

LONG-COVID IN PEDIATRIA

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Conseguenze a lungo termine dell'infezione da SARS-CoV-2 nei soggetti di età pediatrica

Sindrome infiammatoria multisistemica del bambino (MIS-C)

MIS-C è una sindrome che colpisce meno dello 0,1% dei bambini con infezione da SARS-CoV-2 e che si sviluppa da 2 a 6 settimane da questa, in genere in soggetti di età scolare, con un quadro clinico spesso estremamente grave.

Interessa più organi ed apparati, specie cuore, cute e mucose, intestino, come conseguenza dell'attivazione di un intenso processo infiammatorio immuno-mediato.

Per certi aspetti, specie quando si manifesta con shock e sindrome dell'attivazione macrofagica, può richiamare il quadro clinico della sindrome di Kawasaki grave.

LONG-COVID

Tutto ciò che segue la sintomatologia già presente in fase acuta di COVID-19 o compare a distanza di essa e non può essere attribuito ad una qualsiasi patologia nota.

In realtà, cosa sia LONG-COVID, quale sia la sua reale frequenza, quali siano le manifestazioni lo caratterizzino, quanto queste durino, quale sia la loro patogenesi e se e come esse debbano essere affrontate non è perfettamente chiarito.

DEFINITIONS OF LONG COVID (LC) FOR ADULTS

WHO: People 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 alternative diagnoses.

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. 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 postCOVID-19 syndrome (12 weeks or more)

NIH: Clinical manifestations after 4 weeks from SARS-CoV-2 infection

DEFINITION FOR LONG COVID IN CHILDREN

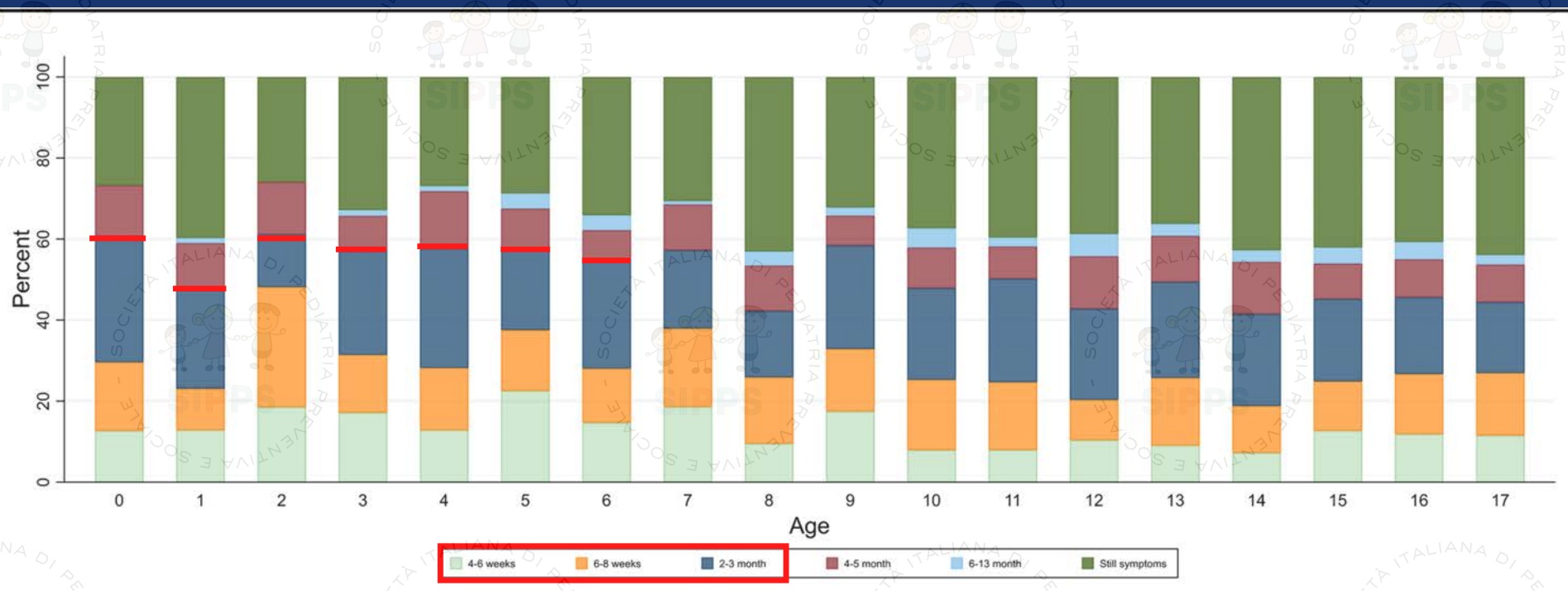
(from Stephenson T, et al. Arch Dis Child 2022)

Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis.

The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time

Duration of symptoms from date of positive RT-PCR SARS-CoV-2 test

(from Borch L, et al. Europ J Pediatr 2022)



RAGIONI CHE GIUSTIFICANO LE ATTUALI IMPERFETTE CONOSCENZE SUL LONG-COVID PEDIATRICO

Mancanza di una definizione universalmente condivisa

Grandi limitazioni metodologiche negli studi disponibili

Inclusione di casi senza certa dimostrazione di infezione da SARS-CoV-2

Raccolta di informazioni per intervista o con questionari senza alcun controllo della veridicità delle affermazioni

Variabile durata del follow-up

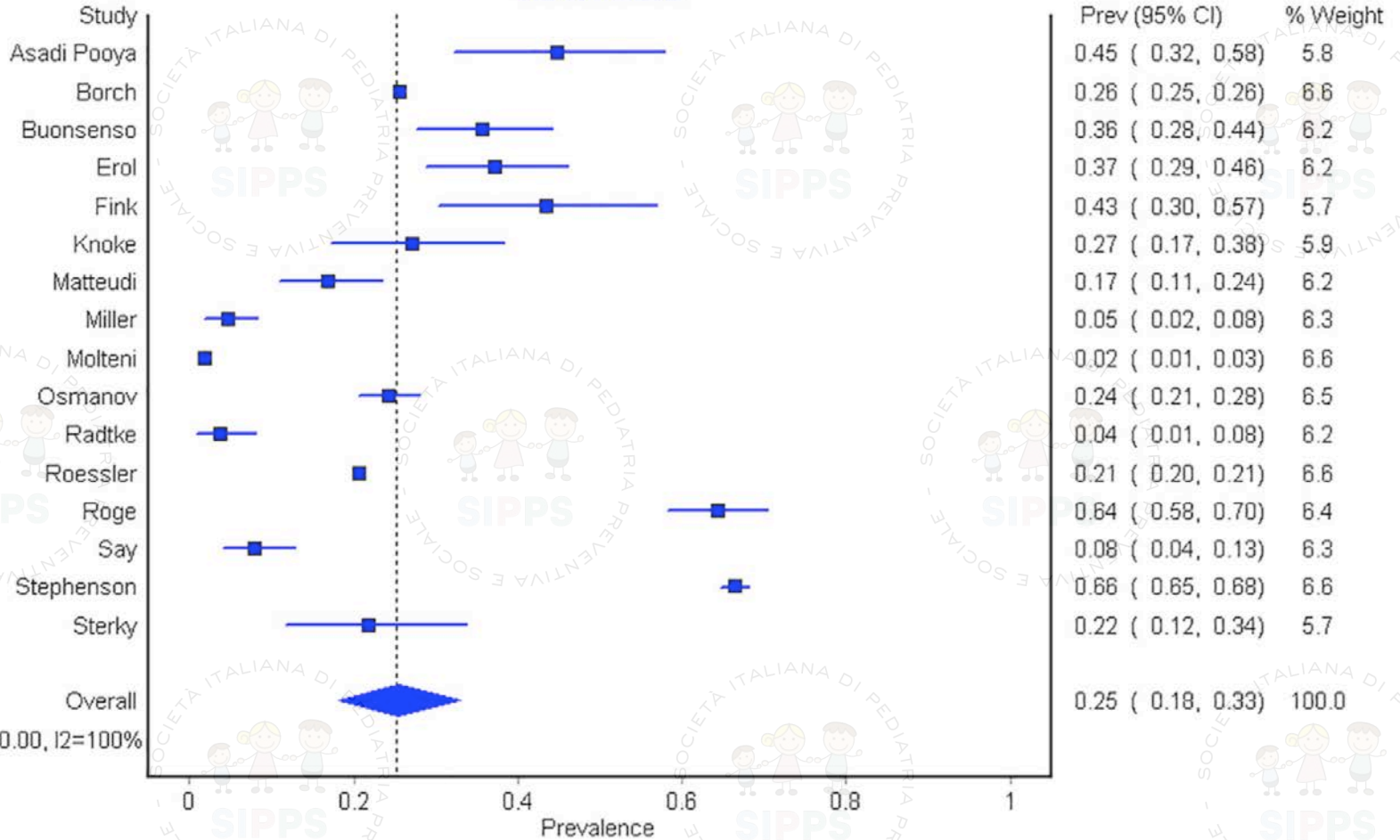
Informazioni limitate a segni e sintomi di malattia decisi a priori

Mancanza di una popolazione di controllo

Forest plot of pooled prevalence of long-COVID overall in children and adolescents.

(from Lopez-Leon S, et al. Nature Sci Rep 2022)

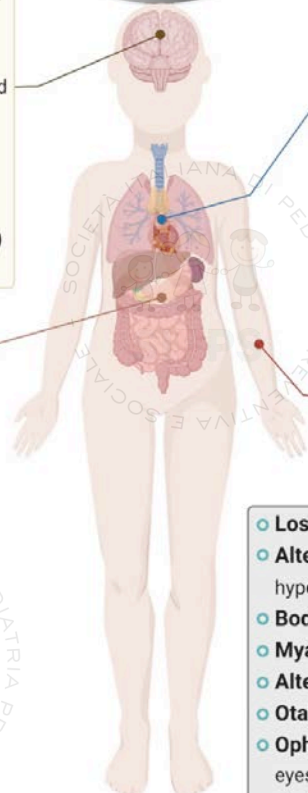
Random effects



Long-COVID in children and adolescents



25.24%



Neuropsychiatric (%)

- **Mood** 16.50 (sad, tense, angry, anxiety, depression)
- **Fatigue** 9.66
- **Sleep disorder** 8.42 (insomnia, hypersomnia, poor sleep quality)
- **Headache** 7.84
- **Cognition** 6.27 (confusion, impaired concentration, learning difficulties, memory loss)
- **Dizziness** 4.40
- **Neurological abnormalities** 0.86 (pins and needles, tremor, numbness)
- **Balance problems** 0.54

Cardiorespiratory (%)

- **Respiratory symptoms** 7.62
- **Sputum/nasal congestion** 7.53
- **Orthostatic intolerance** 6.92
- **Exercise intolerance** 5.73
- **Chest pain** 4.62
- **Rhinorrhea** 4.15
- **Cough** 3.80
- **Sore throat** 2.47
- **Chest tightness** 2.45
- **Variations in heart rate** 2.29
- **Palpitations** 1.27

Dermatologic/Teguments (%)

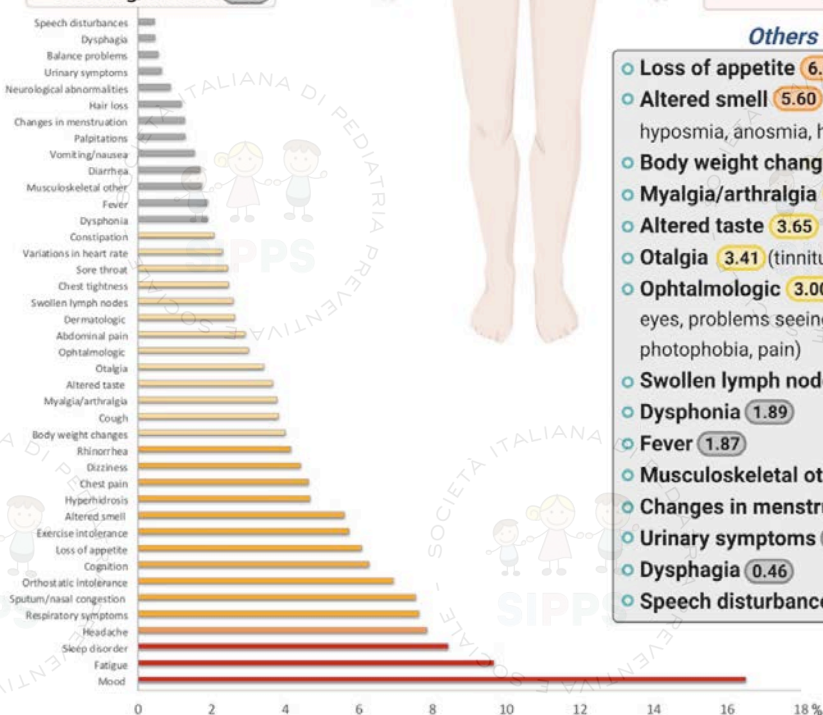
- **Hyperhidrosis** 4.66
- **Dermatologic** 2.61 (dry skin, itchy skin, rashes, hives)
- **Hair loss** 1.17

Others (%)

- **Loss of appetite** 6.07
- **Altered smell** 5.60 (phantom smell, hyposmia, anosmia, hyperosmia)
- **Body weight changes** 3.99
- **Myalgia/arthralgia** 3.76
- **Altered taste** 3.65
- **Otalgia** 3.41 (tinnitus, earache or vertigo)
- **Ophthalmologic** 3.00 (conjunctivitis, dry eyes, problems seeing/blurred vision, photophobia, pain)
- **Swollen lymph nodes** 2.58
- **Dysphonia** 1.89
- **Fever** 1.87
- **Musculoskeletal other** 1.72
- **Changes in menstruation** 1.27
- **Urinary symptoms** 0.63
- **Dysphagia** 0.46
- **Speech disturbances** 0.44

Gastrointestinal (%)

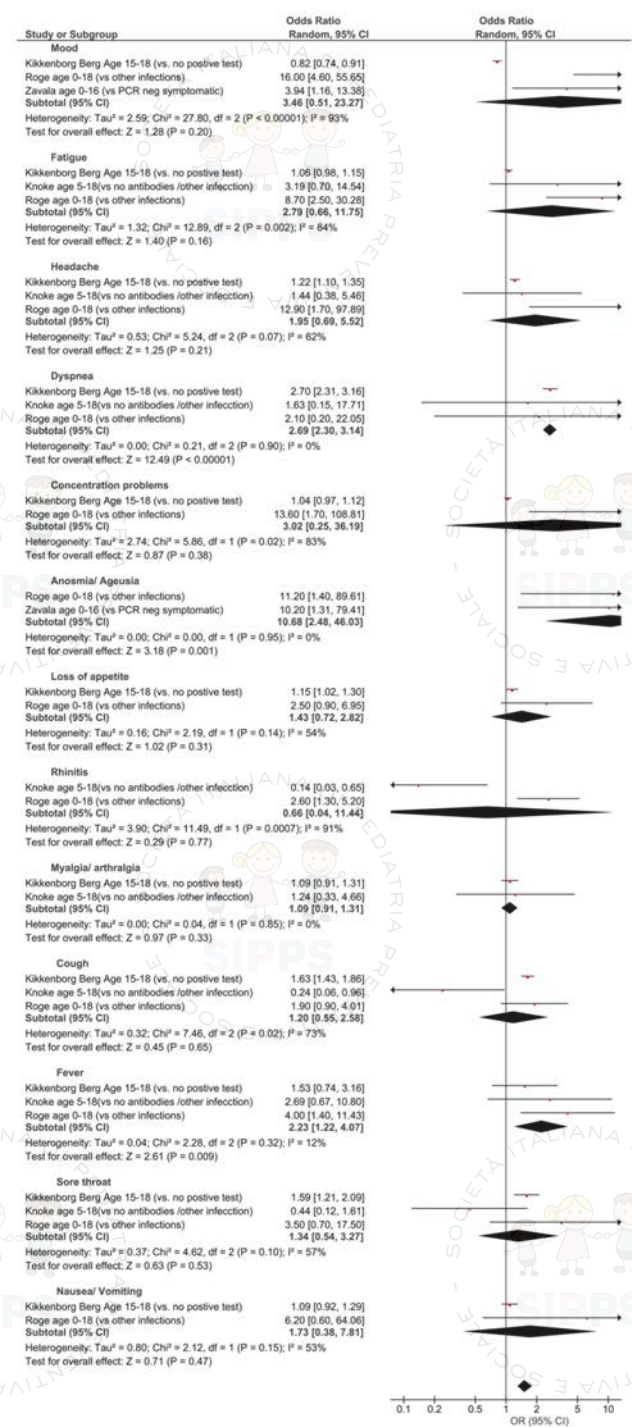
- **Abdominal pain** 2.91
- **Constipation** 2.05
- **Diarrhea** 1.68
- **Vomiting/nausea** 1.53



The pooled prevalence of LC in children and adolescents

(from Lopez-Leon S, et al. Nature Sci Rep 2022)

Systematic review and meta-analysis of 21 studies including 80.071 children and adolescents with symptoms persisting or emerging after 4 weeks from SARS-CoV-2 infection



Rischio di insorgenza dei sintomi: confronto tra casi e controlli

(from Lopez-Leon S, et al. Nature Sci Rep 2022)

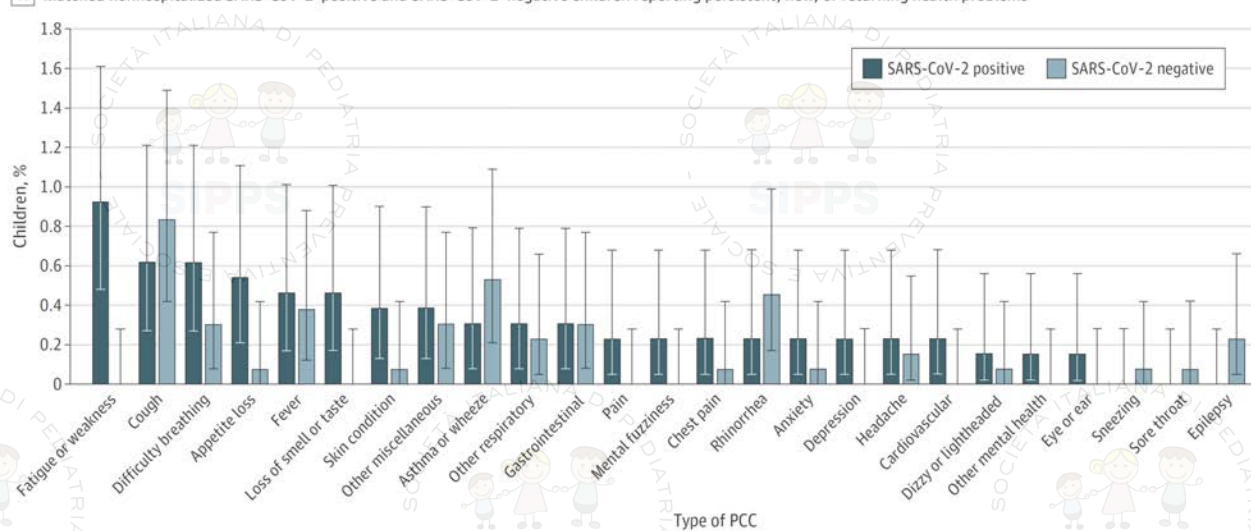
La comparazione è stata effettuata solo per:
umore, senso di affaticamento, cefalea, dispnea, problemi di concentrazione, anosmia/perdita del gusto, perdita dell'appetito, rinite, mialgie/artralgie, tosse, febbre, mal di gola, nausea/vomito.

In confronto ai controlli, i bambini con LC hanno presentato un maggior rischio per
**dispnea persistente (OR 2.69; 95% CI 2.30-3.14),
 anosmia/perdita del gusto (OR 10.68; 95% CI 2.48-46.03)
 febbre (OR 2.23; 95% CI 1.2-4.07).**

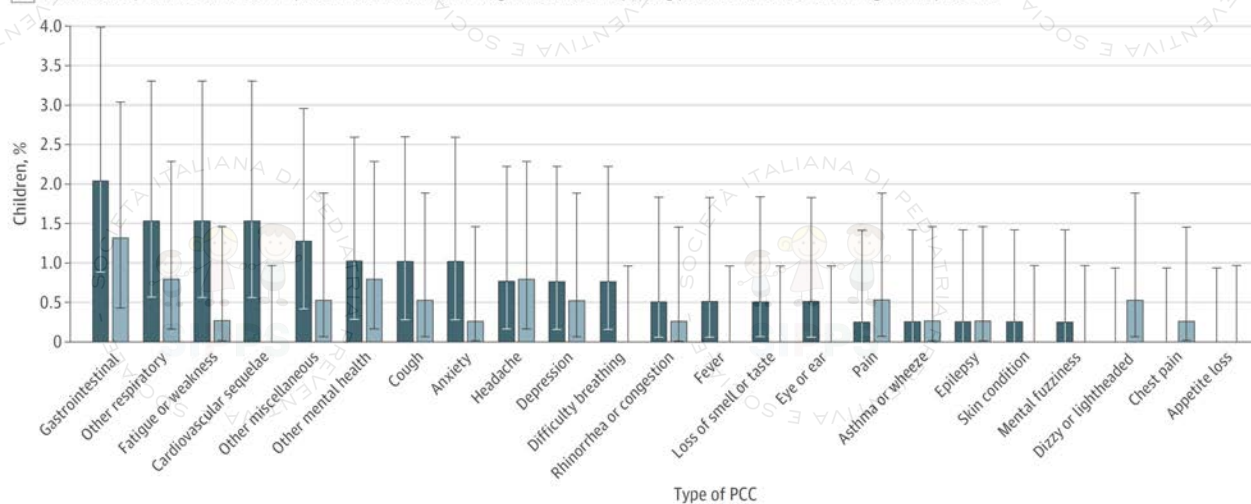
Segni e sintomi rilevati in bambini con COVID-19 90 giorni dopo l'infezione e in un gruppo controllo

(da Funk AL, et al. JAMA Pediatr 2022)

A Matched nonhospitalized SARS-CoV-2-positive and SARS-CoV-2-negative children reporting persistent, new, or returning health problems



B Matched hospitalized SARS-CoV-2-positive and SARS-CoV-2-negative children reporting persistent, new, or returning health problems



Dopo 90 giorni dall'infezione, il 9.8% dei bambini ospedalizzati e il 4,6% di quelli non ospedalizzati con COVID-19 presentavano sintomi in confronto al 5,2% e 2,7% dei controlli. Il rischio di LC era più alto negli infetti che nei controlli (aOR 1,63; 95% CI 1,14-2,35). Inoltre, significativamente maggiore era la presenza di manifestazioni cliniche sistemiche (affaticamento, debolezza, febbre (aOR 2,44; 95% CI 1,19-5,00).

Symptom burden and health-related quality of life in COVID-19 cases and controls

(from Kikkenborg-Berg S, et al. Lancet Child Adolesc health 2022)

	1-12 months		13-24 months		2-3 years*		4-11 years		12-14 years	
	Cases (n=105)	Controls (n=348)	Cases (n=427)	Controls (n=1062)	Cases (n=917)	Controls (n=2445)	Cases (n=6032)	Controls (n=18372)	Cases (n=3516)	Controls (n=10789)
CSSI-24										
Mean (SD)	NA	NA	NA	NA	2.5 (4.8)	2.5 (4.2)	3.0 (5.1)†	3.4 (4.8)†	4.3 (7.0)†	4.7 (6.2)†
Median (IQR)	NA	NA	NA	NA	1.0 (0.0-3.0)	1.0 (0.0-3.0)	1.0 (0.0-4.0)	2.0 (0.0-5.0)	1.0 (0.0-5.0)	3.0 (1.0-5.0)
PedsQL										
Physical functioning										
Mean (SD)	93.7 (11.2)†	87.8 (12.2)†	94.2 (9.1)†	87.3 (12.0)†	94.8 (10.2)	94.8 (8.2)	94.7 (11.4)†	92.9 (11.8)†	93.0 (13.0)†	91.2 (13.3)†
Median (IQR)	100.0 (91.7-100.0)	91.7 (79.2-100.0)	100.0 (91.7-100.0)	88.9 (80.6-97.2)	100.0 (93.8-100.0)	100.0 (90.6-100.0)	100.0 (93.8-100.0)	96.9 (90.6-100.0)	100.0 (90.6-100.0)	96.9 (87.5-100.0)
Physical symptoms										
Mean (SD)	84.4 (13.0)	85.1 (80.0-92.5)	84.9 (12.9)††	89.1 (9.7)††	NA	NA	NA	NA	NA	NA
Median (IQR)	85.0 (75.0-95.0)	87.5 (80.0-92.5)	87.5 (77.5-95.0)	90.0 (82.5-97.5)	NA	NA	NA	NA	NA	NA
Emotional functioning										
Mean (SD)	75.5 (16.9)	75.8 (13.7)	73.6 (16.2)††	77.0 (12.8)††	75.5 (18.1)	73.5 (15.4)	78.2 (19.1)††	73.3 (18.0)††	83.2 (19.5)††	79.2 (19.2)††
Median (IQR)	75.0 (64.6-89.6)	79.2 (68.8-85.4)	75.0 (62.0-85.4)	77.1 (68.8-87.5)	75.0 (65.0-90.0)	75.0 (65.0-85.0)	80.0 (65.0-95.0)	75.0 (60.0-85.0)	90.0 (70.0-100.0)	85.0 (65.0-95.0)
Social functioning										
Mean (SD)	94.7 (9.3)	93.0 (11.4)	93.3 (11.0)	93.0 (9.9)	93.8 (10.8)†	93.0 (10.8)†	92.3 (13.3)†	89.6 (15.0)†	91.4 (15.4)††	87.9 (17.5)††
Median (IQR)	100.0 (93.8-100.0)	100.0 (87.5-100.0)	100.0 (90.0-100.0)	95.0 (90.0-100.0)	100.0 (90.0-100.0)	100.0 (90.0-100.0)	100.0 (90.0-100.0)	95.0 (85.0-100.0)	100.0 (90.0-100.0)	95.0 (80.0-100.0)
School functioning										
Mean (SD)	NA	NA	NA	NA	92.9 (12.1)	93.0 (11.3)	86.8 (15.3)†	84.2 (15.4)†	83.7 (18.0)†	80.9 (17.8)†
Median (IQR)	NA	NA	NA	NA	100.0 (90.0-100.0)	100.0 (91.7-100.0)	90.0 (80.0-100.0)	90.0 (75.0-95.0)	90.0 (75.0-100.0)	85.0 (70.0-95.0)
Cognitive functioning										
Mean (SD)	87.7 (17.4)	88.6 (16.0)	87.3 (16.5)†	84.7 (16.3)†	NA	NA	NA	NA	NA	NA
Median (IQR)	100.0 (75.0-100.0)	100.0 (75.0-100.0)	94.4 (77.8-100.0)	88.9 (75.0-100.0)	NA	NA	NA	NA	NA	NA

CSSI-24=Children's Somatic Symptoms Inventory. PedsQL=Pediatric Quality of Life Inventory. *Missing school functioning scores: 27 cases, 77 controls. †Statistically significant (p<0.0009), based on Wilcoxon signed rank test. ††Hedges' g>0.2.

New onset of a mental health condition among children and adolescents, by COVID-19 diagnosis

(from Ali MM, et al. Psychiatric services 2022)

Condition	COVID-19 diagnosis (N=2,036,333) ^a		Negative COVID-19 test (N=1,329,662) ^b		ARR ^c	95% CI
	N	%	N	%		
Any mental health condition*	145,159	7.1	45,627	3.4	2.84	2.81–2.87
Diagnosis						
ADHD*	52,257	36.0	14,920	32.7	1.04	1.02–1.06
Anxiety*	62,564	43.1	18,023	39.5	1.08	1.06–1.10
Depression*	30,483	21.0	10,585	23.2	1.93	1.92–1.96
Mood disorder	7,984	5.5	2,418	5.3	1.89	1.85–1.93
Trauma- or stressor-related disorder	32,516	22.4	10,038	22.0	1.96	1.94–1.98
Behavior or conduct disorder*	17,274	11.9	3,513	7.7	1.88	1.85–1.91
Tourette's syndrome or tic disorder	1,887	1.3	365	.8	1.03	.95–1.13
Psychotic disorder	871	.6	274	.6	1.04	.96–1.15
Other mental disorder	1,597	1.1	639	1.4	1.15	1.06–1.26
Median length to psychiatric diagnosis, in days*	33		160			

^a ICD-10 COVID-19 diagnosis codes were B97.29, B34.2, U07.1, and U07.2.

^b ICD-10 COVID-19 test result codes were U0001, U0002, 87635, 86318, 86328, 86769, 87426, 0202U, 0223U, and 0224U.

^c The analysis was adjusted for age and gender. ARR, adjusted risk ratio.

* $p < 0.001$ for difference between children and adolescents with and without a COVID-19 diagnosis.

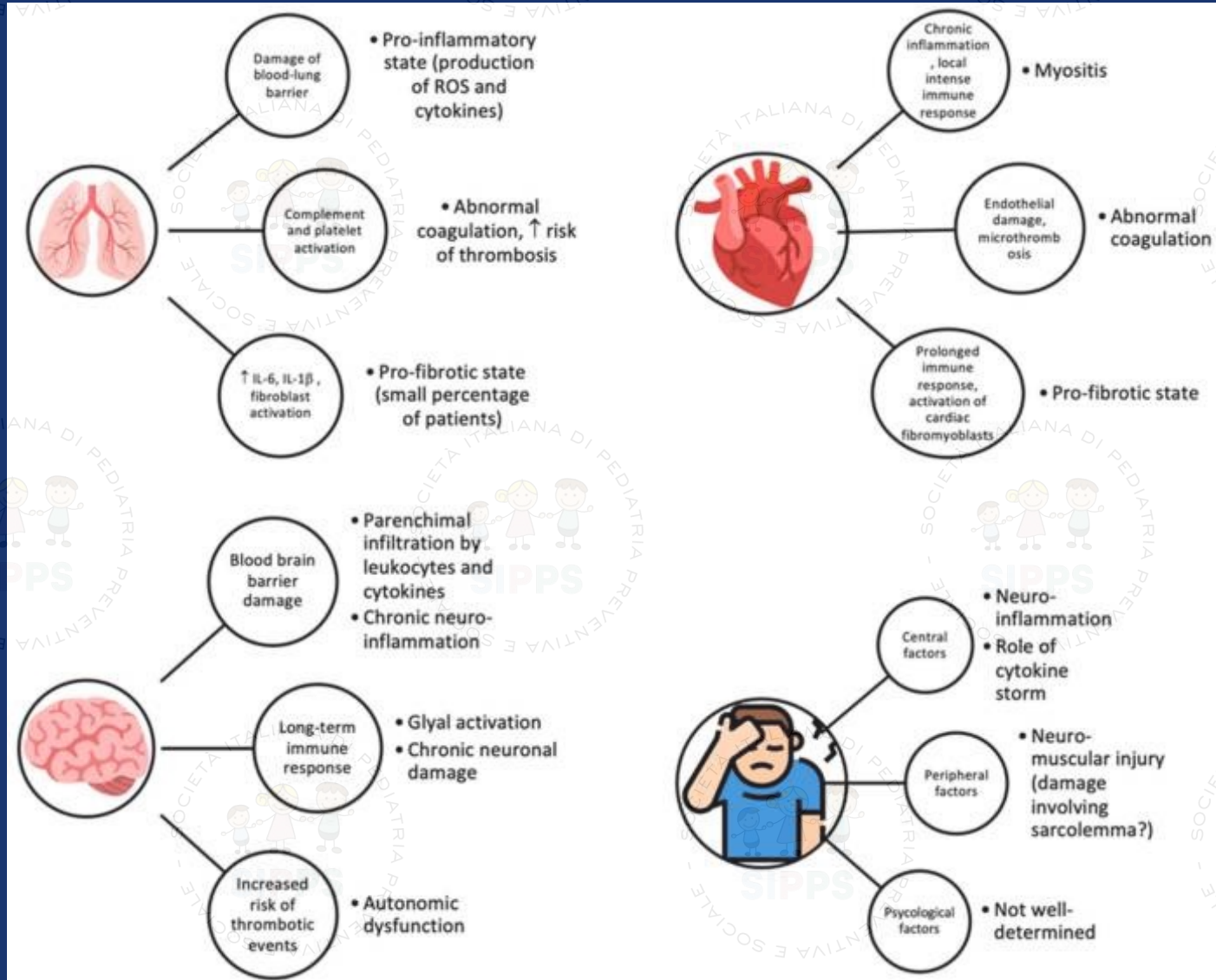
Four potential mechanisms that have been postulated to explain long COVID

(from Stephenson T et al. Curr Opin Infect Dis 2022)

1. Damage occurs to organs during acute infection and some of the damage persists leading to long-term symptoms. For example, the 'CoverScan' study in adults showed persisting multiorgan impairment in adults [53]. Relatively small numbers of children have been admitted to intensive care with severe organ damage as a result of acute SARS-CoV-2 infection. The majority of those with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 appear to be making a full recovery. Therefore, this mechanism seems unlikely to explain persisting post-COVID syndrome in children and young people.
2. The virus persists in the body, and this leads to the persisting symptoms. This would be analogous to the mechanism of persisting or recurrent symptoms from double stranded DNA herpes viruses causing recurrent genital and labial herpes and shingles [54]. There has been a case report of biopsy proven persistence of the nucleopcapsid protein from the SARS-CoV-2 RNA virus in the gut lining of a child with persisting gut symptoms [55]. In autopsies on 44 adults with COVID-19, SARS-CoV-2 was widely distributed, even among patients who died with asymptomatic to mild COVID-19 [56]. Persistent SARS-CoV-2 RNA was detected in multiple anatomic sites, including the brain, for up to 230 days following symptom onset.
3. There is an underlying autoimmune mechanism whereby antibodies raised against the virus cross react against host tissues. This could be analogous to the mechanism of ataxia some weeks after a varicella infection due to an autoimmune inflammation of the cerebellum [57]. We are not aware of any studies supporting this mechanism in post COVID syndrome in children and young people although autoimmunity has been suggested as a factor in adults [58].
4. Finally, perhaps none of the above biological mechanisms explain long COVID. The persistence of symptoms is unexplained as in many postviral syndromes in children.

Proposed organ-specific mechanisms of injury of Long COVID.

(from Crook H, et al. BMJ 2021)



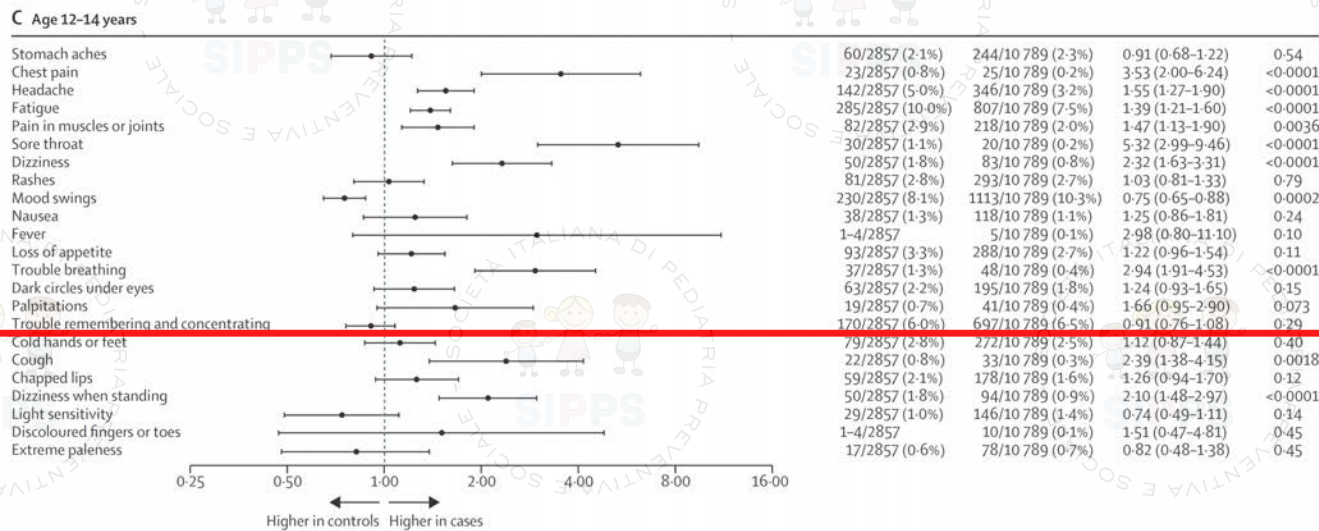
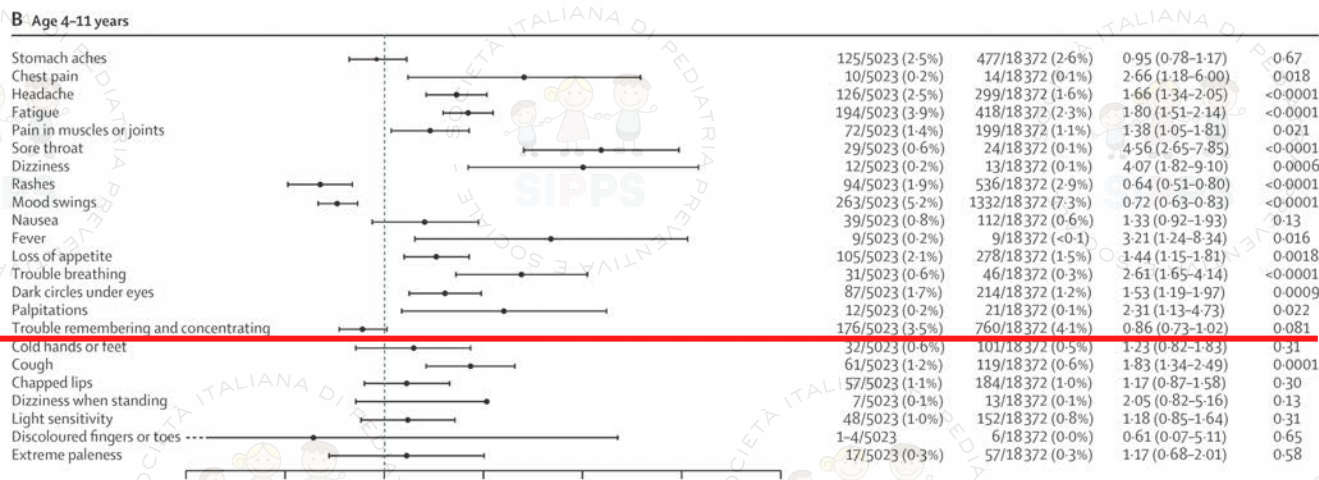
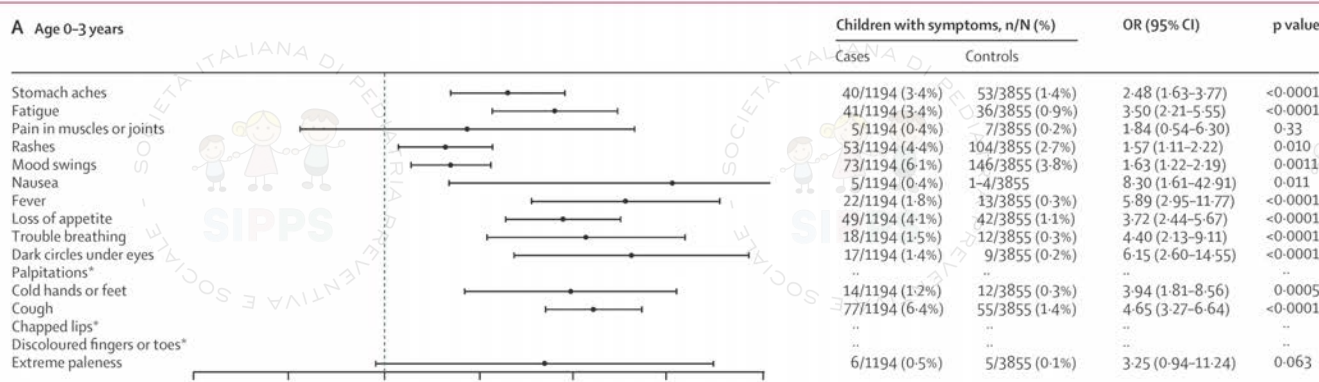
LONG COVID E SINTOMI NEUROPSICHIATRICI

Molti dei sintomi neuropsichiatrici come **scarsa concentrazione, confusione mentale, alterazioni del ritmo del sonno, perdita di memoria, senso di fatica** sono descritti all'interno della disautonomia, una sindrome legata ad una disfunzione del sistema nervosa simpatico o parasimpatico. **Se questa sia legata all'infezione e allo stato infiammatorio con liberazione di citochine che ne consegue non è noto.**

Si deve, tuttavia, notare, che anche nello stress cronico tipico delle situazioni come la pandemia esiste uno stato infiammatorio che, a sua volta, può essere la causa della maggior incidenza di problemi neuropsichiatrici registrati negli adolescenti durante la pandemia, indipendentemente dalla presenza dell'infezione.

Conclusioni deducibili dagli studi disponibili

- Il LONG-COVID esiste ma riguarda un numero di bambini relativamente contenuto perché molte delle manifestazioni cliniche riferite a distanza dall'infezione possono essere ritrovate anche in controlli non infetti.
- La elevata percentuale di casi con problematiche cliniche, spesso di tipo neuropsichiatrico, anche tra i controlli fa pensare che una parte dei segni e sintomi di LONG-COVID dipenda da un meccanismo legato all'infezione e/o ad uno stato infiammatorio persistente negli infetti e dallo stress psicologico legato alla pandemia nei non infetti.
- La durata in tutti i casi non è definita.



Forest plot of symptoms lasting at least 2 months in cases and controls

(from Kikkenborg-Berg S, et al. Lancet Child Adolesc Health 2022)