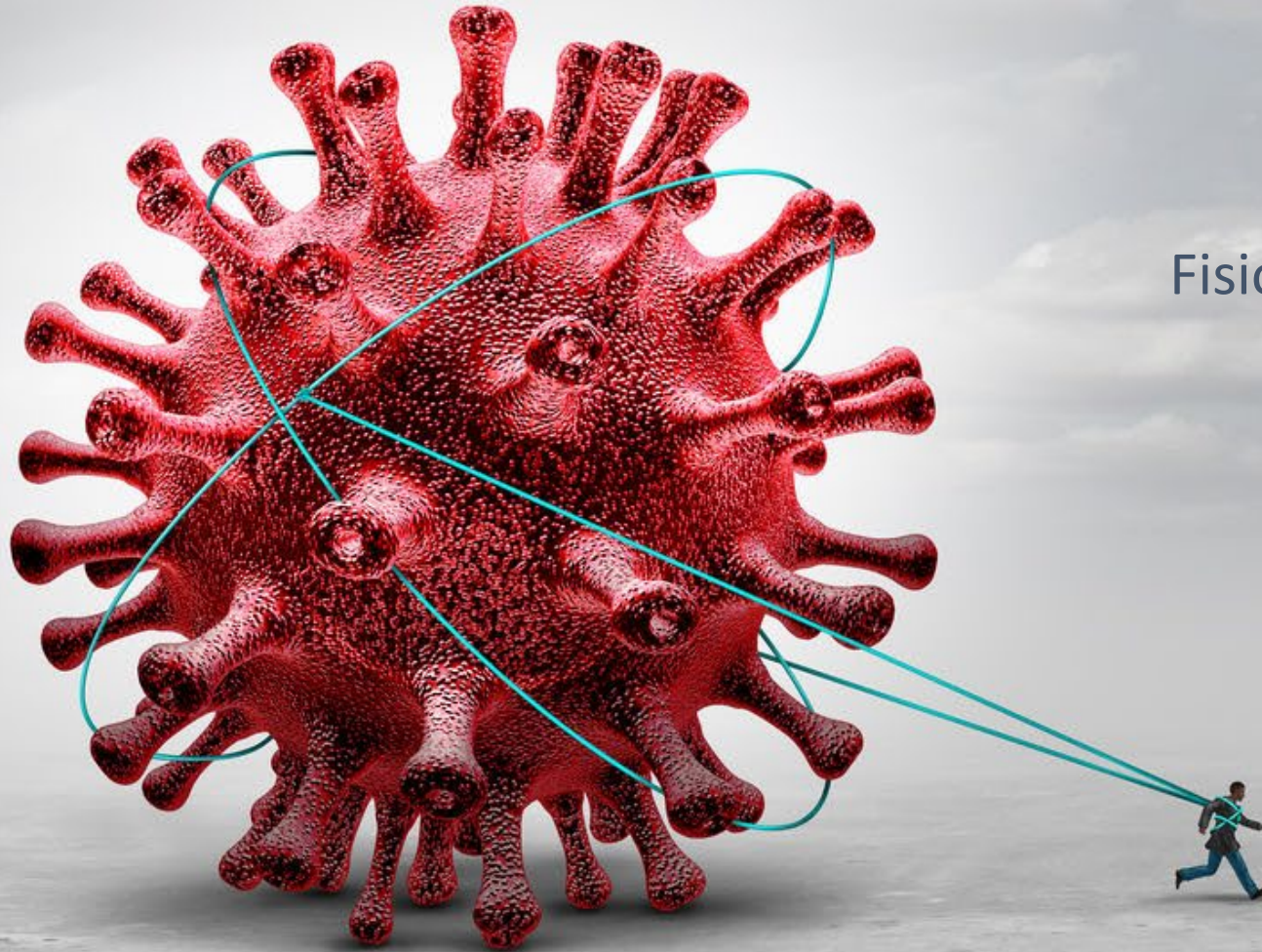


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LONG COVID IN ETA' PEDIATRICA

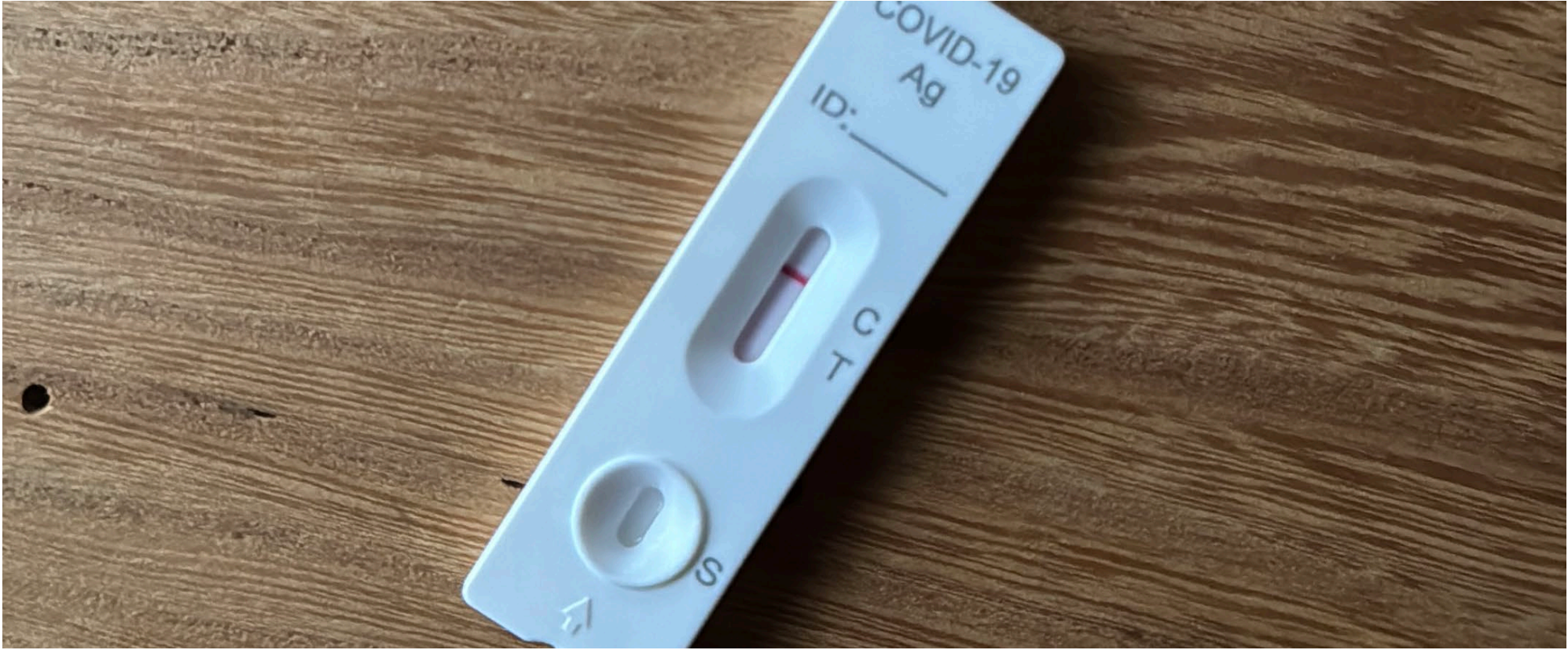
Valentina Fainardi

Clinica Pediatrica
Fisiopatologia Respiratoria Infantile
Università di Parma



XXVIII Congresso Nazionale, Torino, 10-12 ottobre 2024





Outline

1. Definition
2. Pathogenesis
3. Epidemiology
4. Risk factors
5. Symptoms
6. Data of our cohort
7. Conclusions

1. Definition



World Health
Organization

COVID-19: world total
cases



776,386,491 +85,007
increase on previous 7 days

Reported COVID-19 cases

World, 7 days to 22 September 2024



Persistence of symptoms in
1-45% of the infected people



Long COVID occurs in individuals with SARS-CoV-2 infection, usually **after 3 months** with symptoms persisting **at least 2 months** and without alternative diagnosis.

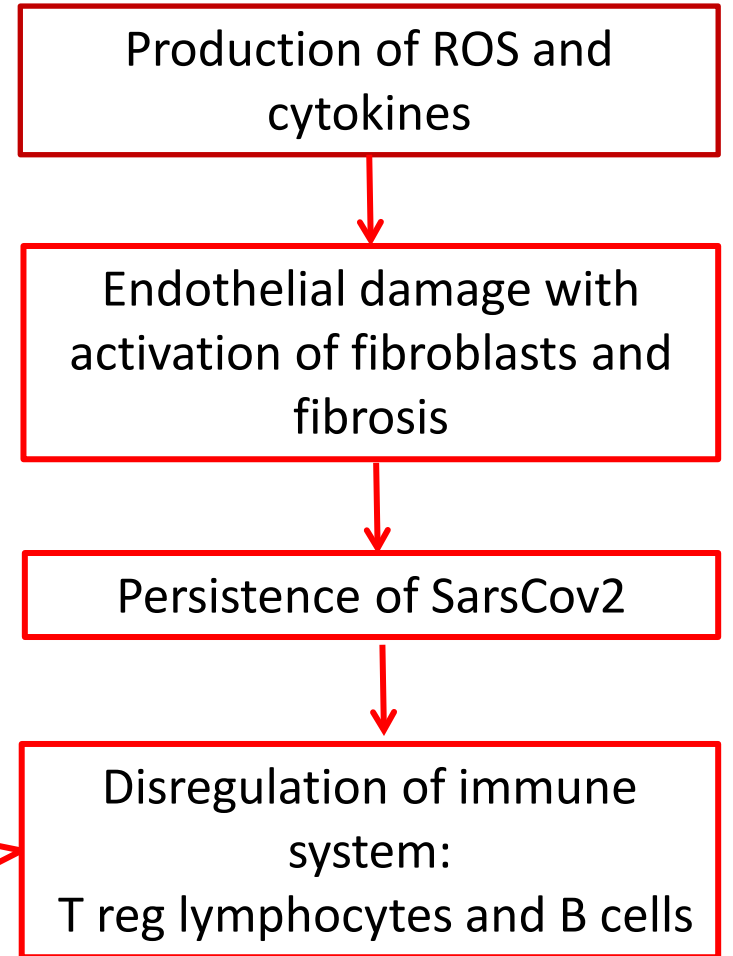
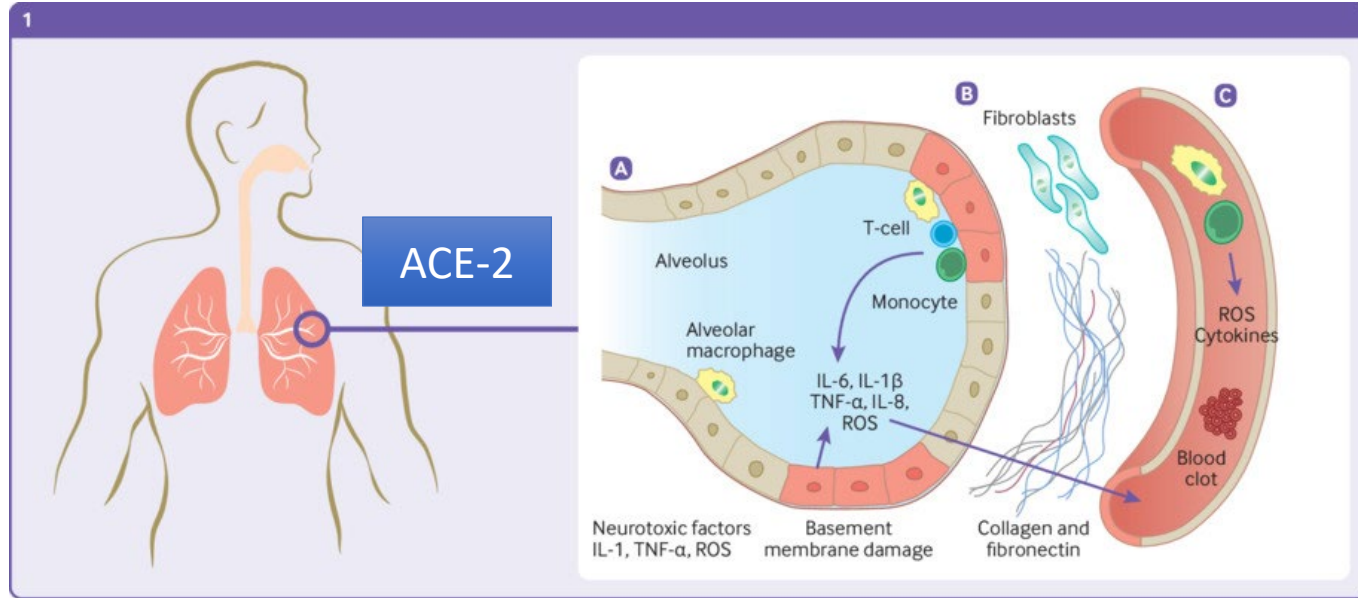
**WHO Definition of Long COVID in
Children and Adolescents [14]**

16 February 2023

“Post COVID-19 condition in children and adolescents occurs in individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing **symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19**”.

“Current evidence suggests that symptoms more frequently reported in children and adolescents with post-COVID-19 condition compared with controls are fatigue, altered smell/anosmia and anxiety. Other symptoms have also been reported. Symptoms generally have an impact on everyday functioning such as changes in eating habits, physical activity, behaviour, academic performance, social functions (interactions with friends, peers, family) and developmental milestones. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. They may also fluctuate or relapse over time. Workup may reveal additional diagnoses, but this does not exclude the diagnosis of post COVID-19 condition. This can be applied to children of all ages, with age-specific symptoms and impact on everyday function taken into consideration”.

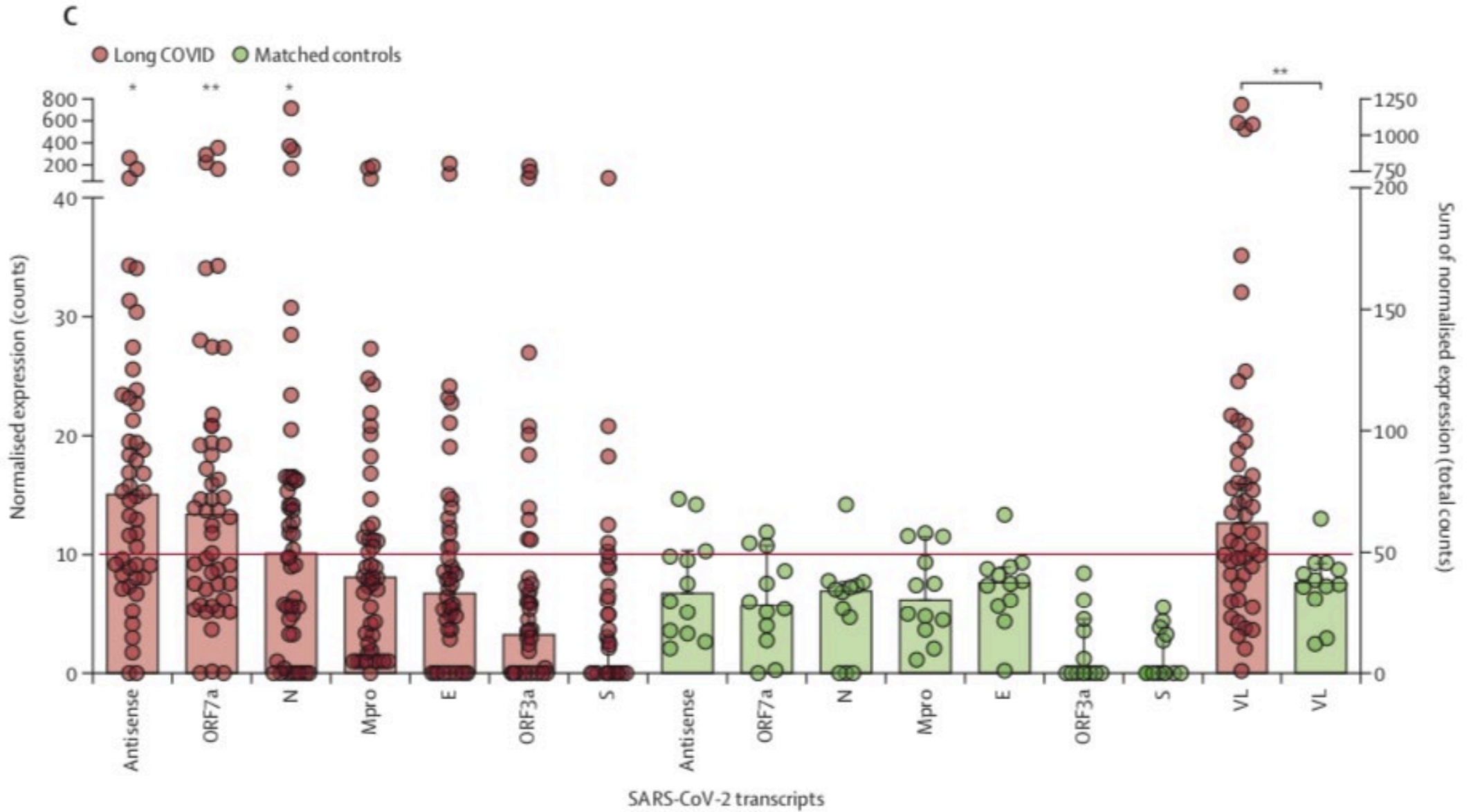
2. Pathogenesis



Chronic inflammation and Long Covid

Autoimmunity ?

Disregulation of immune system:
T reg lymphocytes and B cells



Recovering or Persisting: The Immunopathological Features of SARS-CoV-2 Infection in Children

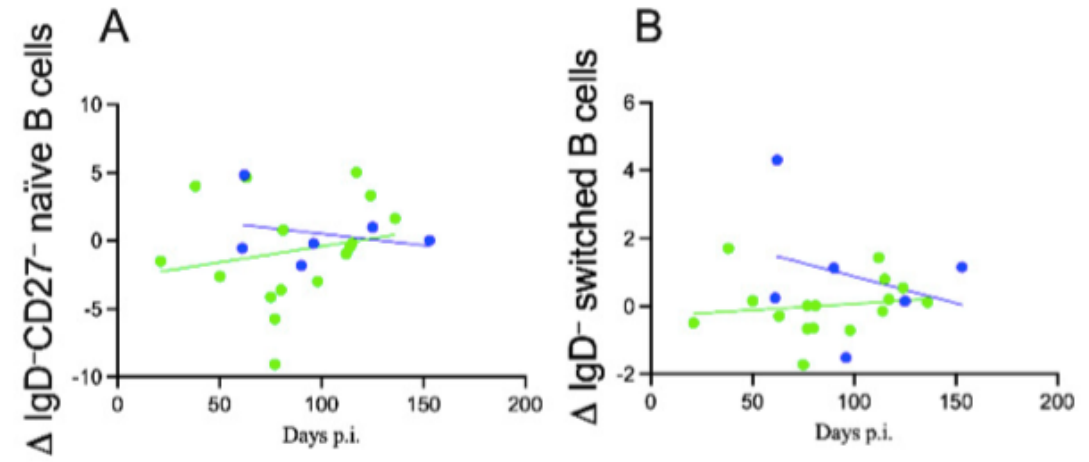
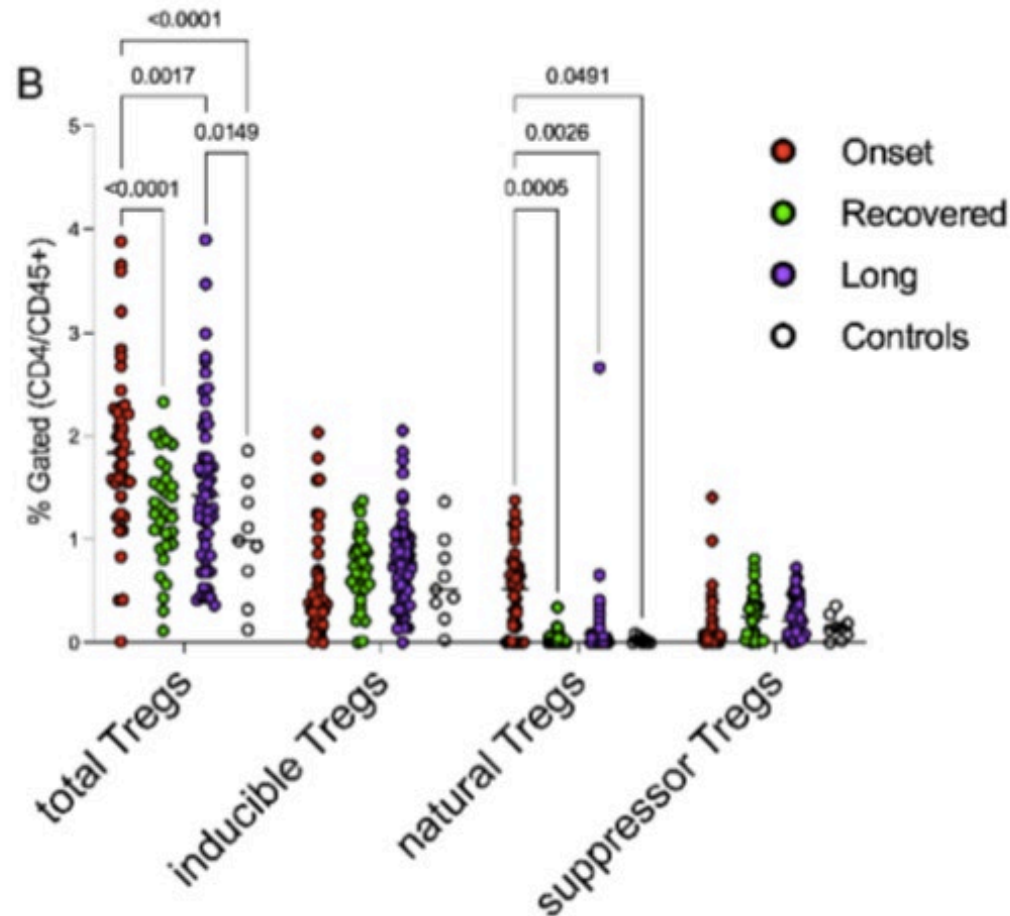
J Clin Med 2022

Danilo Buonsenso^{1,2,*}, Piero Valentini², Cristina De Rose², Maria Tredicine³, Maria del Carmen Pereyra Boza⁴, Chiara Camponeschi^{3,5}, Rosa Morello², Giuseppe Zampino², Anna E. S. Brooks⁶, Mario Rende⁷, Francesco Ria^{3,4}, Maurizio Sanguinetti^{1,4}, Giovanni Delogu^{4,8}, Michela Sali^{1,4,†}, Gabriele Di Sante^{3,7,†} and on behalf of the Gemelli-Pediatric COVID-19 Team[‡]

Children recovered
Vs
Children with Long Covid



Chronic stimulation of innate immunity: T regs and B cells



3. Epidemiology

Preliminary evidence on long COVID in children

Danilo Buonsenso ^{1 2 3}, Daniel Munblit ^{4 5 6}, Cristina De Rose ¹, Dario Sinatti ¹,
Antonia Ricchiuto ¹, Angelo Carfi ⁷, Piero Valentini ^{1 3}

> *Acta Paediatr.* 2021 Jul;110(7):2208-2211. doi: 10.1111/apa.15870. Epub 2021 Apr 18.

Methods: cross-sectional study. **Questionnaire** for 129 parents of children with SARS-CoV2 (Gemelli, Roma)

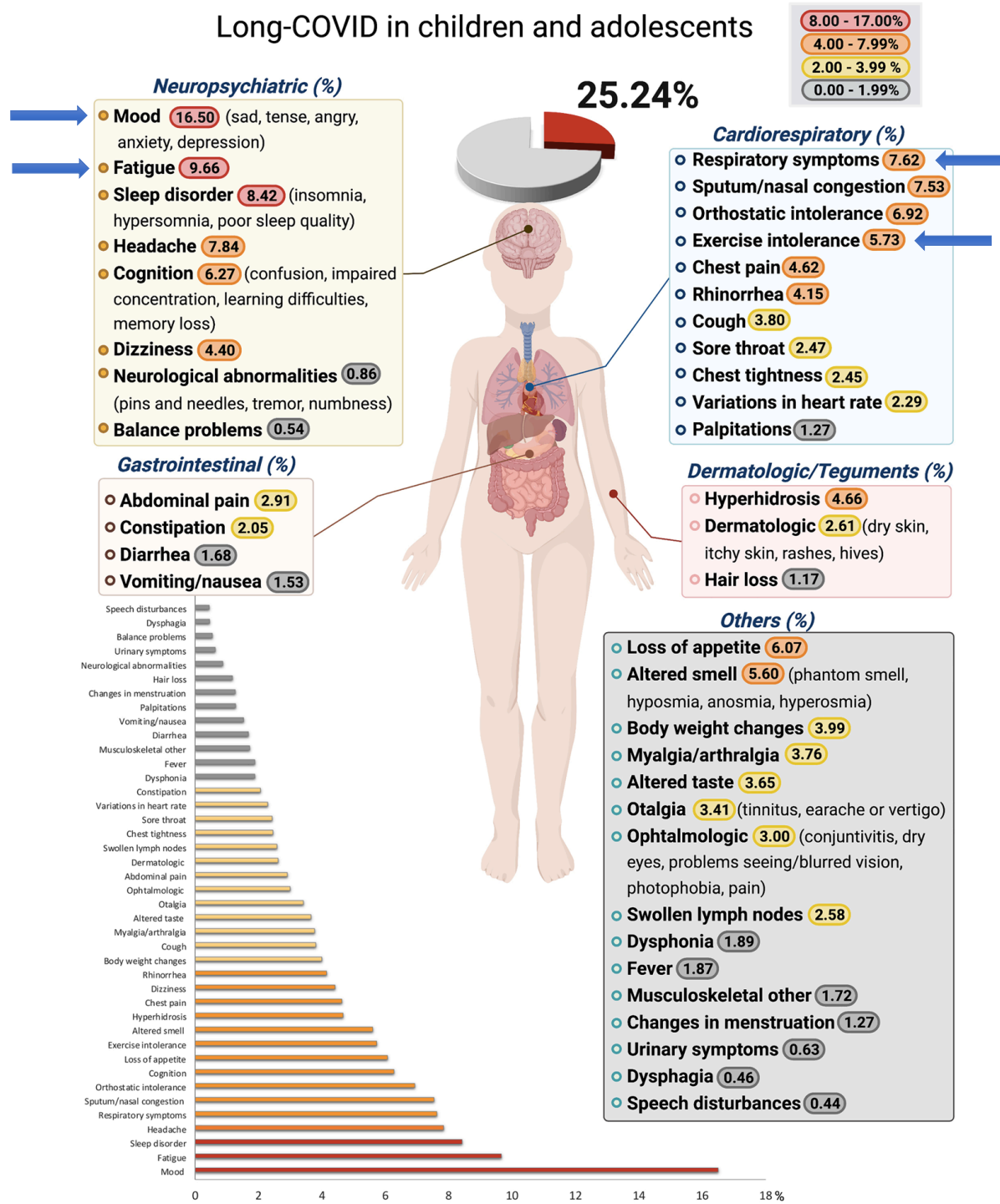
Follow-up: >120 days from infection

| | |
|--|------------|
| Persistent symptoms | |
| <i>None</i> | 54 (41.9%) |
| <i>1 or 2</i> | 46 (35.7%) |
| <i>3 or more</i> | 29 (22.5%) |
| Any persisting symptom at follow-up | |
| <i>< 60 days</i> | 31 (24%) |
| <i>60-119 days</i> | 30 (23.3%) |
| <i>120 or more days</i> | 68 (52.7%) |

| First Author | Study Period | Country | Number of Paediatric Patients/Type of Study Population | Study Type | Main SARS-CoV-2 Variant(s) | Definition Long COVID | Study Focus | Key Findings | Comments |
|-------------------------|-------------------------------|---------|--|---|----------------------------------|--|--|--|---|
| Pinto Pereira 2023 [56] | September 2020 to March 2021 | England | n = 6407 SARS-CoV-2 positive patients aged 11–17 years n = 6542 SARS-CoV-2 negative controls Questionnaire-based study 6 months after acute illness | National cohort study | n.d. | Delphi definition | To evaluate physical and mental health 6 months after SARS-CoV-2 infection | 24.5% of SARS-CoV-2 positive patients and 17.8% of negative controls had Long COVID symptoms at 6 months after infection. Common symptoms in both groups: Tiredness, shortness of breath, and headaches. | |
| Roessler 2022 [58] * | January 2019 to December 2020 | Germany | n = 11,950 patients aged 0–17 years with COVID-19 n = 59,750 matched control group Mean follow-up time: 236 days after acute illness | Retrospective matched cohort study based on health insurance data | Pre-Omicron variants | WHO definition, but symptoms >3 months after diagnosis of COVID-19 | To evaluate morbidity after COVID-19 in children and adolescents | Incidence Rate Ratios (IRR) of documented health-related problems was significantly higher in the COVID-19 group (IRR: 1.3, 95% CI: 1.25–1.35, p < 0.01). Specific outcomes with the highest IRR were malaise/fatigue/exhaustion (IRR 2.3), cough (IRR 1.7), throat/chest pain (1.7). | Data from German statutory health insurance organisations. |
| Mizrahi 2023 [49] * | March 2020 to October 2021 | Israel | n = 118,308 SARS-CoV-2 positive patients <18 years n = 118,308 negative controls Electronic medical records from an Israeli nationwide healthcare organisation | Retrospective nationwide cohort study | Wild-type, Alpha, Delta variants | Divided into early (30–180 days) and late (180–360 days) time periods after infection Defined as prolonged or new symptoms >4 weeks after acute onset | To determine clinical sequelae of Long COVID during the first year after mild SARS-CoV-2 infection | Elevated risk according to age group: Age 0–4: Conjunctivitis (HR 1.18, 1.08–1.29) and dyspnoea (HR 1.22, 1.11–1.35) only during the early phase Age 5–11: Conjunctivitis (HR 1.24, 1.07–1.43) only during the early phase. Sore throat (HR 1.54, 1.20–1.97) only during the late phase Age 12–18 Anosmia and dysgeusia (HR 23.5, 5.48–100.86), dyspnoea (HR 1.7, 1.36–2.12) and weakness (HR 1.66, 1.41–1.96) only during the early phase In the entire cohort (including adults), there was a trend for anosmia/dysgeusia, dyspnoea, weakness, chest pain, and palpitations to decline over time. | Only patients with mild disease. Study included additional adult cases and controls. Anosmia and dysgeusia were grouped together in the analysis. |

4. Symptoms

21 studies (2020-2022)
n=80,071 children and adolescents



Prevalence of symptoms of post-COVID-19 condition (long COVID) in children hospitalized with COVID-19: A systematic review of observational studies 2024, *Ped Pulm*





Maíra Machado da Silva MSc  | Maryellen Nepomuceno Benites MSc  |
 Yasmin Marques Castro MSc | Paulo Victor Moura MD  | Linjie Zhang MD, PhD 

TABLE 2 Systemic symptoms of post-COVID-19 condition (≥3 months to <12 months after COVID-19).

| Symptoms | Number of events | Sample size | Duration of follow-up | Prevalence (95% CI) | <i>I</i> ² |
|--------------------------------|------------------|-------------|-----------------------|---|-----------------------|
| Exercise intolerance | | | | 29% , 95% CI: 7%–57% | |
| Bogusławski 2022 ⁷ | 23 | 41 | ≥3 months | 56% (40%–72%) | |
| Demirbuga 2023 ¹⁵ | 6 | 116 | ≥3 months | 5% (2%–11%) | |
| Asadi-Pooya 2021 ¹² | 12 | 58 | ≥3 months | 21% (11%–33%) | |
| Penner 2021 ¹⁸ | 18 | 40 | ≥6 months | 45% (29%–62%) | |
| Fatigue | | | | 9% , 95% CI: 4%–14%, <i>I</i> ² =92% | |
| Sleep disturbances | | | | 6% , 95% CI: 3%–9%, <i>I</i> ² =65% | |
| Cough and dyspnea | | | | 5% , 95% CI: 1%–11%), <i>I</i> ² =93% | |

Use of cardiopulmonary exercise testing to identify mechanisms of exertional symptoms in children with long COVID

2023

Adam Lowe MD^{1,2} | Arash Sabati MD^{1,3} | Rajeev Bhatia MD^{1,4}

23 participants, 14 years old (9–17 years) → **47%** presented with **decreased exercise capacity**

Symptoms at CPET presentation

| | |
|---------------------|----------|
| Chest pain | 14 (60%) |
| Dyspnea at rest | 9 (39%) |
| Dizziness | 6 (26%) |
| Palpitations | 6 (26%) |
| Dyspnea on exertion | 4 (17%) |
| Syncope | 3 (13%) |
| Tachycardia | 3 (13%) |
| Arrhythmia | 3 (13%) |
| Hypertension | 1 (4%) |

Deconditioning (30%)
Exaggerated hyperventilatory responses (14%)
Asthma (14%)
Leg fatigue (100%)
V/Q mismatch (14%)

RESEARCH

Open Access



Pulmonary function in children post -SARS-CoV-2 infection: a systematic review and meta-analysis

8 articles with 386 patients were included in meta-analysis

Most common symptoms:

- Dyspnea
- Cough
- Exercise intolerance
- Fatigue

| Studies | Estimate (95% C.I.) |
|---|----------------------------------|
| Bottino/ 2021 | 97.330 (94.145, 100.515) |
| Chiara/ 2022 | 99.050 (97.143, 100.957) |
| Dobkin/ 2021 | 107.000 (102.633, 111.367) |
| Ozturk/ 2022 | 105.180 (100.767, 109.593) |
| Palacios/ 2022 | 104.000 (101.714, 106.286) |
| Ipek/ 2022 | 98.670 (93.984, 103.356) |
| Overall (I²=81.7 % , P< 0.001) | 101.725 (98.721, 104.730) |

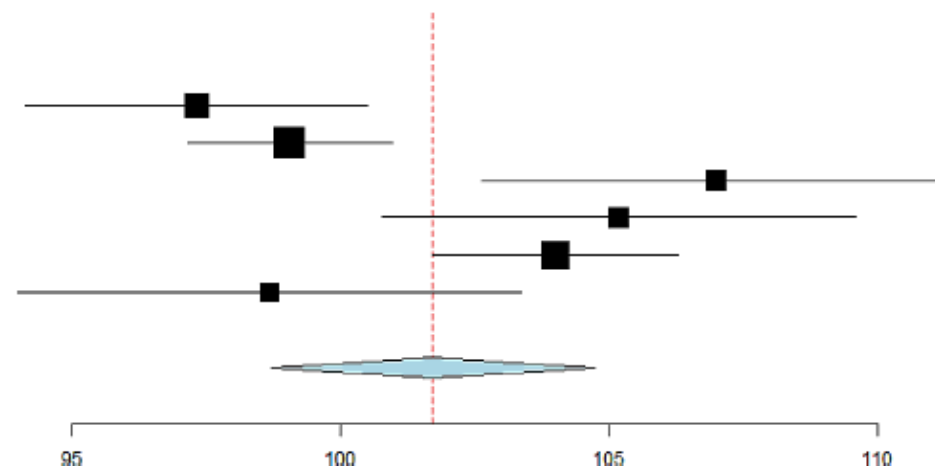


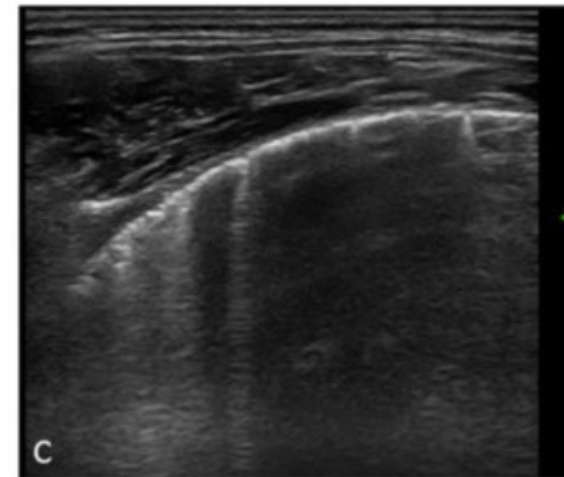
Fig. 2 Pooled mean of FEV1 in included studies

No difference if asthma or severe COVID

Role of Lung Ultrasound in the Follow-Up of Children with Previous SARS-CoV-2 Infection: A Case-Control Assessment of Children with Long COVID or Fully Recovered

J Clin Med 2023

Danilo Buonsenso^{1,2,*}, Rosa Morello¹, Francesco Mariani¹, Cristina De Rose¹, Rossella Cortese³, Luigi Vetrugno⁴ and Piero Valentini¹



1. Recovered children
 2. LC group (>2 weeks) 38.8%
 3. LC respiratory group (persisting respiratory symptoms for at least 2 weeks after SARS-CoV-2 infection) 16.1%
 4. LC12 group (symptoms for at least 12 weeks after SARS-CoV-2 infection)
- N=647** (7.9 yrs)

“LUS was mostly normal or only found minimal pathological findings of unclear significance in all patients, with no differences when we compared children with Long COVID or who recovered”.

COVID-19 Pediatric Follow-Up: Respiratory Long COVID-Associated Comorbidities and Lung Ultrasound Alterations in a Cohort of Italian Children

2024, Children

Cristiana Indolfi ¹, Angela Klain ^{1,*}, Giulio Dinardo ¹, Elisabetta D'Addio ¹, Serena Ferrara ¹, Fabio Decimo ¹, Giorgio Ciprandi ², Maria Angela Tosca ³ and Michele Miraglia del Giudice ¹

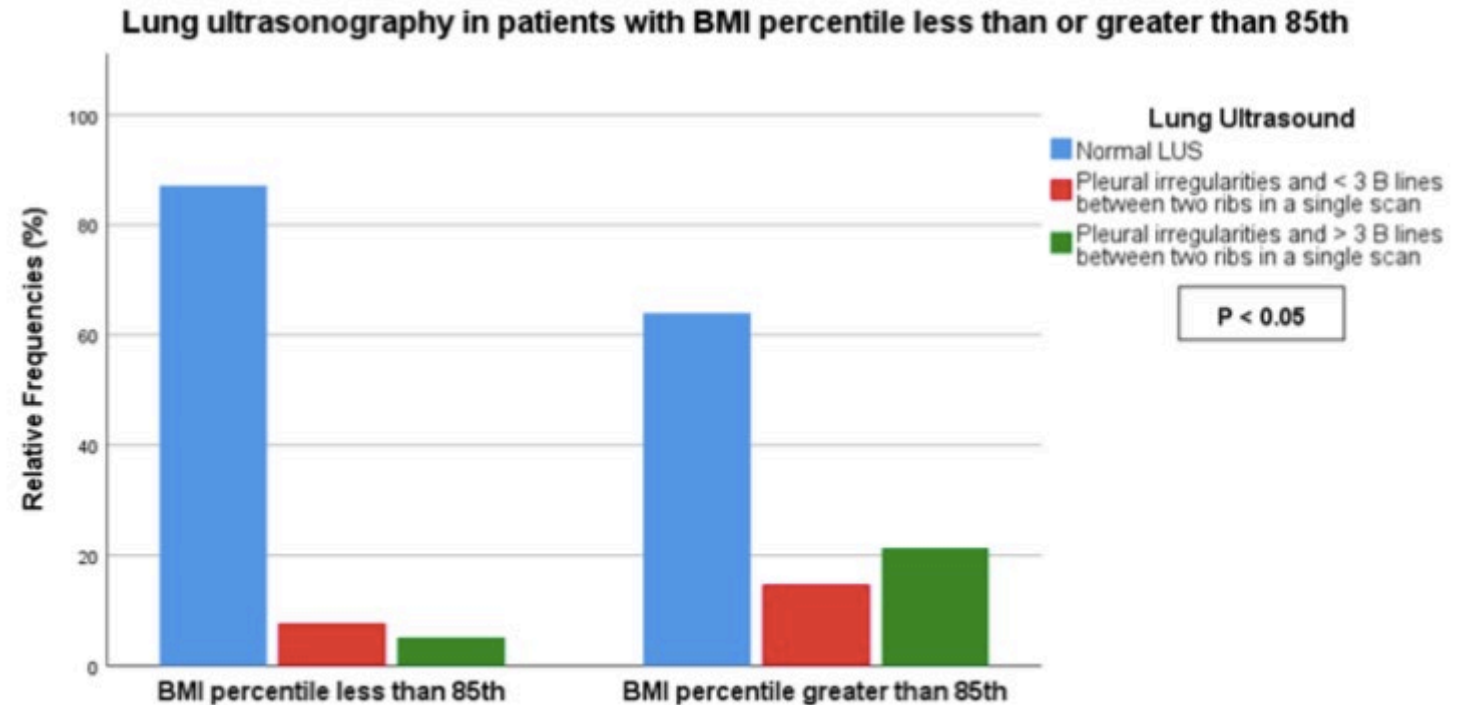
Subjects: Covid at least 1 month before. Cough and/or dyspnea for more than 4 weeks from the diagnosis

Methods: SIMRI protocol: a) collection of data; (b) physical examination; (c) BMI assessment; (d) baseline spirometry and after bronchodilation test; (e) six-minute walking test; (f) LUS

Results: N=104 (8.9 yrs).

Higher BMI = lung ultrasound alterations (irregular pleural line, B lines and consolidations).

Asthma was not a risk factor.



5. Risk factors

Pediatric post COVID-19 condition: an umbrella review of the most common symptoms and associated factors

Aurora Heidar Alizadeh ¹, Mario Cesare Nurchis ², Jacopo Garlasco³, Alessandro Mara³, 2024

European Journal of Public Health, Vol. 34, No. 3, 517–523

6 systematic reviews (153 studies)

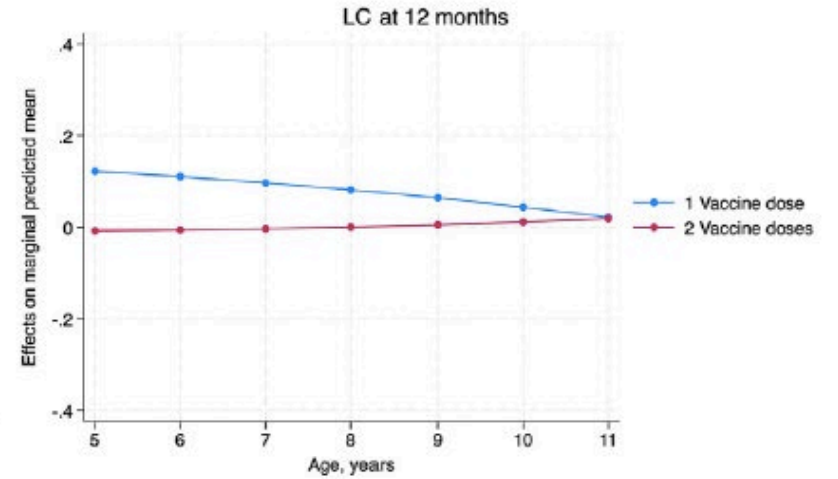
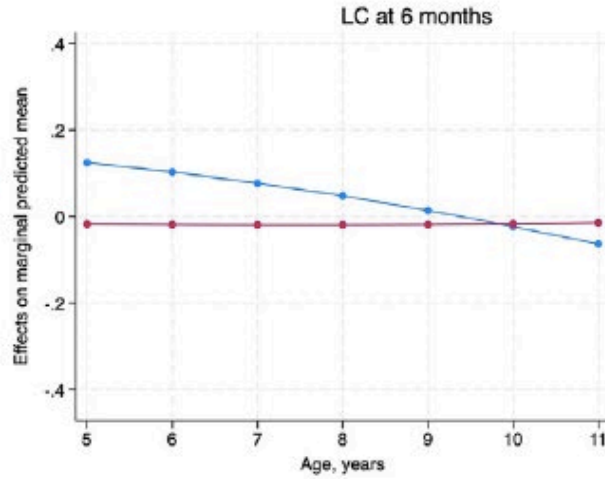
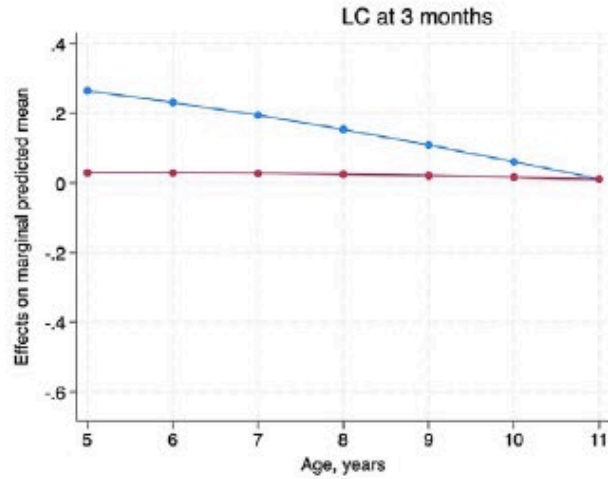
Symptoms

| | |
|----------------------|------------------------|
| Fatigue 9-47% | Diarrhoea |
| Dyspnea 7-43% | Fever |
| Headache | Anosmia |
| Myalgia | Cognitive disturbances |
| Abdominal pain | Palpitations |
| Chest pain | Mood disorders |
| Sleep disturbances | Reduced activity |
| Cough | Sore throat |
| | Muscle weakness |

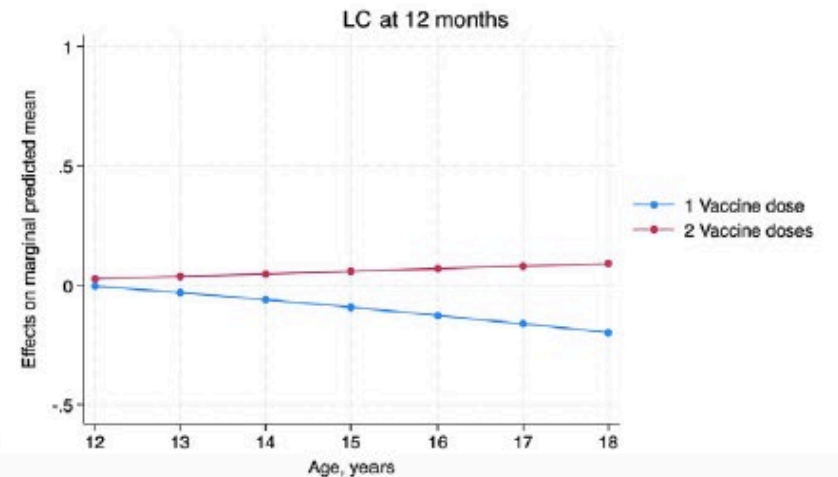
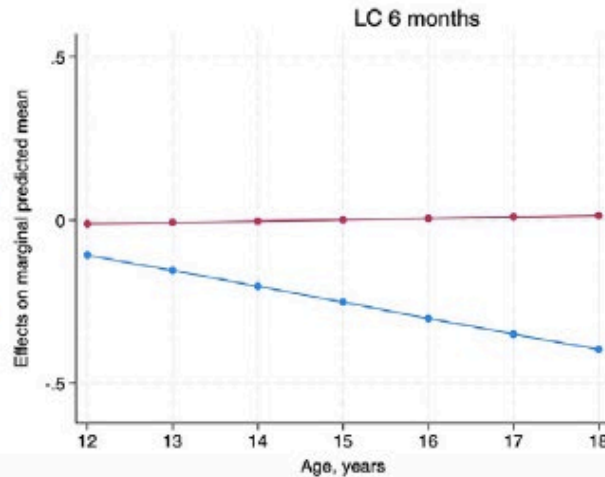
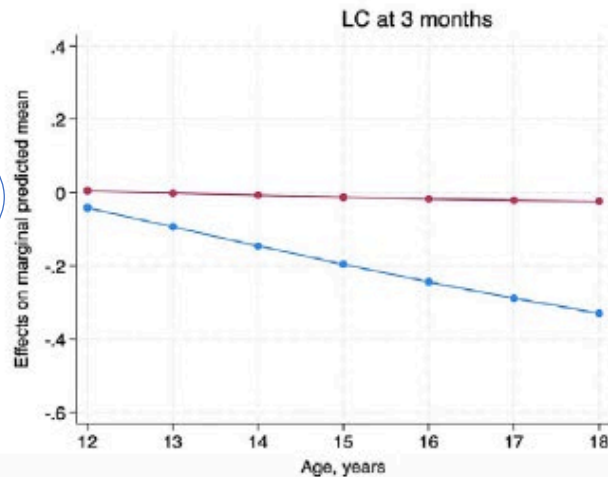
- Comorbidities such as **obesity/overweight** and **allergic rhinitis**
- **Female** gender OR 1.72 (95% CI 1.39–2.12)
- **Age** OR 1.09 per 1-year increase (95% CI 1.05–1.12) (**14-17 yrs**)
- **Severe** COVID-19 OR 2.78 (95% CI 1.78–4.33)

The role of vaccines

6-11 yrs



12-18 yrs



Impact of Age and Sex Interaction on Post-Acute Sequelae of COVID-19: An Italian Cohort Study on Adults and Children

Matteo Puntoni ^{1,*}, Susanna Esposito ², Laura Patrizi ¹, Chiara Maria Palo ¹, Michela Deolmi ², Giovanni Autore ², Valentina Fainardi ², Caterina Caminiti ¹ and on behalf of the University Hospital of Parma LONG-COVID Research Team [†]

International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Global Adult and Pediatric COVID-19 follow-up working groups

Obiettivo primario

Valutare prevalenza e caratteristiche cliniche del Long COVID nei bambini.

Obiettivo secondario

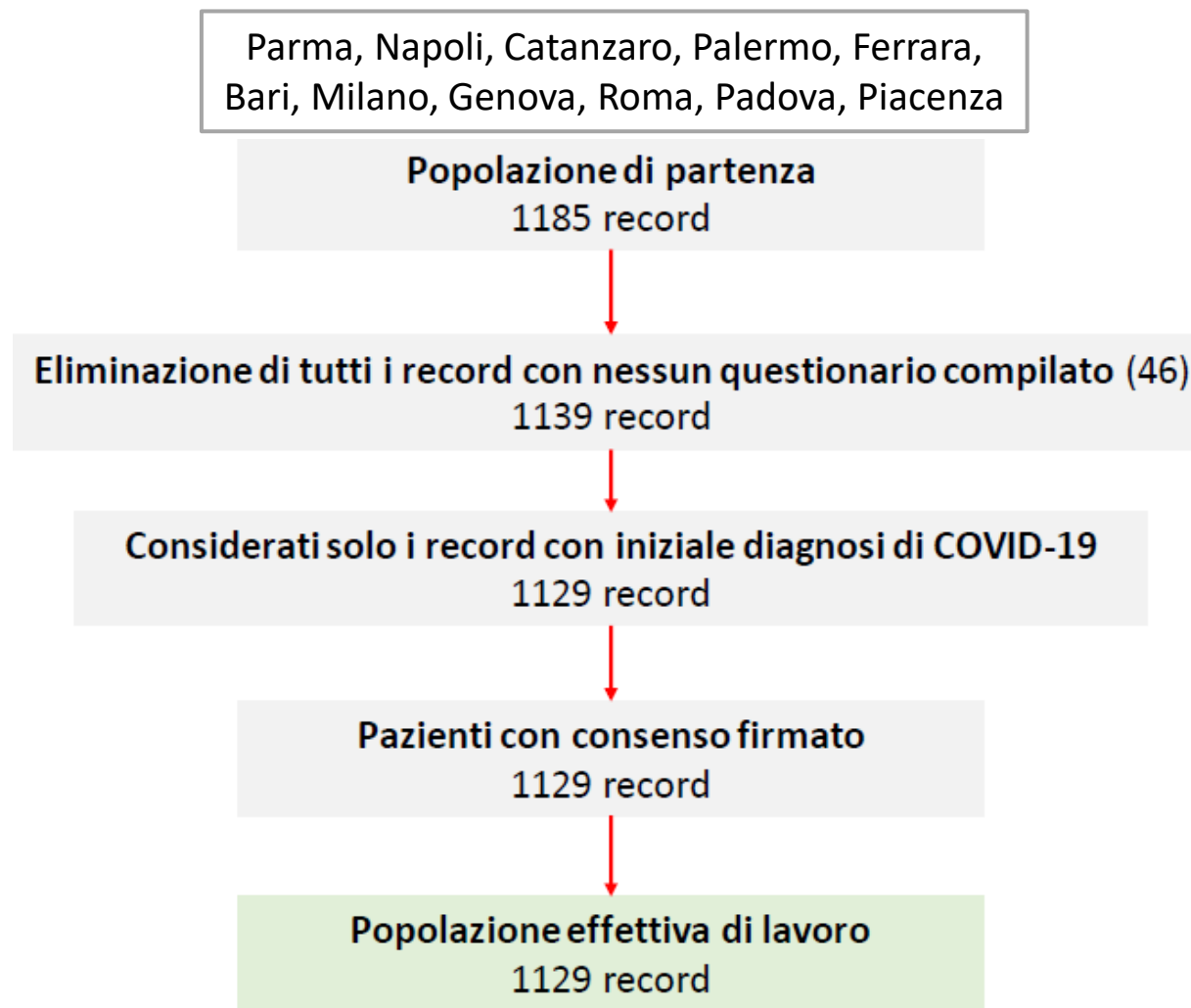
Valutare il sesso o l'età della popolazione in esame come possibili fattori determinanti del Long COVID pediatrico.

✓ Periodo di arruolamento dello studio

1 gennaio 2022

31 marzo 2022

Infezione da COVID nei 3 mesi precedenti



LIVELLO 1

COMPILAZIONE SCHEDA

DATI
DEMOGRAFICI

STORIA CLINICA
E
COMORBIDITÀ

SEGNI E SINTOMI
DELL'INFEZIONE DA
SARS-CoV2
IN FASE ACUTA

TASSO DI
OSPEDALIZZAZIONE

TRATTAMENTO
RICEVUTO

STATUS
VACCINALE

SVILUPPO DI
MANIFESTAZIONI
CLINICHE SPECIFICHE

QUALITÀ DELLA VITA

SVILUPPO DI
MANIFESTAZIONI
CLINICHE
NON SPECIFICHE

LIVELLO 2

Nei pazienti che lamentavano sintomatologia persistente (febbre, tosse, astenia...) è stato richiesto di approfondire la raccolta dati compilando ulteriori quesiti, standardizzati ma personalizzati.

Sesso

| | |
|--------------------------|--------------------------|
| M:586 (51.9%) | F:543 (48.1%) |
|--------------------------|--------------------------|

Età media: 7.7 (dev. St. 4.37)

| | |
|-----------------|--------------------|
| 0-1 anno | 137 (12.1%) |
|-----------------|--------------------|

| | |
|-----------------|--------------------|
| 2-5 anni | 186 (16.5%) |
|-----------------|--------------------|

| | |
|------------------|--------------------|
| 6-11 anni | 604 (53.5%) |
|------------------|--------------------|

| | |
|-------------------|--------------------|
| 12-17 anni | 202 (17.9%) |
|-------------------|--------------------|

Follow-up a 1-3 mesi, 3-6 mesi e 6-12 mesi

| | | |
|-----------------------|-----------------------------|--------------------------------|
| QUESTIONARIO 1 | 1129 PAZIENTI (100%) | 72 GIORNI (TRA T0 E Q1) |
| QUESTIONARIO 2 | 854 PAZIENTI (75.6%) | 92 GIORNI (TRA Q1 E Q2) |
| QUESTIONARIO 3 | 729 PAZIENTI (74.6%) | 92 GIORNI (TRA Q2 E Q3) |

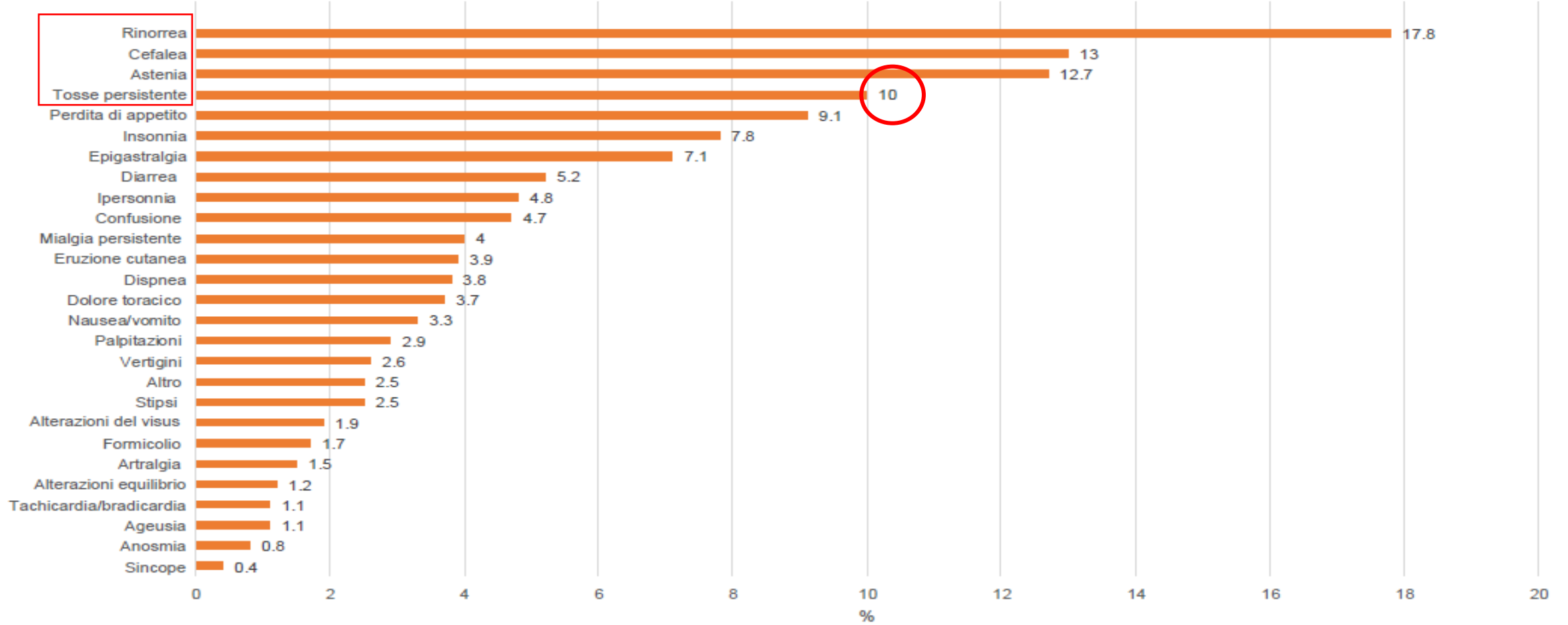
| | Almeno 1 sintomo | Almeno 1 sintomo a 3 mesi da COVID-19 | Almeno 1 sintomo a 3 mesi, durata >2 mesi |
|--|-------------------------|--|---|
| Sintomi muscoloscheletrici | 119 (10.5%) | 90 (8.0%) | 24 (2.1%) |
| Sintomi cardiovascolari | 54 (4.8%) | 30 (2.7%) | 6 (0.5%) |
| Sintomi respiratori | 490 (43.4%) | 355 (31.4%) | 83 (7.4%) |
| Sintomi neurologici e disfunzioni cognitive | 313 (27.7%) | 230 (20.4%) | 51 (4.5%) |
| Sintomi dermatologici | 76 (6.7%) | 46 (4.1%) | 8 (0.7%) |
| Sintomi gastrointestinali | 250 (22.1%) | 173 (15.3%) | 37 (3.2%) |
| Alterazioni del sensorio | 23 (2.0%) | 14 (1.2%) | 2 (0.2%) |
| Disturbi del sonno | 212 (18.8%) | 136 (12.1%) | 30 (2.7%) |
| Astenia | 244 (21.6%) | 169 (15.0%) | 40 (3.5%) |
| Scarso appetito | 174 (15.4%) | 113 (10.0%) | 22 (2.0%) |
| Tutti i sintomi | 774 (68.6%) | 571 (50.6%) | 183 (16.2%) |

Difficoltà a respirare
Dolore/compressione toracica
Tosse persistente
Rinorrea
Congestione nasale

LONG COVID ←

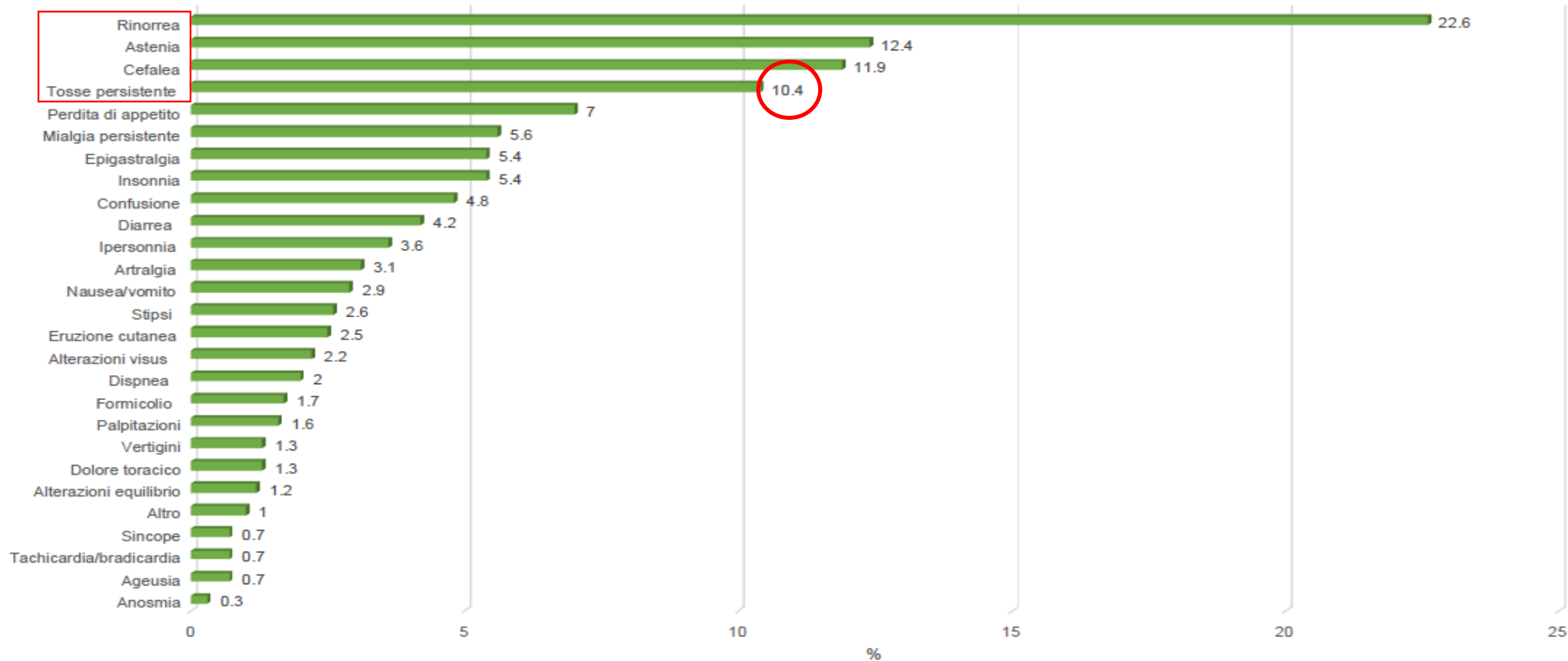
Q 1 - 1-3 mesi

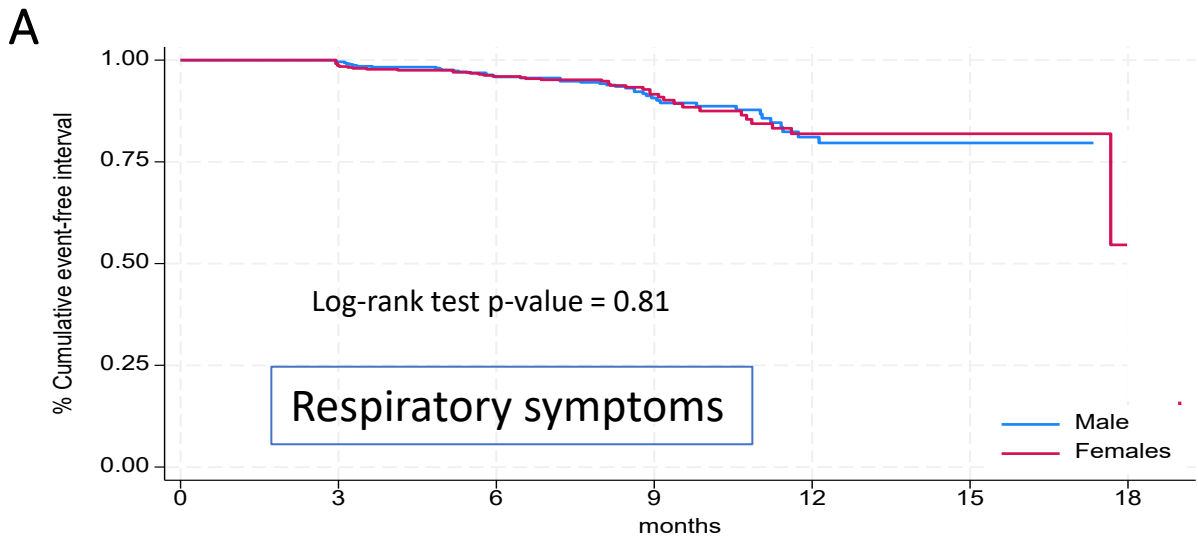
% sintomatologia ultimi 7 giorni



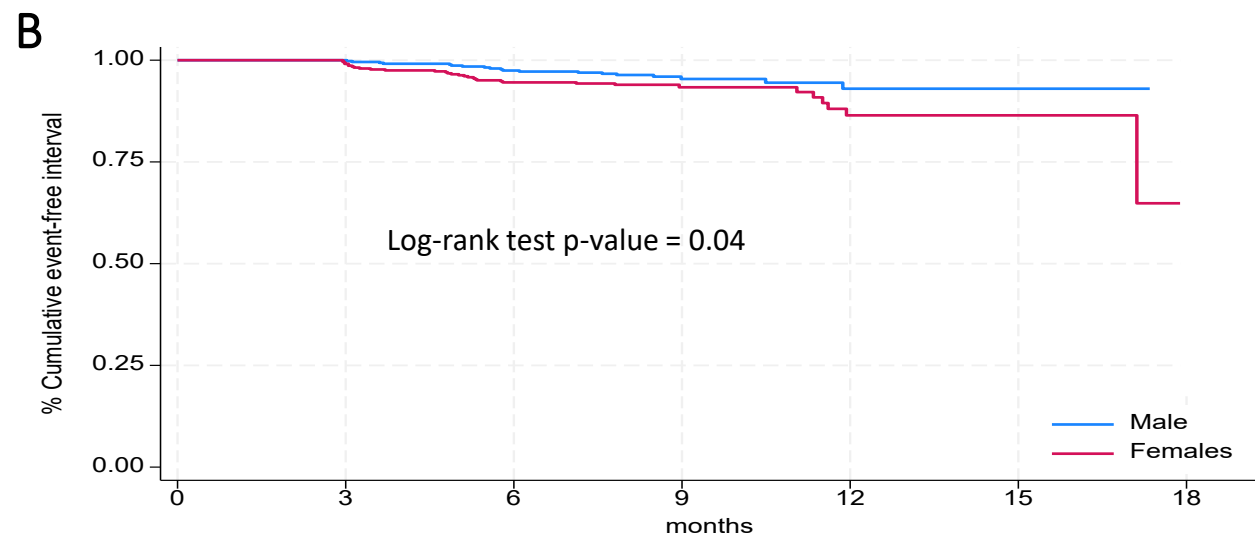
Q 3 - 6-12 mesi

% sintomatologia ultimi 7 giorni

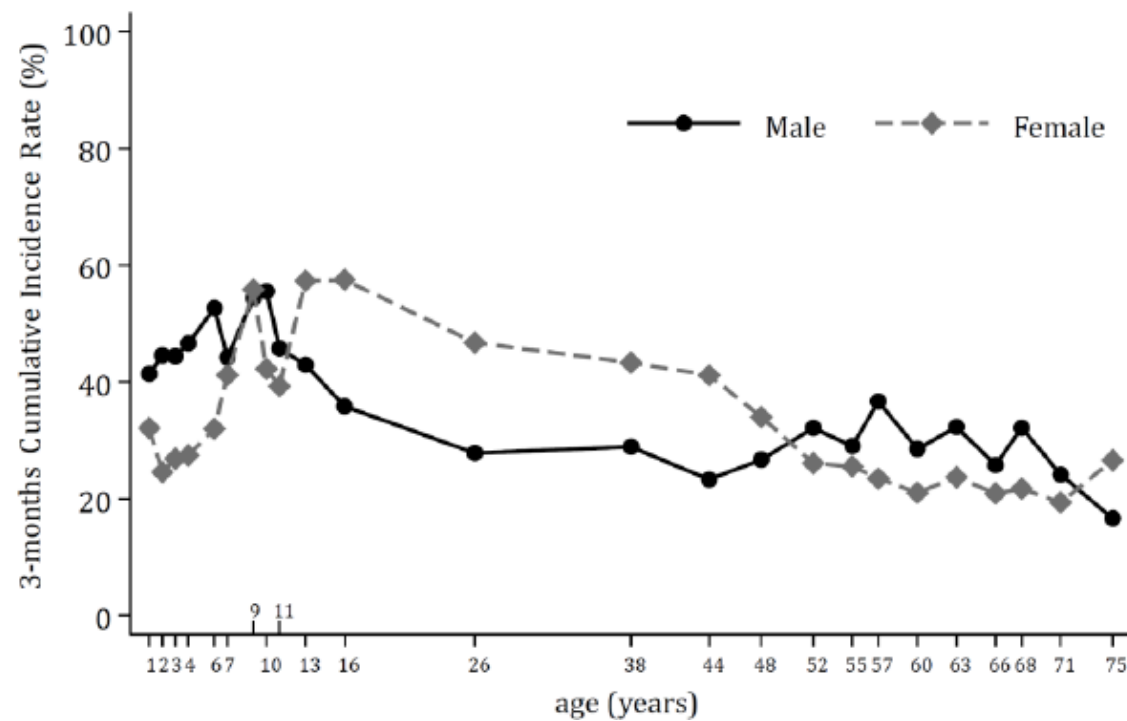




| Number at risk | | 0 | 3 | 6 | 9 | 12 | 15 | 18 | | | | | |
|----------------|-----|-----|-----|------|-----|------|-----|------|----|-----|----|-----|---|
| Males | 585 | (2) | 467 | (16) | 378 | (14) | 156 | (10) | 57 | (1) | 35 | (0) | 0 |
| Females | 543 | (6) | 435 | (11) | 365 | (11) | 139 | (10) | 52 | (0) | 35 | (1) | 2 |



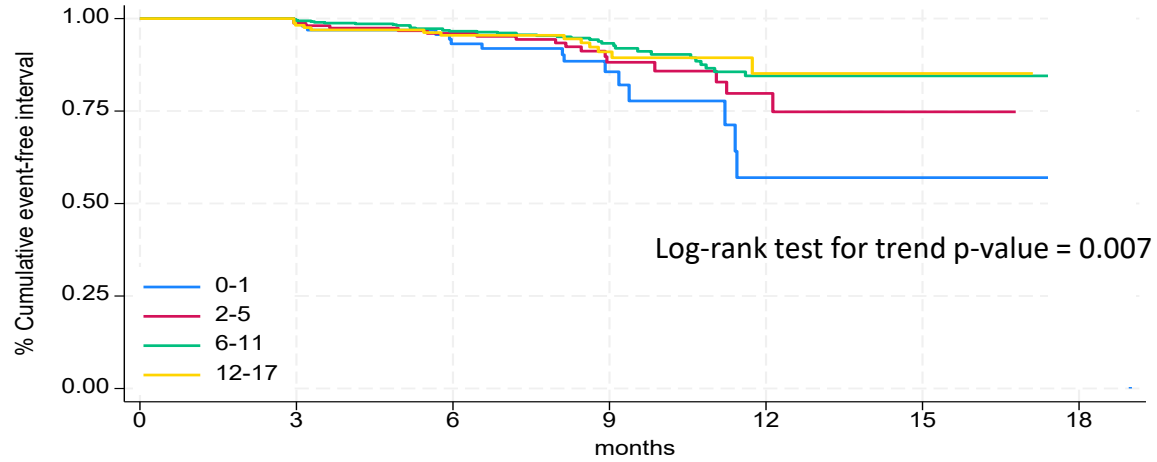
| Number at risk | | 0 | 3 | 6 | 9 | 12 | 15 | 18 | | | | | |
|----------------|-----|-----|-----|------|-----|-----|-----|-----|----|-----|----|-----|---|
| Males | 585 | (0) | 469 | (11) | 386 | (6) | 161 | (2) | 59 | (0) | 35 | (0) | 0 |
| Females | 543 | (4) | 436 | (19) | 363 | (3) | 137 | (5) | 53 | (0) | 36 | (1) | 2 |



Neurological symptoms and cognitive dysfunction

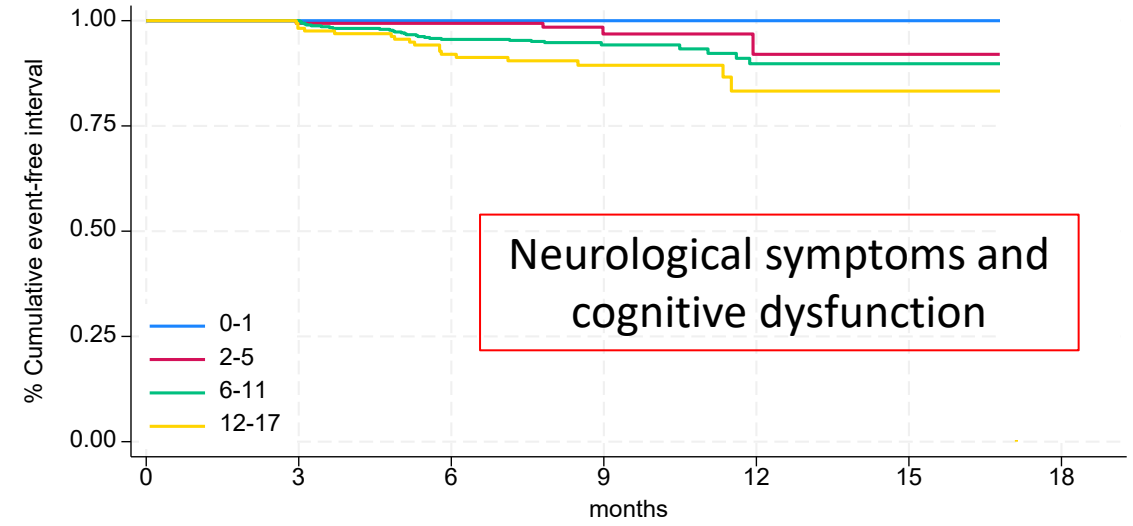
- Difficoltà di equilibrio
- Confusione
- Perdita di concentrazione
- Svenimento
- Problemi di vista
- Cefalea
- Vertigini

Respiratory symptoms

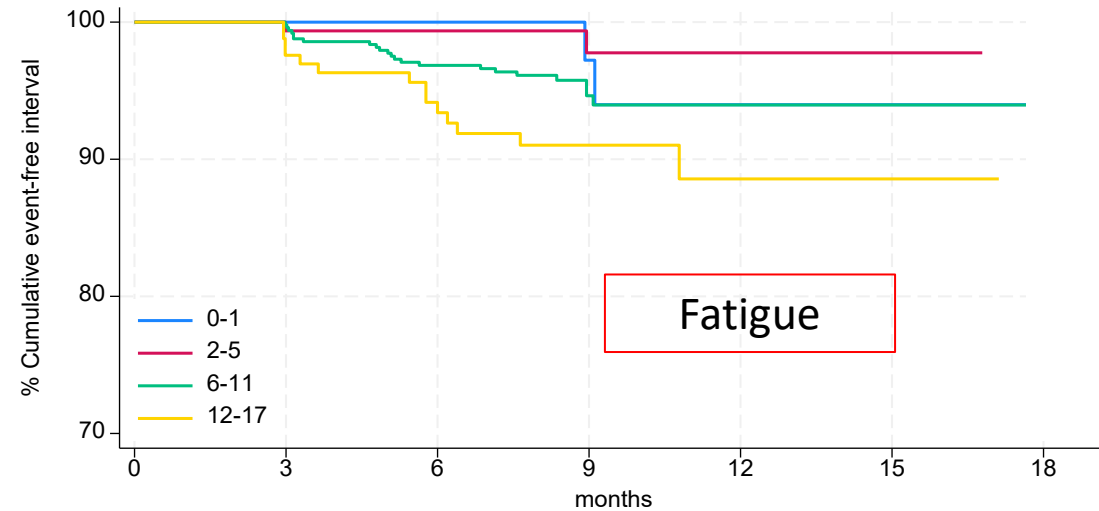


| Number at risk | | | | | | | | | | | | | |
|----------------|-----|-----|-----|------|-----|------|-----|------|----|-----|----|-----|---|
| 0-1 | 136 | (1) | 95 | (5) | 75 | (4) | 29 | (5) | 8 | (0) | 6 | (1) | 1 |
| 2-5 | 186 | (2) | 153 | (4) | 128 | (7) | 56 | (3) | 16 | (1) | 9 | (0) | 0 |
| 6-11 | 604 | (2) | 494 | (14) | 415 | (10) | 152 | (10) | 67 | (0) | 46 | (0) | 1 |
| 12-17 | 202 | (3) | 160 | (4) | 125 | (4) | 58 | (2) | 18 | (0) | 9 | (0) | 0 |

— 0-1
— 2-5
— 6-11
— 12-17



| Number at risk | | | | | | | | | | | | | |
|----------------|-----|-----|-----|------|-----|-----|-----|-----|----|-----|----|-----|---|
| 0-1 | 136 | (0) | 96 | (0) | 81 | (0) | 32 | (0) | 8 | (0) | 6 | (0) | 1 |
| 2-5 | 186 | (1) | 154 | (0) | 132 | (2) | 58 | (1) | 17 | (0) | 9 | (0) | 0 |
| 6-11 | 604 | (0) | 495 | (21) | 413 | (4) | 152 | (4) | 68 | (0) | 47 | (0) | 1 |
| 12-17 | 202 | (3) | 160 | (9) | 123 | (3) | 56 | (2) | 19 | (0) | 9 | (1) | 0 |



| Number at risk | | | | | | | | | | | | | |
|----------------|-----|-----|-----|------|-----|-----|-----|-----|----|-----|----|-----|---|
| 0-1 | 136 | (0) | 96 | (0) | 81 | (1) | 32 | (1) | 8 | (0) | 6 | (0) | 1 |
| 2-5 | 186 | (1) | 154 | (0) | 132 | (1) | 58 | (0) | 17 | (0) | 9 | (0) | 0 |
| 6-11 | 604 | (1) | 494 | (14) | 416 | (6) | 151 | (1) | 67 | (0) | 47 | (0) | 1 |
| 12-17 | 202 | (4) | 159 | (5) | 125 | (4) | 56 | (1) | 19 | (0) | 9 | (0) | 0 |

Conclusions

- **25%** (17% nella nostra casistica) of children and adolescents may be affected by Long Covid
- **Fatigue** and **respiratory symptoms (cough and exercise intolerance)** are the commonest symptoms
- **Lung function** and **lung anatomy** are not influenced by Covid infection
- Female gender, older age, hospitalization,, obesity and allergic rhinitis are risk factors for Long Covid
- **Adolescents and girls** seem to be most affected by neurological symptoms
- Spontaneous resolution of the condition is common
- Appropriate **follow-up** protocols are needed for these subjects (and treatment?)
- **Vaccination** protects against Long Covid



“Nuovi orizzonti...”

...in Pneumologia Pediatrica

Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection

Danilo Buonsenso*, Daniela Di Giuda*, Louise Sigfrid, Daniele Antonio Pizzuto, Gabriele Di Sante, Cristina De Rose, Ilaria Lazzareschi, Michela Sali, Fabiana Baldi, Daniela Pia Rosaria Chieffo, Daniel Munblit†, Piero Valentini†

Case-report: ragazza, 14 anni
(Roma, Italia)

Mild-COVID19 (fase acuta)

Febbricola (37,3°C)
Rinite
Anosmia
Ageusia

Dopo 30 giorni

Cefalea
Dolore toracico
Fatigue
Tachicardia

Dopo 7 mesi

RICOVERO

per persistenza di sintomi

1. **6-min walktest** → tachicardia nel 1° min (FC >155bpm) + facile affaticabilità

2 **CPET** → lieve ipertensione polmonare

3. **EE** → ↑ IL-6, IL-1, TNF-α, B-cells
↓ regulatory T-cells

STATO INFIAMMATORIO

4. **Sierologia** → ↑ IgG e IgA per SARS-CoV2

Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection

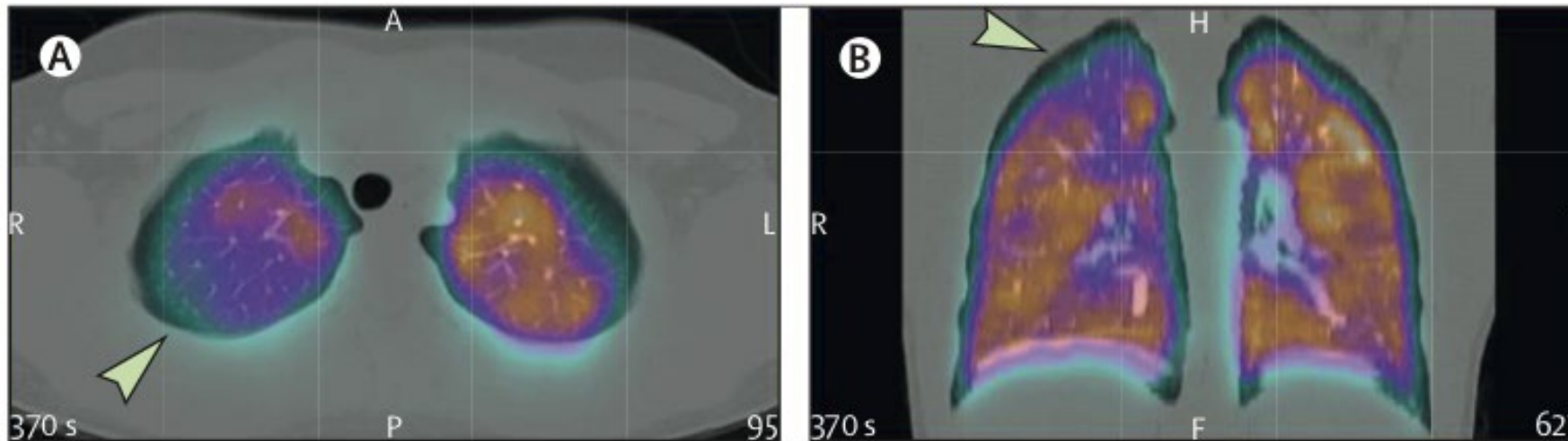
Danilo Buonsenso*, Daniela Di Giuda*, Louise Sigfrid, Daniele Antonio Pizzuto, Gabriele Di Sante, Cristina De Rose, Ilaria Lazzareschi, Michela Sali, Fabiana Baldi, Daniela Pia Rosaria Chieffo, Daniel Munblit†, Piero Valentini†

V/Q SPECT (Single photon emission computed tomography)



DIFETTI DI PERFUSIONE significativi al segmento apicale del lobo destro

NB: non corrispondenza con alterazioni di parenchima alla TC eseguita in contemporanea



Evidence of lung perfusion defects and ongoing inflammation in an adolescent with post-acute sequelae of SARS-CoV-2 infection

Danilo Buonsenso, Daniela Di Giuda*, Louise Sigfrid, Daniele Antonio Pizzuto, Gabriele Di Sante, Cristina De Rose, Ilaria Lazzareschi, Michela Sali, Fabiana Baldi, Daniela Pia Rosaria Chieffo, Daniel Munblit†, Piero Valentini†*

Diagnosi: "pulmonary circulation dysfunction with possible peripheral microvascular and endothelial damage».

Terapia: methylprednisolone 2 g/kg once daily for 2 weeks, then tapered over the next 4 weeks + low molecular weight heparin with a plan of changing to oral anticoagulants and continuation of therapy for 6–9 months in total.

Characterizing Long COVID in Children and Adolescents

- Multicenter longitudinal observational cohort study from 60 US health care and community settings between March 2022 and December 2023
- 6-11 years vs 12-17 years
- 898 school-age children (751 infected vs 147 uninfected); mean age, 8.6 years;
- 14 symptoms in both school-age children and adolescents were more common in those with SARS-CoV-2 infection with 4 additional symptoms in school-age children only and 3 in adolescents only.

| Participant characteristic | No. (%) | | | |
|----------------------------|------------------------------|----------------------|-----------------------|-----------------------|
| | School-age children (6-11 y) | | Adolescents (12-17 y) | |
| | Infected (n = 751) | Uninfected (n = 147) | Infected (n = 3109) | Uninfected (n = 1369) |
| Age, mean (SD), y | 9 (2) | 8 (2) | 15 (1) | 15 (1) |
| Sex assigned at birth | | | | |
| Female | 362 (48) | 78 (53) | 1537 (49) | 592 (43) |
| Male | 389 (52) | 69 (47) | 1572 (51) | 776 (57) |

A School-age children (6-11 y)

| Symptoms | No. (%) | | Adjusted risk difference (95% CI), % | Adjusted odds ratio (95% CI) |
|--|------------------|--------------------|--------------------------------------|------------------------------|
| | Infected (n=751) | Uninfected (n=147) | | |
| General symptoms | | | | |
| Daytime tiredness, sleepiness, or low energy | 96 (12.8) | 8 (5.4) | 7.4 (2.9 to 11.9) | 2.57 (1.29 to 5.87) |
| Trouble sleeping | 83 (11.1) | 5 (3.4) | 7.7 (4 to 11.4) | 3.56 (1.56 to 10.28) |
| Tired after walking | 64 (8.5) | 3 (2) | 6.3 (3.1 to 9.5) | 4.38 (1.59 to 18.14) |
| Poor appetite | 49 (6.5) | 3 (2) | 3.9 (1 to 6.8) | 3.04 (1.09 to 12.68) |
| Eye, ear, nose, and throat | | | | |
| Dark circles | 51 (6.8) | 5 (3.4) | 3.8 (0.3 to 7.2) | 2.20 (0.94 to 6.42) |
| Stuffy nose | 81 (10.8) | 8 (5.4) | 4.2 (-0.1 to 8.5) | 1.86 (0.92 to 4.29) |
| Chapped lips | 51 (6.8) | 4 (2.7) | 3.4 (0.2 to 6.6) | 2.33 (0.93 to 7.82) |
| Heart and lungs | | | | |
| Dry cough | 64 (8.5) | 6 (4.1) | 3.9 (0.2 to 7.7) | 2.05 (0.94 to 5.41) |
| Palpitation during exercise | 41 (5.5) | 2 (1.4) | 4 (1.5 to 6.5) | 4.11 (1.24 to 25.43) |
| Feeling lightheaded or dizzy | 43 (5.7) | 1 (0.7) | 5.2 (3 to 7.3) | 9.16 (1.96 to 163.19) |

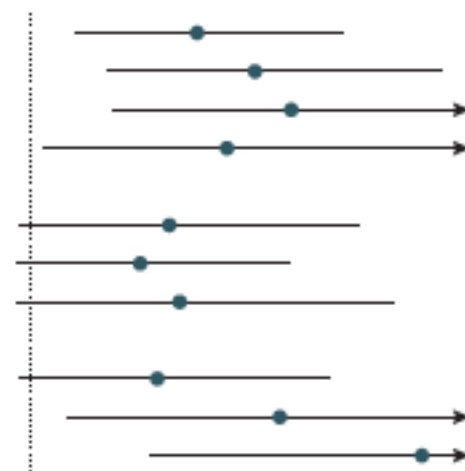
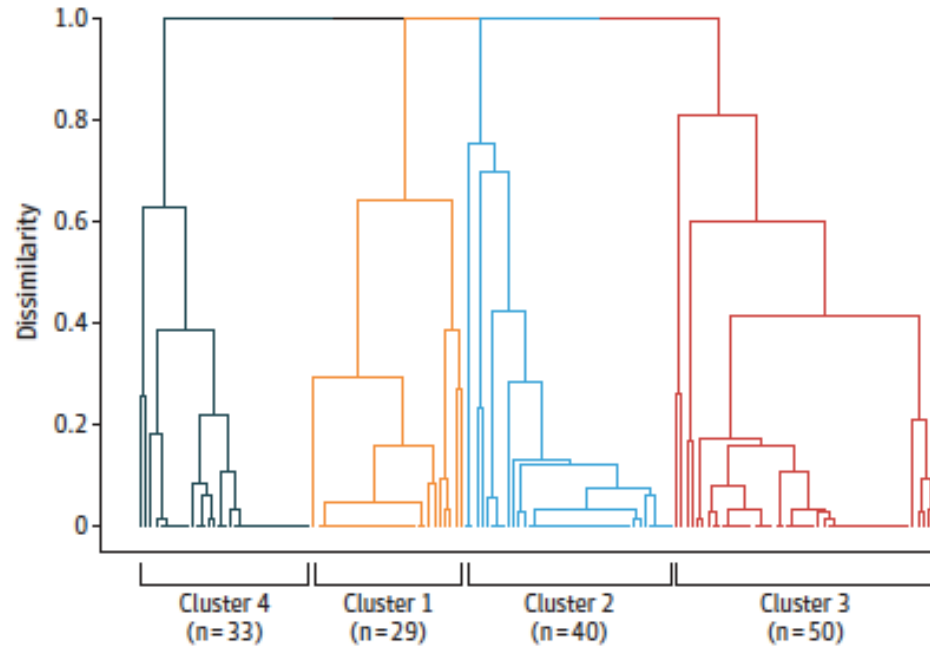


Figure 5. Defining Subgroups of Postacute Sequelae of SARS-CoV-2 Infection (PASC)–Probable Participants

A Clustering dendrogram among school-age children

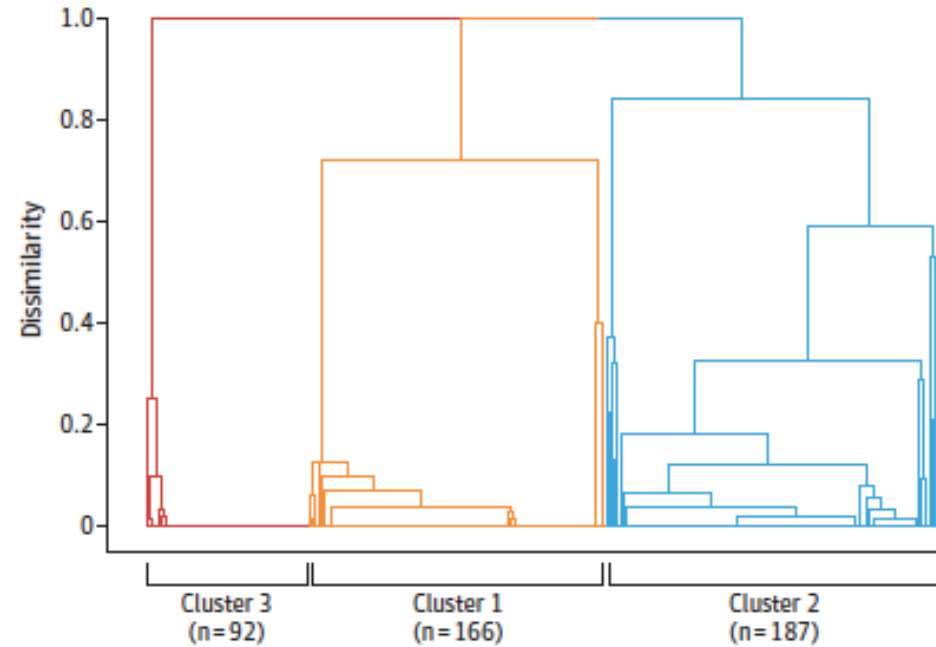


Cluster 1 had high rates of many symptoms and the highest symptom burden.

Cluster 2 was characterized by high rates of headache (95%), body/muscle/joint pain (60%), and daytime tiredness/sleepiness or low energy (52%). Cluster 3 was characterized by higher rates of trouble sleeping (64%) and trouble with memory/focusing (62%).

Cluster 4 was characterized predominantly by stomach pain (100%) and nausea/vomiting (61%)

B Clustering dendrogram among adolescents



Cluster 1 had high rates of many symptoms, similar to the first school-age cluster.

Cluster 2 was characterized by high rates of daytime tiredness/sleepiness or low energy (89%) and body/muscle/joint pain (87%).

Cluster 3 was characterized by having change/loss in smell or taste (100%), with relatively low rates of all other symptoms.

| First Author | Study Period | Country | Number of Paediatric Patients/Type of Study Population | Study Type | Main SARS-CoV-2 Variant(s) | Definition Long COVID | Study Focus | Key Findings | Comments |
|-------------------------|-------------------------------|----------------|---|---|----------------------------|---|--|--|--|
| Pinto Pereira 2023 [56] | September 2020 to March 2021 | England | n = 6407 SARS-CoV-2 positive patients aged 11-17 years n = 6542 SARS-CoV-2 negative controls Questionnaire-based study 6 months after acute illness | National cohort study | n.d. | Delphi definition | To evaluate physical and mental health 6 months after SARS-CoV-2 infection | 24.5% of SARS-CoV-2 positive patients and 17.8% of negative controls had Long COVID symptoms at 6 months after infection. Common symptoms in both groups: Tiredness, shortness of breath, and headaches. | |
| Roessler 2022 [58] * | January 2019 to December 2020 | Germany | n = 11,950 patients aged 0-17 years with COVID-19 n = 59,750 matched control group Mean follow-up time: 236 days after acute illness | Retrospective matched cohort study based on health insurance data | Pre-Omicron variants | WHO definition, but symptoms >3 months after diagnosis of COVID-19 | To evaluate morbidity after COVID-19 in children and adolescents | Incidence Rate Ratios (IRR) of documented health-related problems was significantly higher in the COVID-19 group (IRR: 1.3, 95% CI: 1.25-1.35, p < 0.01). Specific outcomes with the highest IRR were malaise/fatigue/exhaustion (IRR 2.3), cough (IRR 1.7), throat/chest pain (1.7). | Data from German statutory health insurance organisations. |
| Stephenson 2022 [63] | January to March 2021 | United Kingdom | n = 3065 SARS-CoV-2 positive adolescents aged 11-17 years n = 3739 matched negative controls | Longitudinal cohort study | Mainly Alpha | Persistent symptoms for more than 3 months after SARS-CoV-2 infection | To evaluate the incidence and clinical phenotype of Long COVID | At 3 months 2038 (66.5%) positive participants and 1993 (53.3%) negative controls had any symptoms, and 928 (30.3%) from the positive group and 603 (16.2%) from the control group had three or more symptoms. At 3 months the most common symptoms in the SARS-CoV-2 positive group vs. the control group were: tiredness (39.0% vs. 24.4%), shortness of breath (23.4% vs. 10.4%) and headaches (23.2% vs. 14.2%). All three comparisons were statistically highly significant (p < 0.0001). | |

| | | | | | | | | | |
|---------------------------|----------------------------|---------------|--|---------------------------------------|----------------------------------|--|--|---|---|
| Lorman 2023 [45] | March 2020 to June 2022 | United States | n = 14,399 patients <21 years, divided into 3 cohorts: n = 1309 post-acute Sequelae of SARS-CoV-2 (PASC) cases (using ICD-10 diagnosis U09.9) n = 6545 children with SARS-CoV-2 infection (PCR, antigen, or serology positive) n = 6545 children without SARS-CoV-2 infection | Cohort study | Pre- and post-Omicron variants | NIH definition of PASC Persistent symptoms for >30 days after SARS-CoV-2 infection | To identify clusters of PASC-associated diagnoses | Significant increase was observed in multiple symptoms related to cardiovascular, respiratory, neurological, psychological, endocrine, gastrointestinal, and musculoskeletal systems among children with PASC. Typical symptoms in PASC cases (compared with both control groups) included dyspnoea, abnormalities in breathing, and malaise/fatigue. | Study is based on Electronic Health Records from 9 different hospitals. n = 3806 (26.4%) patients were aged 16–20 years, including n = 346 PASC cases, n = 1730 SARS-CoV-2 negative, and n = 1730 SARS-CoV-2 positive patients. |
| Mizrahi 2023 [49] * | March 2020 to October 2021 | Israel | n = 118,308 SARS-CoV-2 positive patients <18 years n = 118,308 negative controls Electronic medical records from an Israeli nationwide healthcare organisation | Retrospective nationwide cohort study | Wild-type, Alpha, Delta variants | Divided into early (30–180 days) and late (180–360 days) time periods after infection Defined as prolonged or new symptoms >4 weeks after acute onset | To determine clinical sequelae of Long COVID during the first year after mild SARS-CoV-2 infection | 1.22, 1.11–1.35) only during the early phase Age 5–11: Conjunctivitis (HR 1.24, 1.07–1.43) only during the early phase. Sore throat (HR 1.54, 1.20–1.97) only during the late phase Age 12–18 Anosmia and dysgeusia (HR 23.5, 5.48–100.86), dyspnoea (HR 1.7, 1.36–2.12) and weakness (HR 1.66, 1.41–1.96) only during the early phase In the entire cohort (including adults), there was a trend for anosmia/dysgeusia, dyspnoea, weakness, chest pain, and palpitations to decline over time. | Only patients with mild disease. Study included additional adult cases and controls. Anosmia and dysgeusia were grouped together in the analysis. |
| Kikkenborg Berg 2022 [42] | January 2020 to July 2021 | Denmark | n = 10,997 SARS-CoV-2-positive children aged 0–14 years n = 33,016 negative controls Questionnaire-based | Cross-sectional study | Alpha, Delta variants | Persistent symptoms for >8 weeks after the positive SARS-CoV-2 test | To examine the prevalence, severity, and duration of persistent symptoms, as well as impact on quality of life, number of missed school or daycare days, and psychological and social effects after SARS-CoV-2 infection | In all age groups, cases had higher odds of experiencing at least one persistent symptom (for more than 3 months) than controls: 0–3 years age group (435 [36.4%] of 1194 vs. 872 [22.6%] of 3855; OR 1.94 [1.68–2.23], p < 0.0001) 4–11 years age group (1710 [34.0%] of 5023 vs. 5356 [29.2%] of 18,372; OR 1,28 [1.19–1.37], p < 0.0001) 12–14 years age group (1204 [42.1%] of 2857 vs. 3966 [36.8%] of 10,789; 1.26 [1.11–1.32], p < 0.0001). Symptoms significantly more prevalent in the case group included: fatigue, headache, dizziness, sore throat, muscle/joint pain, chest pain, trouble breathing, cough, and loss of appetite | Similar rates of pre-existing co-morbidities in cases and controls. |

NICE guidelines [16]

First published 12/2020
Updated
version 11 November 2021

Acute COVID-19: "Signs and symptoms of COVID-19 for up to 4 weeks".

Ongoing symptomatic COVID-19: "Signs and symptoms of COVID-19 from 4 weeks up to 12 weeks".

Post-COVID-19 syndrome: "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. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed. In addition to the clinical case definitions, the term '**long COVID**' is commonly used to describe signs and symptoms that continue or develop after acute COVID-19. It includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more)".

Department of Health and Human
Services (in collaboration with CDC)
definition of Long COVID and PASC [12]

"Long COVID is a patient created term broadly defined as signs, symptoms, and conditions that continue or develop after initial SARS-CoV-2 infection. The **signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing–remitting pattern and progression or worsen over time, with the possibility of severe and life-threatening events even months or years after infection.** Long COVID is not one condition. It represents many potentially overlapping entities, likely with different biological causes and different sets of risk factors and outcomes.

Post-COVID-19 Conditions is equivalent to the lay term Long COVID, and is used to describe the new, returning, or ongoing health problems people can experience four or more weeks after initial infection with the SARS-CoV-2 virus, the virus that causes COVID-19.

Post-acute Sequelae of SARS-CoV-2 infection is a term used in the scientific and medical communities that refers to ongoing, relapsing, or new symptoms or other health effects occurring after the acute phase of SARS-CoV-2 infection. This definition will be revised in an iterative manner based on existing and new data, medical literature, and feedback from the scientific community".

Previous NIH definition included persistence of symptoms for longer than 30 days.
