexposed could, later on, be diagnosed with COVID-19).

To assess the long-term consequences of COVID-19 infection, children had to have more than 28 days of follow-up after the exposure.

In the first part of the study, the outcome investigated was onset of pathology signals, defined as the presence of at least one outpatient specialist visit prescription not less than 28 days after COVID-19 diagnosis. Seven medical areas were considered: cardiology, neurology, pneumology, gastroenterology, rheumatology, dermatology, and endocrinology.

In the second part of the study, the outcome of interest was onset of long-COVID. Signs and symptoms were selected according to the available literature on long-COVID (**Table III**). Long-COVID was defined as "the presence of at least one of the selected symptoms after 28 days from the index date"; this was based on specialist referrals, clinical diaries, ER visit records, and admission records. Clinical diaries and hospital records were manually searched by two independent clinicians. When diagnosis was not clear or information were missing or conflicting, results were considered "Not acceptable", and consequently not included in the analysis.

Tab. III. Symptoms of long-COVID considered

Diagnostic group	Symptoms
Neurologic sequelae	Focal deficits
	Hearing loss
	Seizures
	Cognitive impairment (including attention deficits, amnestic problems, learning disabilities in children)
	Visual impairment
	Headache (migraine)
	Asthenia or Fatigue
	Vertigo
	Motor impairment (including palsy)
Mental-Psychological sequelae	Anxiety
	Depression
	Mood disorder
	Disturbance of emotions specific to childhood and adolescence
	Insomnia
	Hypersomnia
	Hyperkinetic syndrome of childhood
	Lack of concentration
	Developmental disorders
	Behavior disorders
	Eating disorders (nervous anorexia, bulimia)
	Communication disorder
Metabolic/endocrinological sequelae	Obesity
	Metabolic syndrome
	Poor growth (Variation of growth percentile)
	Hyperglycemia or diabetes
	Hyper or hypothyroidism
Osteo-muscular sequelae	Persistent muscle pain
	Joint pain or swelling
Respiratory sequelae	Nasal congestion/ rhinorrhea

	Persistent cough
	Asthma with broncospasm
Cardiovascular sequelae	Palpitations
	Chest tightness
	Chest pain
Gastrointestinal sequelae	Constipation
	Stomach/abdominal pain
	Diarrhea
Other	Altered smell
	Altered taste
	Skin rashes

To account for potential confounding – due to the unspecific nature of long-COVID symptoms – we also considered the presence of long-COVID symptoms in the 12 months before the index date. Clinical characteristics (number of specialist visits, number of antibiotics, number of contacts with the FP, and fiscal exemption for pre-term birth) were evaluated in the minimum available retrospective follow-up of the risk set (the case and its matching control).

3.3 STATISTICAL ANALYSIS

Data analysis was performed on the whole cohort and then stratified according to the length of follow up (up to 3, 6 and 12 months of follow-up after the 28 days of the acute phase).

Quantitative variables were categorized, considering the 33rd and 66th percentiles of their distributions. Socio-demographic and clinical characteristics evaluated were sex, year of birth, number of outpatient visit prescriptions, number of antibiotics, number of visits, and fiscal exemption for preterm birth. They were compared between exposed and unexposed children, and the association between these variables and the exposure was evaluated with Chi-squared tests.

Cox regression model was used to estimate the Hazard Ratios (HR), and the 95% confidence interval, for each outcome group.

The observation period begins at the index date (when diagnosis of COVID-

19 is made) and ends when the outcome of interest appears, at the end of the study or at the end of the follow-up.

Stratified analyses were then conducted according to the length of follow-up (up to 3, between 3 and 6, and over 6 months of follow-up after the 28 days of the acute phase). Subgroups analyses reduced statistical power of the study but allow for the evaluation of the changing in HR over time. This method was used in both phases of the study.

Analyses were performed using the Statistical Analysis System software (version 9.4; SAS Institute, Cary, North Carolina). Statistical significance was set at the 0.05 level.

4. RESULTS

From February 1st, 2020, to November 11th, 2021 there were 111.415 pediatric patients registered in the Veneto Pedianet database. Of these, 82'299 were excluded because they had not performed a COVID-19 test, 806 because they were older than 14 years, and 2'611 because of missing criteria for well child-visits. Among the remaining population, 2605 had a laboratory-confirmed diagnosis of COVID-19, instead 22'582 had not. Positives were matched 1:1 with negatives according to sex, age, and paediatrician, resulting in a cohort of 4'570 patients. According to the length of follow-up, patients were distributed as follows: 4'750 in the short-term cohort, 3'564 in the intermediate one, 3'010 in the long one (**fig. 13**).

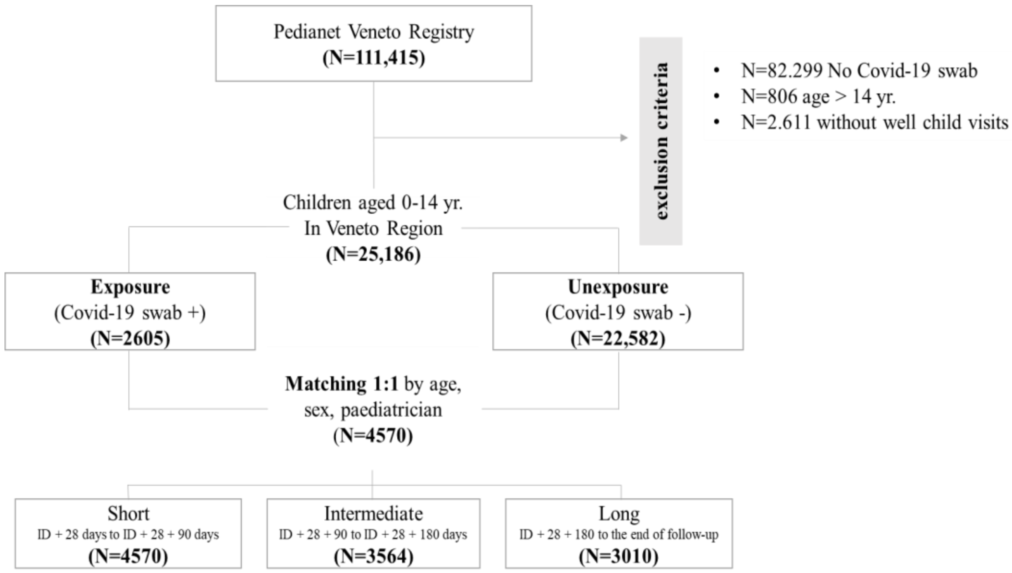

Figure 13 - Cohort selection. ID = index date

Table IV shows absolute and relative frequencies of socio-demographic and clinical characteristics, as well as p-values obtained with Chi-squared test, applied to evaluate the association between these variables and SARS-CoV-2 infection.

No significant association was found among variables considered, so there was no significant difference between cases and controls before the index date. Of note, both in exposed and unexposed, number of visits was distributed homogenously, with more than 30% of subjects performing a large number of visits (≥ 35) in the year before infection. Also, other variables were distributed homogenously, except for fiscal exemption for preterm births.

Tab. IV. Frequencies and Chi-squared test with α=0,05.

Sociodemographic and clinical characteristics	COVID-19 (N=2.285) N	(%)	No COVID-19 (N=2.285) N	(%)	p-value
Year of birth					
0 (2007-2010)	865	37.86	865	37.86	
1 (2011- 2015)	770	33.7	769	33.65	M.V.
2 (2016-2021)	650	28.45	651	28.49	
Sex					
F	1040	45.51	1040	45.51	M.V.
M	1245	54.49	1245	54.49	
Number of visits*					
0-13	751	32.87	783	34.27	
14-34	759	33.22	778	34.05	0.27
≥35	775	33.92	724	31.68	
Number of outpatient visits*					
0	1007	44.07	1013	44.33	
1 - 2	674	29.5	690	30.2	0.73
≥3	604	26.43	582	25.47	
Antibiotic treatment*					
0-1	880	38.51	880	38.51	0.66
2-5	654	28.62	678	29.67	
≥6	751	32.87	727	31.82	
Preterm birth*					
no	2223	97.29	2214	96.89	0.43
yes	62	2.71	71	3.11	

** Calculated on the minimum available retrospective follow-up of the risk set*

Table V and **figure 14** represents estimates of the stratified analysis on pathology signals; frequencies of outcomes and HR for each category are shown.

Tab. V. Stratified analysis of pathology signals – Cox model. Pedianet, 2020-2021. N=4.570.

	N° of children		**N° of outcomes**			
	Covid-19	No Covid-19	Covid-19	No Covid-19	**HR**	**(95% CI)**
SHORT						
Cardiology	2285	2285	56	25	2.22	(1.39 – 3.56)
Neurology	2285	2285	131	98	1.32	(1.02 – 1.72)
Pneumology	2285	2285	12	4	3.19	(1.02 – 9.97)
INTERMEDIATE						
Cardiology	1782	1782	39	20	1.91	(1.11 – 3.27)
Neurology	1782	1782	100	100	0.97	(0.74 – 1.28)
Pneumology	1782	1782	7	4	1.74	(0.51 – 5.95)

LONG						
Cardiology	1505	1505	45	32	1.36	(0.86 – 2.14)
Neurology	1505	1505	120	86	1.40	(1.06 – 1.85)
Pneumology	1505	1505	9	8	0.82	(0.31 – 2.12)

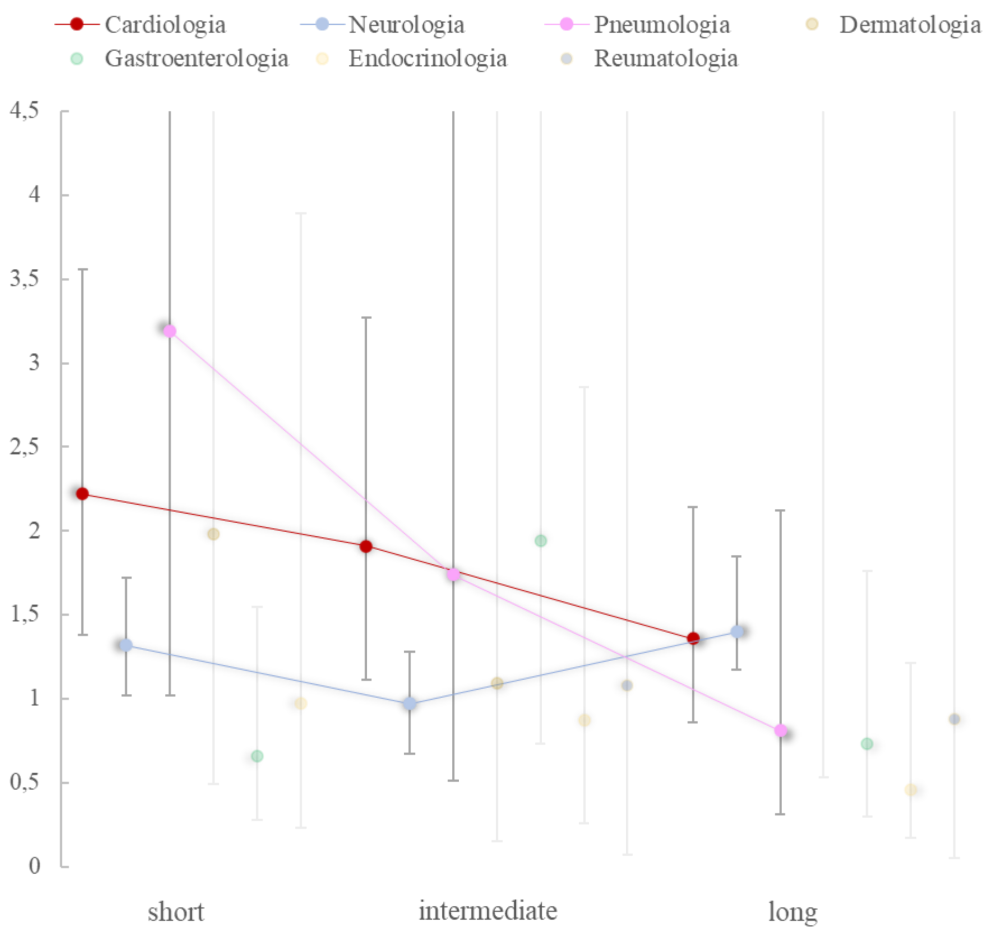

Figure 14 - Analysis of pathology signals

In the short term pneumology, cardiology and neurology prescriptions showed a significant difference, with an HR of 3.19 (95% IC: 1.02 – 9.97), 2.22 (1.39 – 3.56), and 1.32 (1.02 – 1.72), respectively; exposed had a triple or double risk of having a prescription for pneumology and cardiology visit.

In the intermediate follow-up cohort, the trend decreased and only cardiology remained a significant sign of pathology with a risk of 2-fold greater in exposed children compared to unexposed (1.11 – 3.27).

Finally, in the long-term, only neurological signs are slightly significant, with an HR_{neuro} of 1.40 (1.11 – 3.27).

Overall, cardiology and pneumology areas were the most common signs of pathology in the short-term, but their HR decreased over time, whereas neurology prescriptions showed an increase in the long-term, but without a marked difference among exposed and unexposed. All the other outcomes had confidence intervals that contains the unit, meaning there was no significant difference between exposed and unexposed. This might be due to an inadequate sample size for the parameters observed.

In the second part of the study, the actual onset of pathology was evaluated, manually reading specialist referrals, clinical diaries, ER visit records, and admission records. The number of outcomes was lower than expected from the first analyses number of subjects in the matched cohort, because of several number of inputs had been classified as "Not acceptable". Moreover, only outcomes that presented in a relevant number of subjects were analysed, so in the following tables not all symptoms described in **table III** (see previous chapter) are displayed. **Table VI** shows results of the second stratified analysis.

Tab. VI. Stratified analysis of pathology onset – Cox model. Pedianet, 2020-2021. N=4.570.

short-term period (N=4570)					
	N. of Outcome				
	No Covid	Covid	HR	(95% CI)	*minimum detectable risk*
Overall	127	136	1,05	(0.83 - 1.34)	*1,4*
Cardiology	10	8	0,78	(0.31 - 1.99)	*3*
Respiratory	14	17	1,18	(0.58 - 2.4)	*2,5*
Asthma_broncospasmo	2	8	4,15	(0.87 - 19.74)	*7*
Gastrology	9	15	1,66	(0.72 - 3.79)	*3*
Neurology	39	48	1,21	(0.79 - 1.84)	*1,7*
Visual impairment	15	27	1,81	(0.96 - 3.41)	*2,5*
Headache	5	7	1,34	(0.43 - 4.23)	*4*
Mental disorders	45	41	0,89	(0.58 - 1.35)	*1,7*
Communication disorder	11	19	1,710	(0.81 – 3.6)	*3*
Osteomuscolar sequelae	8	7	0,840	(0.3 - 2.31)	*3,4*
Others	11	22	2	(0.97 - 4.13)	*2,6*
Skin rashes	5	9	1,84	(0.62 - 5.5)	*4*

intermediate period (N=3564)				
	N. of Outcome			
	No Covid	Covid	HR	(95% CI)
OVERALL	94	113	1,17	(0.89 - 1.54)
Cardiology	4	5	1,22	(0.33 - 4.55)
Respiratory	17	21	1,21	(0.64 - 2.3)
Asthma_broncospasmo	4	3	0,71	(0.16 - 3.19)
Gastrology	6	16	2,64	(1.03 - 6.75)
Neurology	26	32	1,24	(0.74 - 2.08)
Visual impairment	13	16	1,27	(0.61 - 2.64)
Headache	5	6	1,19	(0.36 - 3.91)
Mental disorders	28	30	1,04	(0.62 - 1.73)
Communication disorder	7	9	1,25	(0.46 - 3.36)
			0	
Osteomuscolar sequelae	7	7	0,99	(0.35 - 2.83)
			0	
Others	12	22	1,78	(0.88 - 3.58)
Skin rashes	4	10	2,42	(0.76 - 7.71)

long period (N=3010)				
	N. of Outcome			
	No Covid	Covid	HR	(95% CI)
OVERALL	111	114	1,01	(0.77 - 1.31)
Cardiology	7	9	1,25	(0.47 - 3.37)
Respiratory	16	15	0,87	(0.43 - 1.76)
Asthma_broncospasmo	5	5	0,97	(0.28 - 3.37)
Gastrology	15	9	0,58	(0.25 - 1.34)
Neurology	36	37	1,02	(0.65 - 1.62)
Visual impairment	24	19	1,02	(0.65 - 1.62)
Headache	2	11	5,38	(1.19 - 24.34)
Mental disorders	39	35	0,88	(0.56 - 1.39)
Communication disorder	15	13	0,83	(0.39 - 1.75)
			0	
Osteomuscolar sequelae	5	9	1,72	(0.57 - 5.13)
			0	
Others	16	13	0,8	(0.38 - 1.66)
Skin rashes	2	5	2,32	(0.45 - 11.98)

Considering all the outcomes and their confidence intervals, there were no significant differences among exposed and unexposed, in all follow-up periods;

overall hazard ratio is respectively HR_{short} 1.05 (0.83 – 1.54), $HR_{intermediate}$ 1.17 (1.11 – 3.27), HR_{long} 1.40 (1.11 – 3.27). Thus, apparently, the increased number of prescriptions does not imply a real new burden of pathology. However, if we take into account values of the minimum detectable risk for each outcome, it can be seen that a higher number of subjects is needed to demonstrate a clinically significant difference.

Even in absence of statistical significance, it was possible to see a trend over time in the outcomes of interest. For example, contrarily to results of the first part of the study, cardiovascular pathologies slightly increased during time, with an HR_{cardio} that ranges from 0.78 in the short-term to 1.22 and 1.25 in the intermediate and long-term, respectively. On the other hand, respiratory sequelae mirrored the findings of prescriptions analysis: their burden decreased over time, and it was no longer significant in the long-term; asthma with bronchospasm was the most common symptom reported, especially in the short-term period. Neurological sequelae tended to remain slightly above the level of significance, but they decreased in the long-term (HR_{neuro} in the short, intermediate, and long-term period of 1.21, 1.24, 1.02, respectively), with visual impairment and headache being the most important ones.

Moreover, pathologies of other areas were of interest. Gastroenterology symptoms and communication disorders were particularly increased in the intermediate period (HR_{gastro} 2.64 (1.03 – 6.75) and $HR_{comm.\ d.}$ 1.25 (0.46 – 3.36)). Osteo-muscular sequelae became important in the long-term (1.72, 0.57 – 5.1), whereas skin rashes were a sign of long-COVID that was highly present over time (HR_{short} 1.84, $HR_{intermediate}$, 2.42 HR_{long} 2.32).

5. DISCUSSION

This retrospective, nested cohort study conducted on paediatric patients aged 0-14 years of Veneto region, evaluated the burden of disease consequent to COVID-19 and the risk of developing symptoms related to long-COVID, by comparing exposed to unexposed children.

In the first part of the study, specialistic prescriptions were analysed and significant differences were found between the two cohorts. Notably, subjects with a previous diagnosis of COVID-19 were at higher risk of having a prescription for a cardiological (HR: 2.22, 95% IC:1.39 – 3.56), a pneumological (HR_{fissa}:3.19, 95% IC: 1.02 – 9.97) or a neurological (HR: 1.32, 95% IC:1.02 – 1.72), visit compared to unexposed. This trend decreases with time, but it increases for the neurological area up to 12 months.

Secondly, symptoms and diagnosis related to prescriptions were assessed. Interestingly, increased prescriptions do not correspond to an increase of symptoms. In fact, considering each symptom, no significant differences were found between COVID-19 exposed and unexposed groups. This result might be due to the small sample size. Even though the sample size was high at the beginning of the analysis, when assessing symptoms and diagnosis many subjects were classified as "Not acceptable" due to lack of information in order to avoid wrong classifications. This is a limitation of using an extrapolated database.

However, taking into account trends of diagnosis, interesting findings should be noticed. Cardiovascular and pneumological sequelae were found, even if of slight significance; likewise, in NICE guidelines is stated that children tend to manifest long-COVID mainly with respiratory or cardiological symptoms. (91) Signs of organ damage at the cardiopulmonary exercise testing (CPET) were also detected in the case report of Buonsenso et al. and abnormalities in the respiratory functioning test were found in the study of Ashkenazi-Hoffnung et al. (108,136) This may reflect effects of organ damage caused by the virus that, however, improve over time.

Neurological consequences were of note in our study, as they were among literature: all Ludvigsson's patients suffered from headaches post-COVID, fatigue and the so-called “brain fog” are also reported in many studies. (129,130,132,147) Brackel et al. found high neurocognitive disfunction among Dutch paediatrician’s patients, among which concentrating difficulties (45%) and headaches (38%) were the most common one. The strength of this study is that is based on paediatricians’ direct experience, avoiding milder and self-reported symptoms (139) On the contrary, our study showed a slight increase in visual impairment (HR_{short} 1.81 95% IC (0.96 - 3.41)), which is not a common finding in literature.

Mental health problems, except from communication disorders, were not different among exposed and unexposed. Likewise, other studies conducted with a control group, like the CLoCK study, did not show significant differences in this category. (135) In fact, psychiatric disorders may be caused by lockdown measures rather than the virus alone.

Gastroenterology symptoms are important in the short and mid-term according to our data; this may reflect the same mechanism demonstrated in adults, with SARS-CoV-2 persisting in the GI tract several weeks after a negative throat swab. (120) Also skin rashes and osteo-muscular sequelae were less reported among children, but they were demonstrated in adults. As for our data, skin rashes are a common sign of acute COVID-19 that could persist for months; (123) arthromialgia was reported in adults even 1 year after the acute phase. (125)

Our result is in contrast with part of the current literature on long-COVID in children. In their preliminary study, Buonsenso et al. found a high prevalence of long-COVID symptoms: 66.6% of the children had at least one persisting symptom between 60 and 120 days after diagnosis, 27.1% after 120 days and 42.6% were distressed by these symptoms. However, there was no control group, and some patients were only interviewed through a phone call. In a large metanalysis Lopez-Leon et al. found a prevalence of 25.24%, (148)

On the contrary, studies who included a control group found smaller differences among cases and controls, in line with our study. Radtke et al. reported a prevalence of symptoms lasting more than 12 weeks of 4% in exposed and 2% in unexposed. The most common symptoms were tiredness (3%), difficulty concentrating (2%), and increased need for sleep (2%). However, there was not a statistical comparison between the two groups. (132) In the CLoCK study, one of the largest in term of sample size, a higher prevalence of physical symptoms was found in previously infected compared to test-negative, whereas fatigue, mental symptoms and wellbeing shown no significant difference. (135) However, among studies there is also heterogeneity in the selection of controls. For example, Roge et al. use as controls children with other infections and cognitive sequelae resulted as the most common. (38)

Different results may be attributed to differences in definitions and methodology. Many published studies suffer from limitations in design and bias, among which selection bias is the most common one; patients are often highly selected and evaluated in an outpatient specialistic setting or with an anonymous questionnaire, so symptoms are more likely to be overestimated. The current lack of an evidence-based definition of long-COVID in children contributes to variance among studies. Moreover, many studies have a sample size smaller than ours. On the contrary, this was a population-based study, relying on real world data; this allowed us to have a higher sample size and a population representative of children in Veneto region.

Since this study is highly representative of a population, even if it is a regional one, the high prevalence of long-COVID in children described in previous studies may be unreliable and should be further studied.

The absence of differences between exposed and unexposed may also be attributed to lockdown measures in response to COVID-19 and stress related to the pandemic. Some of the outcomes evaluated may, in fact, also be functional symptoms. For example, whereas in adults the diarrhoea was demonstrated to be a sign of long-COVID (149), in our subjects a high number of gastrointestinal symptoms was found but no significant differences were shown between the two cohorts; abdominal pain was one of the observed outcomes, but it may have a functional origin rather than an organic one.

To better understand the present study, strength and limitations must be evaluated. Strengths of this study include the population-based design, representative of paediatric population of Veneto region; exclusion criteria based on well-child visits reduced misclassification bias on exposure (partially) and outcomes. A wide spectrum of symptoms was manually searched. Finally, the control group was useful to compare the real increase in symptoms in the exposed population.

This study has also some limitations. One of the most critical issues was the small sample size; although many studies on long-COVID used even a smaller sample size, the one used in this study might have influenced the results. Given the low prevalence of COVID-19 in children, and, consequently, low prevalence of long-term sequelae, a larger population must be tested to obtain significant results. Furthermore, stratified analysis were necessary to highlight changing of HR during time, but this procedure further reduced sample size with a consequent loss of statistical power. To this reason, we plan to improve the study cohort with and higher number of controls matched to each case, resulting in a 1:5 match between cases and controls. Lastly, given data were extrapolated from a pre-existing database, many symptoms were classified as “Not acceptable” because information was incomprehensible, incomplete or incoherent. As it can be seen, the number of outcomes is relatively small in relation to the cohort studied, due to the the large number of “Non acceptable” outcomes. Another issue is related to the clinical course of COVID-19 in children. Our study classified as cases only those with a positive swab test, but since infection in children is often asymptomatic, it is possible that some were not tested but acquired infection anyway, especially in the first period of the pandemic.

Moreover, although Pedianet is representative of the entire Italian paediatric population, the study was restricted to Veneto region according to the nasopharyngeal swabs’ regional registry.

Additionally, some symptoms might have been missed in our analysis because they need a specialistic visit to be further evaluated, or they must be asked or assessed with a pre-existing questionnaire, normally used in other studies to assess long-COVID sequelae.

Ultimately, the study ended before the predominance of Omicron variant and the consequent increase in paediatric infections, so effects of this period were not assessed. Also, quarantine measures started to ease in the last months, therefore lockdown effects on symptoms may now have less impact than in our analysis.

To further understand repercussions of long-COVID in children it will be necessary to extend the study to a larger sample size and to include the Omicron-predominance phase in the analysis. A large multicentre study will be useful to increase the power of the study.

Comprehension of post-COVID conditions is of utmost importance not only to provide necessary healthcare services and to prevent debilitating consequences, but also to weigh pros and cons of strict lockdown measures against the spread of SARS-CoV-2.

6. CONCLUSIONS

Our retrospective nested cohort study showed an increased number of prescriptions for cardiology, pulmonary and neurology specialistic visits after COVID-19 infection among previously exposed, reflecting a possible clinical consequence related to SARS-CoV-2 in the pediatric population. Considering the minimum detectable risk for some specific symptoms or diagnosis, we interestingly observed that improving the size of the study cohort could allow us to achieve the statistical power to find some differences in the incidence of the analysed clinical outcomes. These findings suggested us that children, as adults, after SARS-CoV-2 infection could be suffer from Long Covid syndrome.

Further population-based studies are needed to assess the impact of Long Covid in children, also considering the emergence of new variants of concern.

7. REFERENCES

1. Coronaviruses [Internet]. [cited 2022 Apr 14]. Available from: https://www.ecdc.europa.eu/en/covid-19/latest-evidence/coronaviruses
2. Tutto sulla pandemia di SARS-CoV-2 [Internet]. [cited 2022 Apr 14]. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2
3. CDC Museum COVID-19 Timeline | David J. Sencer CDC Museum | CDC [Internet]. [cited 2022 Apr 13]. Available from: https://www.cdc.gov/museum/timeline/covid19.html
4. Timeline of WHO's response to COVID-19 [Internet]. [cited 2022 Apr 13]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline?gclid=Cj0KCQjw16KFBhCgARIsALB0g8LHEhhQckbxc3THQ5NLV6-CrqYZlgI1uN_6EZ2EUa5K8fRG3m-1M-IaAimOEALw_wcB#!
5. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data [Internet]. [cited 2022 Apr 14]. Available from: https://covid19.who.int/
6. Weekly epidemiological update on COVID-19 - 25 May 2022 [Internet]. [cited 2022 May 27]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2022
7. CDC COVID Data Tracker: Total Cases and Deaths by Race/Ethnicity, Age, and Sex [Internet]. [cited 2022 Jun 8]. Available from: https://covid.cdc.gov/covid-data-tracker/#demographics
8. REPORT ESTESO ISS [Internet]. Available from: https://www.iss.it/cov19-cosa-fa-iss-varianti
9. Bellino S, Punzo O, Rota MC, del Manso M, Urdiales AM, Andrianou X, et al. COVID-19 Disease Severity Risk Factors for Pediatric Patients in Italy. Pediatrics. 2020 Oct 1;146(4).
10. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr 7;323(13):1239–42.
11. Ladhani SN, Amin-Chowdhury Z, Davies HG, Aiano F, Hayden I, Lacy J, et al. COVID-19 in children: analysis of the first pandemic peak in England. Archives of Disease in Childhood. 2020;105(12):1180.
12. COVID-19: Clinical manifestations and diagnosis in children - UpToDate [Internet]. [cited 2022 Jun 8]. Available from: https://www.uptodate.com/contents/covid-19-clinical-manifestations-and-

diagnosis-in-children?search=covid%2019%20children&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3#H4155540577

13. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: Where do we Stand? Archives of Medical Research. 2022 Jan 1;53(1):1.

14. Reopening K-12 Schools During the COVID-19 Pandemic. Reopening K-12 Schools During the COVID-19 Pandemic. 2020 Oct 8;

15. Children and COVID-19: State-Level Data Report [Internet]. [cited 2022 Jun 7]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/

16. Infografica web - Dati della Sorveglianza integrata COVID-19 in Italia [Internet]. [cited 2022 Jun 7]. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard

17. Howard-Jones AR, Bowen AC, Danchin M, Koirala A, Sharma K, Yeoh DK, et al. COVID-19 in children: I. Epidemiology, prevention and indirect impacts. Journal of Paediatrics and Child Health. 2022 Jan 1;58(1):39–45.

18. Clarke KEN, Jones JM, Deng Y, Nycz E, Lee A, Iachan R, et al. Seroprevalence of Infection-Induced SARS-CoV-2 Antibodies — United States, September 2021–February 2022. MMWR Morbidity and Mortality Weekly Report [Internet]. 2022 Apr 29 [cited 2022 Jun 8];71(17):606–8. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7117e3.htm

19. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. medRxiv. 2022 Jan 13;

20. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Archives of Disease in Childhood. 2021 May 1;106(5):440.

21. Zachariah P. COVID-19 in Children. Infectious Disease Clinics of North America. 2022 Mar 1;36(1):1–14.

22. Dhochak N, Singhal T, Kabra SK, Lodha R. Pathophysiology of COVID-19: Why Children Fare Better than Adults? Indian Journal of Pediatrics. 2020 Jul 1;87(7):537–46.

23. Samuel S, Friedman RA, Sharma C, Ganigara M, Mitchell E, Schleien C, et al. Incidence of arrhythmias and electrocardiographic abnormalities in symptomatic pediatric patients with PCR-positive SARS-CoV-2 infection, including drug-induced changes in the corrected QT interval. Heart Rhythm. 2020 Nov 1;17(11):1960–6.

24. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. Aliment Pharmacol Ther. 2020 May 1;51(9):843–51.

25. Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. Pediatr Pulmonol. 2020 May 1;55(5):1169–74.

26. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 Infection in Children. N Engl J Med. 2020 Apr 23;382(17):1663–5.

27. Perez A, Kogan-Liberman D, Sheflin-Findling S, Raizner A, Ahuja KL, Ovchinsky N. Presentation of Severe Acute Respiratory Syndrome-Coronavirus 2 Infection as Cholestatic Jaundice in Two Healthy Adolescents. J Pediatr. 2020 Nov 1;226:278–80.

28. Samies NL, Yarbrough A, Boppana S. Pancreatitis in Pediatric Patients With COVID-19. J Pediatric Infect Dis Soc. 2021 Jan 1;10(1):57–9.

29. Brisca G, Mallamaci M, Tardini G, Martino L, Chianucci B, Ricci M, et al. SARS-CoV-2 Infection May Present as Acute Hepatitis in Children. Pediatr Infect Dis J [Internet]. 2021 [cited 2022 Jun 9];40(5):E214–5. Available from: https://pubmed.ncbi.nlm.nih.gov/33591076/

30. Fink EL, Robertson CL, Wainwright MS, Roa JD, Lovett ME, Stulce C, et al. Prevalence and Risk Factors of Neurologic Manifestations in Hospitalized Children Diagnosed with Acute SARS-CoV-2 or MIS-C. Pediatr Neurol. 2022 Mar 1;128:33–44.

31. King JA, Whitten TA, Bakal JA, McAlister FA. Symptoms associated with a positive result for a swab for SARS-CoV-2 infection among children in Alberta. CMAJ. 2021 Jan 4;193(1):E1–9.

32. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020 May 1;34(5):e212–3.

33. Galván Casas C, Català A, Carretero Hernández G, Rodríguez-Jiménez P, Fernández-Nieto D, Rodríguez-Villa Lario A, et al. Classification of the cutaneous manifestations of COVID-19: a rapid prospective nationwide consensus study in Spain with 375 cases. Br J Dermatol. 2020 Jul 1;183(1):71–7.

34. Stewart DJ, Hartley JC, Johnson M, Marks SD, du Pré P, Stojanovic J. Renal dysfunction in hospitalised children with COVID-19. Lancet Child Adolesc Health. 2020 Aug 1;4(8):e28–9.

35. Raina R, Mawby I, Chakraborty R, Sethi SK, Mathur K, Mahesh S, et al. Acute kidney injury in COVID-19 pediatric patients in North America: Analysis of the virtual pediatric systems data. PLoS One. 2022 Apr 1;17(4).

36. Clinical management of COVID-19 patients: living guideline, 23 November 2021 [Internet]. [cited 2022 Jun 9]. Available from: https://app.magicapp.org/#/guideline/j1WBYn

37. Dong Y, Dong Y, Mo X, Hu Y, Qi X, Jiang F, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020 Jun 1;145(6):20200702.

38. Roge I, Smane L, Kivite-Urtane A, Pucuka Z, Racko I, Klavina L, et al. Comparison of Persistent Symptoms After COVID-19 and Other Non-SARS-CoV-2 Infections in Children. Frontiers in Pediatrics. 2021 Oct 29;9:1177.

39. Marks KJ, Whitaker M, Anglin O, Milucky J, Patel K, Pham H, et al. Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, July 2021–January 2022. MMWR Morbidity and Mortality Weekly Report. 2022;71(7):271–8.

40. Shi DS, Whitaker M, Marks KJ, Anglin O, Milucky J, Patel K, et al. Hospitalizations of Children Aged 5–11 Years with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, March 2020–February 2022. MMWR Morbidity and Mortality Weekly Report. 2022 Apr 22;71(16):574–81.

41. Beck A, Gandhi M. Adjudicating Reasons for Hospitalization Reveals That Severe Illness From COVID-19 in Children Is Rare. Hospital Pediatrics. 2021 Aug 1;11(8):e159–60.

42. Webb NE, Osburn TS. Characteristics of Hospitalized Children Positive for SARS-CoV-2: Experience of a Large Center. Hospital Pediatrics. 2021 Aug 1;11(8):e133–41.

43. Charles Bailey L, Razzaghi H, Burrows EK, Bunnell ; H Timothy, Peter ;, Camacho EF, et al. Assessment of 135 794 Pediatric Patients Tested for Severe Acute Respiratory Syndrome Coronavirus 2 Across the United States Supplemental content. JAMA Pediatr. 2021;175(2):176–84.

44. Pennington AF, Kompaniyets L, Summers AD, Danielson ML, Goodman AB, Chevinsky JR, et al. Risk of Clinical Severity by Age and Race/Ethnicity among Adults Hospitalized for COVID-19 - United States, March-September 2020. Open Forum Infectious Diseases. 2021 Feb 1;8(2).

45. Shekerdemian LS, Mahmood NR, Wolfe KK, Riggs BJ, Ross CE, McKiernan CA, et al. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr. 2020 Sep 1;174(9):868–73.

46. Wanga V, Gerdes ME, Shi DS, Choudhary R, Dulski TM, Hsu S, et al.

Characteristics and Clinical Outcomes of Children and Adolescents Aged. MMWR Morb Mortal Wkly Rep. 2021 Dec 31;70(5152):1766–72.

47. Shane AL, Sato AI, Kao C, Adler-Shohet FC, Vora SB, Auletta JJ, et al. A Pediatric Infectious Diseases Perspective of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Novel Coronavirus Disease 2019 (COVID-19) in Children. J Pediatric Infect Dis Soc. 2020;9(5):596–608.

48. Bright A, Glynn-Robinson AJ, Kane S, Wright R, Saul N. The effect of COVID-19 public health measures on nationally notifiable diseases in Australia: preliminary analysis. Commun Dis Intell (2018). 2020 Oct 5;44.

49. Ackerson BK, Sy LS, Glenn SC, Qian L, Park CH, Riewerts RJ, et al. Pediatric Vaccination During the COVID-19 Pandemic. Pediatrics [Internet]. 2021 Jul 1 [cited 2022 Jun 9];148(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33858983/

50. Murthy BP, Zell E, Kirtland K, Jones-Jack N, Harris LT, Sprague C, et al. Impact of the COVID-19 Pandemic on Administration of Selected Routine Childhood and Adolescent Vaccinations - 10 U.S. Jurisdictions, March-September 2020. MMWR Morb Mortal Wkly Rep. 2021;70(23):840–5.

51. Muhoza P, Danovaro-Holliday MC, Diallo MS, Murphy P, Sodha S v., Requejo JH, et al. Routine Vaccination Coverage - Worldwide, 2020. MMWR Morb Mortal Wkly Rep. 2021 Oct 29;70(43):1495–500.

52. Vaccination in Acute Humanitarian Emergencies: A Framework for decision-making. 2020;

53. Lazzerini M, Barbi E, Apicella A, Marchetti F, Cardinale F, Trobia G. Delayed access or provision of care in Italy resulting from fear of COVID-19. The Lancet Child & Adolescent Health. 2020 May 1;4(5):e10–1.

54. Lee L, Mannix R, Guedj R, Chong SL, Sunwoo S, Woodward T, et al. Paediatric ED utilisation in the early phase of the COVID-19 pandemic. Emergency Medicine Journal. 2021 Feb 1;38(2):100–2.

55. Vincent House S. PROTECT A GENERATION The impact of COVID-19 on children's lives SAVE THE CHILDREN INTERNATIONAL. [cited 2022 Jun 9]; Available from: www.savethechildren.net

56. Ashikkali L, Carroll W, Johnson C. The indirect impact of COVID-19 on child health. Paediatr Child Health (Oxford). 2020 Dec 1;30(12):430–7.

57. Rundle AG, Park Y, Herbstman JB, Kinsey EW, Wang YC. COVID-19–Related School Closings and Risk of Weight Gain Among Children. Obesity. 2020 Jun 1;28(6):1008–9.

58. Pietrobelli A, Pecoraro L, Ferruzzi A, Heo M, Faith M, Zoller T, et al. Effects

of COVID-19 Lockdown on Lifestyle Behaviors in Children with Obesity Living in Verona, Italy: A Longitudinal Study. Obesity. 2020 Aug 1;28(8):1382–5.

59. COVID-19 and children - UNICEF DATA [Internet]. [cited 2022 Jun 9]. Available from: https://data.unicef.org/covid-19-and-children/

60. Interim Guidance on Supporting the Emotional and Behavioral Health Needs of Children, Adolescents, and Families During the COVID-19 Pandemic [Internet]. [cited 2022 Jun 12]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/interim-guidance-on-supporting-the-emotional-and-behavioral-health-needs-of-children-adolescents-and-families-during-the-covid-19-pandemic/

61. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global Prevalence of Depressive and Anxiety Symptoms in Children and Adolescents During COVID-19: A Meta-analysis. JAMA Pediatr. 2021 Nov 1;175(11):1142–50.

62. Viner RM, Russell SJ, Croker H, Packer J, Ward J, Stansfield C, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. The Lancet Child & Adolescent Health [Internet]. 2020 May 1 [cited 2022 Jun 12];4(5):397. Available from: /pmc/articles/PMC7270629/?report=abstract

63. The Impact of COVID-19 on children 15 A P R I L 2 0 2 0.

64. Pieh C, Plener PL, Probst T, Dale R, Humer E. Assessment of Mental Health of High School Students During Social Distancing and Remote Schooling During the COVID-19 Pandemic in Austria. JAMA Netw Open. 2021;4(6).

65. Creswell C, Shum A, Pearcey S, Skripkauskaite S, Patalay P, Waite P. Young people's mental health during the COVID-19 pandemic. Lancet Child Adolesc Health. 2021 Aug 1;5(8):535–7.

66. Mayne SL, Hannan C, Davis M, Young JF, Kelly MK, Powell M, et al. COVID-19 and Adolescent Depression and Suicide Risk Screening Outcomes. Pediatrics. 2021 Sep 1;148(3).

67. Sacco MA, Caputo F, Ricci P, Sicilia F, de Aloe L, Bonetta CF, et al. The impact of the Covid-19 pandemic on domestic violence: The dark side of home isolation during quarantine. Med Leg J. 2020 Jul 1;88(2):71–3.

68. Humphreys KL, Myint MT, Zeanah CH. Increased Risk for Family Violence During the COVID-19 Pandemic. Pediatrics. 2020 Jul 1;146(1).

69. Sidpra J, Abomeli D, Hameed B, Baker J, Mankad K. Rise in the incidence of abusive head trauma during the COVID-19 pandemic. Arch Dis Child. 2021 Mar 1;106(3).

70. Bhopal S, Buckland A, McCrone R, Villis AI, Owens S. Who has been missed? Dramatic decrease in numbers of children seen for child protection assessments during the pandemic. Arch Dis Child. 2021 Feb 1;106(2).

71. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: A narrative review with recommendations. Psychiatry Research. 2020 Nov 1;293:113429.

72. • COVID-19 cases, recoveries, and deaths | Statista [Internet]. [cited 2022 Jun 4]. Available from: https://www.statista.com/statistics/1087466/covid19-cases-recoveries-deaths-worldwide/

73. del Rio C, Collins LF, Malani P. Long-term Health Consequences of COVID-19. Vol. 324, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1723–4.

74. Key Points | Evaluating and Caring for Patients with Post-COVID Conditions | CDC [Internet]. [cited 2022 Apr 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html

75. O'Sullivan O. Long-term sequelae following previous coronavirus epidemics. Clinical Medicine. 2021 Jan 1;21(1):e68–70.

76. Onder G, Floridia M, Giuliano M, Noce C lo, Tiple D, Bertinato L, et al. Indicazioni ad interim sui principi di gestione del Long-COVID Versione del 1° luglio 2021.

77. Emergency use ICD codes for COVID-19 disease outbreak [Internet]. [cited 2022 Apr 21]. Available from: https://www.who.int/standards/classifications/classification-of-diseases/emergency-use-icd-codes-for-covid-19-disease-outbreak

78. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC [Internet]. [cited 2022 Jun 12]. Available from: https://www.cdc.gov/mis/mis-c/hcp/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis%2Fhcp%2Findex.html

79. Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19 [Internet]. [cited 2022 Jun 12]. Available from: https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19

80. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) clinical features, evaluation, and diagnosis - UpToDate.

81. Soma VL, Shust GF, Ratner AJ. Multisystem inflammatory syndrome in

children. Current Opinion in Pediatrics. 2021 Feb 1;33(1):152–8.

82. Multisystem Inflammatory Syndrome in Children (MIS-C) Interim Guidance [Internet]. [cited 2022 Jun 12]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/multisystem-inflammatory-syndrome-in-children-mis-c-interim-guidance/

83. Information for Healthcare Providers about Multisystem Inflammatory Syndrome in Children (MIS-C) | CDC [Internet]. [cited 2022 Jun 13]. Available from: https://www.cdc.gov/mis/mis-c/hcp/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fmis%2Fhcp%2Findex.html

84. COVID-19: Multisystem inflammatory syndrome in children (MIS-C) management and outcome - UpToDate.

85. Godfred-Cato S, Bryant B, Leung J, Oster ME, Conklin L, Abrams J, et al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1074–80.

86. Kaushik A, Gupta S, Sood M, Sharma S, Verma S. A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection. Pediatr Infect Dis J. 2020;39(11):E340–6.

87. Capone CA, Misra N, Ganigara M, Epstein S, Rajan S, Acharya SS, et al. Six Month Follow-up of Patients With Multi-System Inflammatory Syndrome in Children. Pediatrics. 2021 Oct 1;148(4).

88. Callard F, Perego E. How and why patients made Long Covid. Soc Sci Med. 2021 Jan 1;268.

89. Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, et al. Long COVID, a comprehensive systematic scoping review. Infection. 2021 Dec 1;49(6):1163–86.

90. Post-COVID Conditions: Information for Healthcare Providers [Internet]. [cited 2022 Apr 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html

91. Overview | COVID-19 rapid guideline: managing the long-term effects of COVID-19 | Guidance | NICE [Internet]. [cited 2022 Apr 20]. Available from: https://www.nice.org.uk/guidance/NG188

92. Mahase E. Covid-19: What do we know about “long covid”? BMJ. 2020 Jul 14;370.

93. Fernández-De-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V,

Cuadrado ML, Florencio LL, Rey U, et al. Defining Post-COVID Symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An Integrative Classification. Public Health. 2021;18:2621.

94. A clinical case definition of post COVID-19 condition by a Delphi consensus. 2021.

95. Esposito S, Principi N, Azzari C, Cardinale F, di Mauro G, Galli L, et al. Italian intersociety consensus on management of long covid in children. Italian Journal of Pediatrics. 2022 Dec 1;48(1):42.

96. Rajan S, Khunti K, Alwan N, Steves C, Greenhalgh T, Macdermott N, et al. In the wake of the pandemic Preparing for Long COVID HEALTH SYSTEMS AND POLICY ANALYSIS. 2021 [cited 2022 Apr 21]; Available from: http://www.euro.who.int/en/about-us/partners/

97. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK Statistical bulletins - Office for National Statistics [Internet]. [cited 2022 May 28]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/previousReleases

98. Buonsenso D, Munblit D, de Rose C, Sinatti D, Ricchiuto A, Carfi A, et al. Preliminary evidence on long COVID in children. Acta Paediatrica. 2021 Jul 1;110(7):2208–11.

99. Blomberg B, Mohn KGI, Brokstad KA, Zhou F, Linchausen DW, Hansen BA, et al. Long COVID in a prospective cohort of home-isolated patients. Nature Medicine 2021 27:9. 2021 Jun 23;27(9):1607–13.

100. Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK - Office for National Statistics [Internet]. [cited 2022 May 28]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/technicalarticleupdatedestimatesoftheprevalenceofpostacutesymptomsamongpeoplewithcoronaviruscovid19intheuk

101. Stephenson T, Pereira SP, Shafran R, de Stavola B, Rojas N, Zavala M, et al. Long COVID - the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study. 2021 Aug 10;

102. Fainardi V, Meoli A, Chiopris G, Motta M, Skenderaj K, Grandinetti R, et al. Long COVID in Children and Adolescents. Life 2022, Vol 12, Page 285. 2022 Feb 14;12(2):285.

103. Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. Nature Medicine 2021 27:7.

2021 Jun 17;27(7):1129–30.

104. Akbarialiabad H, Taghrir MH, Abdollahi A, Ghahramani N, Kumar M, Paydar S, et al. Long COVID, a comprehensive systematic scoping review. Infection. 2021 Dec 1;49(6):1163.

105. Umesh A, Pranay K, Pandey RC, Gupta MK. Evidence mapping and review of long-COVID and its underlying pathophysiological mechanism. Infection. 2022 Apr 30;

106. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. Nature Immunology 2022 23:2. 2022 Feb 1;23(2):194–202.

107. Sante G di, Buonsenso D, Rose C de, Valentini P, Ria F, Sanguinetti M, et al. Immune profile of children with post-acute sequelae of SARS-CoV-2 infection (Long Covid). medRxiv. 2021 May 10;2021.05.07.21256539.

108. Buonsenso D, di Giuda D, Sigfrid L, Antonio Pizzuto D, di Sante G, de Rose C, et al. Case Report International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Global Support Centre, Centre for Tropical Medicine and Global Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection. www.thelancet.com/child-adolescent. 2021;5.

109. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. eClinicalMedicine. 2021 Aug 1;38.

110. Hayes LD, Ingram J, Sculthorpe NF. More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review. Frontiers in Medicine. 2021 Nov 1;8:750378.

111. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review 2 Running Title: Post COVID-19 Condition Meta-Analysis 3 4.

112. van Kessel SAM, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. Family Practice. 2022 Jan 19;39(1):159.

113. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK - Office for National Statistics [Internet]. [cited 2022 May 30]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6may2022

114. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a

systematic review and meta-analysis. Scientific Reports 2021 11:1. 2021 Aug 9;11(1):1–12.

115. Rajpal S, Tong MS, Borchers J, Zareba KM, Obarski TP, Simonetti OP, et al. Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection. JAMA Cardiol. 2021 Jan 1;6(1):116–8.

116. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiology. 2020 Nov 1;5(11):1265–73.

117. COVID-19: Neurologic complications and management of neurologic conditions - UpToDate [Internet]. [cited 2022 May 31]. Available from: https://www.uptodate.com/contents/covid-19-neurologic-complications-and-management-of-neurologic-conditions?search=COVID-19:%20Neurologic%20complications%20and%20managementof%20neurologic%20conditions&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3546538889

118. Martelletti P, Bentivegna E, Spuntarelli & v, Luciani & M. Long-COVID Headache.

119. Schou TM, Joca S, Wegener G, Bay-Richter C. Psychiatric and neuropsychiatric sequelae of COVID-19 – A systematic review. Brain, Behavior, and Immunity. 2021 Oct 1;97:328.

120. Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. Lancet Gastroenterol Hepatol. 2020 Jul 1;5(7):629–30.

121. Wei XS, Wang X, Niu YR, Ye LL, Peng WB, Wang ZH, et al. Diarrhea Is Associated With Prolonged Symptoms and Viral Carriage in Corona Virus Disease 2019. Clin Gastroenterol Hepatol. 2020 Jul 1;18(8):1753-1759.e2.

122. Yusuf F, Fahriani M, Mamada SS, Frediansyah A, Abubakar A, Maghfirah D, et al. Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis. F1000Res. 2021;10.

123. McMahon DE, Gallman AE, Hruza GJ, Rosenbach M, Lipoff JB, Desai SR, et al. Long COVID in the skin: a registry analysis of COVID-19 dermatological duration. The Lancet Infectious Diseases. 2021 Mar 1;21(3):313.

124. Karaarslan F, Güneri FD, Kardeş S. Long COVID: rheumatologic/musculoskeletal symptoms in hospitalized COVID-19 survivors at 3 and 6 months. Clinical Rheumatology. 2022 Jan 1;41(1):289.

125. Han Q, Zheng B, Daines L, Sheikh A. Long-Term Sequelae of COVID-19:

A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. Pathogens. 2022 Feb 1;11(2).

126. Bansal R, Gubbi S, Koch CA. COVID-19 and chronic fatigue syndrome: An endocrine perspective. Journal of Clinical & Translational Endocrinology. 2022 Mar 1;27:2214–6237.

127. Sathish T, Kapoor N, Cao Y, Tapp RJ, Zimmet P. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis Running title: Newly diagnosed diabetes in COVID-19.

128. COVID-19: Evaluation and management of adults following acute viral illness - UpToDate [Internet]. [cited 2022 May 31]. Available from: https://www.uptodate.com/contents/covid-19-evaluation-and-management-of-adults-following-acute-viral-illness?search=long%20covid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H385307378

129. Ludvigsson JF. Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19. Acta Paediatrica. 2021 Mar 1;110(3):914–21.

130. Buonsenso D, Munblit D, de Rose C, Sinatti D, Ricchiuto A, Carfi A, et al. Preliminary evidence on long COVID in children. Acta Paediatrica. 2021 Jul 1;110(7):2208–11.

131. Fainardi V, Meoli A, Chiopris G, Motta M, Skenderaj K, Grandinetti R, et al. Long COVID in Children and Adolescents. Life (Basel). 2022 Feb 1;12(2).

132. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. JAMA. 2021 Sep 7;326(9):869–71.

133. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. The Lancet Child & Adolescent Health. 2021 Oct 1;5(10):708–18.

134. Gurdasani D, Akrami A, Bradley VC, Costello A, Greenhalgh T, Flaxman S, et al. Long COVID in children. The Lancet Child and Adolescent Health. 2022 Jan 1;6(1):e2.

135. Stephenson T, Pereira SP, Shafran R, de Stavola B, Rojas N, Zavala M, et al. Long COVID-the physical and mental health of children and non-hospitalised young people 3 months after SARS-CoV-2 infection; a national matched cohort study (The CLoCk) Study. 2021;

136. Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, Ziv A, Bar-On O, Birk E, et al. Long COVID in Children: Observations From a Designated Pediatric

Clinic. Pediatr Infect Dis J. 2021 Dec 1;40(12):e509–11.

137. Buonsenso D, Pujol FE, Munblit D, Mcfarland S, Simpson F. Clinical Characteristics, Activity Levels and Mental Health Problems in Children with Long COVID: A Survey of 510 Children. 2021 Mar 9;

138. Blankenburg J, Wekenborg MK, Reichert J, Kirsten C, Kahre E, Haag L, et al. Mental Health of Adolescents in the Pandemic: Long-COVID-19 or Long-Pandemic Syndrome? SSRN Electronic Journal. 2021 May 21;

139. Brackel CLH, Lap CR, Buddingh EP, van Houten MA, van der Sande LJTM, Langereis EJ, et al. Pediatric long-COVID: An overlooked phenomenon? Pediatric Pulmonology. 2021 Aug 1;56(8):2495–502.

140. Rodriguez-Rubio M, Pinto NP, Manning JC, Kudchadkar SR. Post-intensive care syndrome in paediatrics: setting our sights on survivorship. The Lancet Child & Adolescent Health. 2020 Jul 1;4(7):486–8.

141. Guia clínica per a l'atenció de les persones amb símptomes persistents de COVID-19 Àrea Assistencial Servei Català de la Salut.

142. Post-COVID-19 Conditions in Children and Adolescents [Internet]. [cited 2022 Jun 3]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/post-covid-19-conditions-in-children-and-adolescents/

143. Modified COVID-19 Yorkshire Rehabilitation Screening (C19-YRS) Self-report version.

144. ISARIC Global COVID-19 paediatric follow-up - ISARIC [Internet]. [cited 2022 Jun 4]. Available from: https://isaric.org/research/covid-19-clinical-research-resources/paediatric-follow-up/

145. COVID-19 Interim Guidance: Return to Sports and Physical Activity [Internet]. [cited 2022 Jun 4]. Available from: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/covid-19-interim-guidance-return-to-sports/

146. Morrow AK, Ng R, Vargas G, Jashar DT, Henning E, Stinson N, et al. Postacute/Long COVID in Pediatrics: Development of a Multidisciplinary Rehabilitation Clinic and Preliminary Case Series. Am J Phys Med Rehabil. 2021 Dec 1;100(12):1140–7.

147. Molteni E, Sudre CH, Canas LS, Bhopal SS, Hughes RC, Antonelli M, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. The Lancet Child & Adolescent Health. 2021 Oct 1;5(10):708–18.

148. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo del Valle NC, Perelman C, Sepulveda R, Rebolledo PA, et al. Long-COVID in children and adolescents:

a systematic review and meta-analyses. Scientific Reports 2022 12:1. 2022 Jun 23;12(1):1–12.

149. Marasco G, Cremon C, Barbaro MR, Salvi D, Cacciari G, Kagramanova A, et al. Prevalence of Gastrointestinal Symptoms in Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Results of the Prospective Controlled Multinational GI-COVID-19 Study. American Journal of Gastroenterology. 2022 Jan 1;117(1):147–57.