WOODCOCK INSTITUTE
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TEXAS WOMAN'S UNIVERSITY

National COVID Conference

Symposium for Professionals and Families

What we know and don't know about pediatric long-COVID

UNIVERSITÀ CATTOLICA del Sacro Cuore

Medical Manifestations of SARS-CoV-2 infection and Long Covid in Children and Adolescents

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Conflict of Interest

	No, Nothing to disclose
X	Yes, please specify

Grants to study Long Covid from Pfizer and Roche

JAMA Network | Open

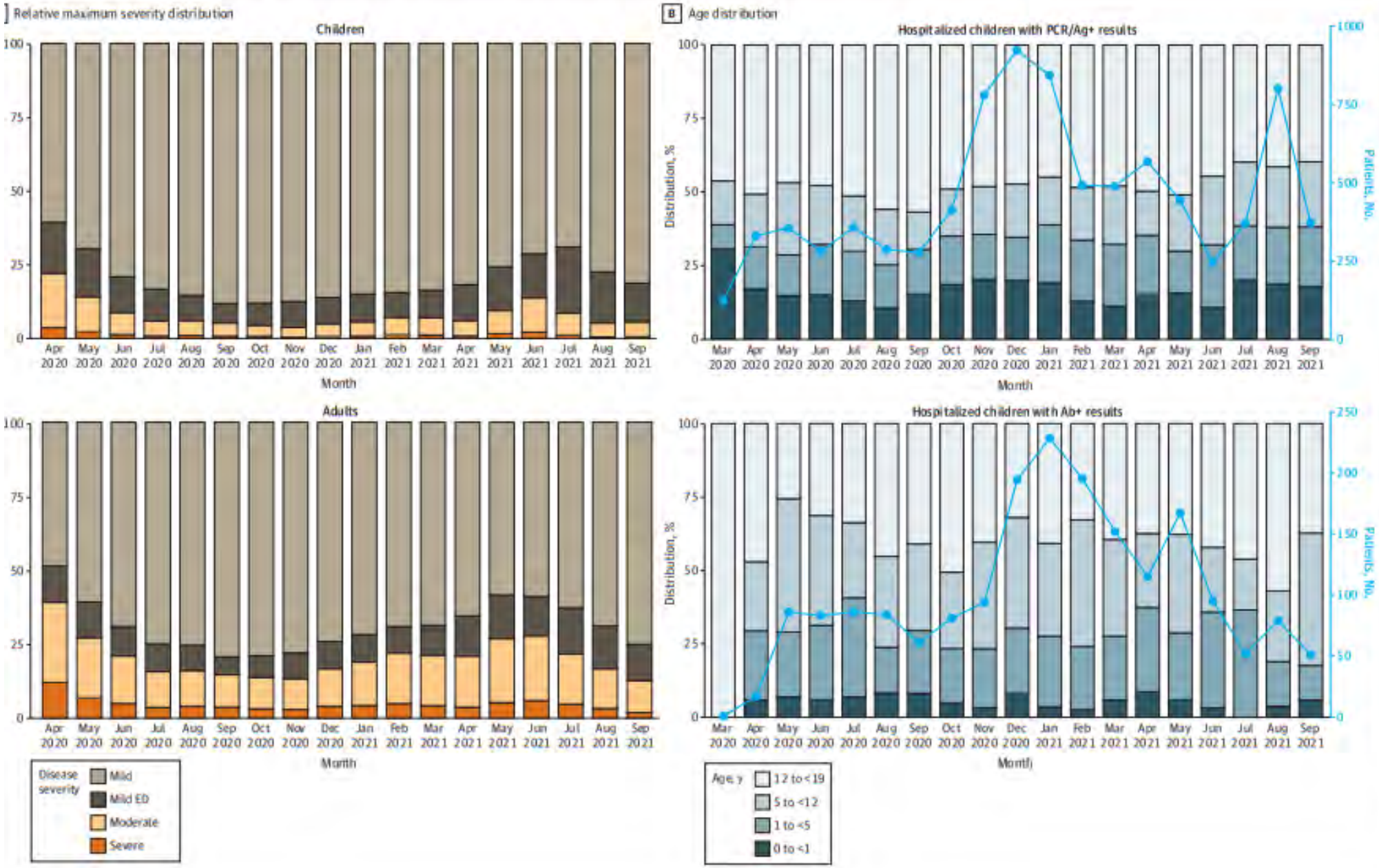
Original Investigation | Pediatrics

Characteristics, Outcomes, and Severity Risk Factors Associated With SARS-CoV-2 Infection Among Children in the US National COVID Cohort Collaborative

SARS-COV-2 Infection

Variable	Delta (N = 1738) No.	Total	%	Pre-Delta (N = 8507) No.	Total	%
Age, y						
<1	298	1738	17	1259	8507	15
1 to <5	339	1738	20	1526	8507	18
5 to <12	389	1738	22	1736	8507	20
12 to 18	712	1738	41	3986	8507	47
Sex						
Male	830	1738	48	4279	8507	50
Female	906	1738	52	4213	8507	50
Race						
Asian	21	1738	1	194	8507	2
Black or African American	611	1738	35	2096	8507	25
Missing/unknown	22	1738	1	301	8507	4
White	753	1738	43	3580	8507	42
Other	323	1738	19	2289	8507	27
Ethnicity						
Hispanic	287	1738	16	2401	8507	28
Non-Hispanic	1262	1738	73	4854	8507	57
Missing/unknown	189	1738	11	1252	8507	15
Preselected conditions						
Obesity[a]	254	765	33	1402	4356	32
Asthma	198	1738	11	801	8507	9
Diabetes (type 1 or 2)	32	1738	2	253	8507	3
Underlying medical conditions						
At least 1 PCCC category	432	1738	25	2205	8507	26
Cardiovascular	154	1738	9	803	8507	9
Heme/immune	162	1738	9	720	8507	8
Metabolic	134	1738	8	694	8507	8
Neuromuscular	143	1738	8	709	8507	8
Gastrointestinal	119	1738	7	649	8507	8
Kidney	88	1738	5	446	8507	5
Respiratory	80	1738	5	419	8507	5
Malignant neoplasm	48	1738	3	344	8507	4
Congenital/genetic	151	1738	9	625	8507	7
Neonatal	64	1738	4	234	8507	3
Clinical outcomes						
Severe	179	1738	10	1242	8507	15
Invasive mechanical ventilation	96	1738	6	700	8507	8
Vasopressor-inotropic support	108	1738	6	760	8507	9
ECMO	<20	1738	0	39	8507	0.5
Death/discharge to hospice	<20	1738	0	122	8507	1

gure 1. Age and Maximum Clinical Severity Distributions Over Time for Children With SARS-CoV-2



Research Letter

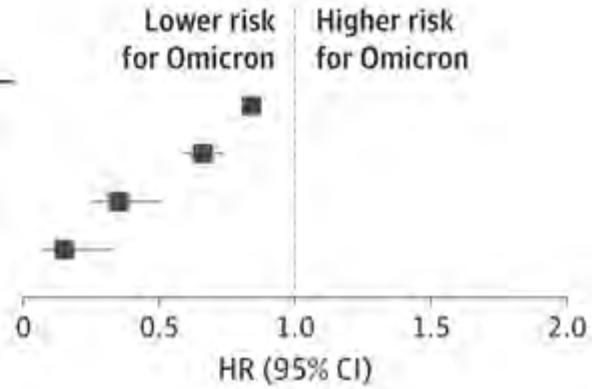
ONLINE FIRST FREE

April 1, 2022

Incidence Rates and Clinical Outcomes of SARS-CoV-2 Infection With the Omicron and Delta Variants in Children Younger Than 5 Years in the US

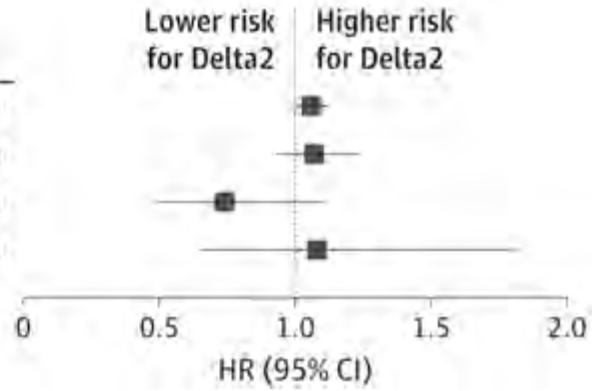
A Omicron vs Delta cohorts

Outcome	Matched Omicron cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	4637 (20.36)	5602 (24.60)	0.84 (0.80-0.87)
Hospitalizations	401 (1.76)	741 (3.25)	0.66 (0.58-0.74)
ICU admissions	38 (0.17)	115 (0.51)	0.35 (0.25-0.51)
Mechanical ventilation	10 (0.04)	51 (0.22)	0.15 (0.07-0.33)



B Delta2 vs Delta cohorts

Outcome	Matched Delta2 cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	2740 (26.33)	2614 (25.12)	1.06 (1.00–1.12)
Hospitalizations	371 (3.56)	360 (3.46)	1.07 (0.93–1.24)
ICU admissions	40 (0.38)	55 (0.53)	0.74 (0.49–1.11)
Mechanical ventilation	30 (0.29)	28 (0.27)	1.08 (0.65–1.82)



Long Covid

SARS-COV-2 Infection

Recovery

JAMA. 2020 Aug 11;324(6):603-605. doi: 10.1001/jama.2020.12603.

Persistent Symptoms in Patients After Acute COVID-19

Angelo Carfì [1], Roberto Bernabei [1], Francesco Landi [1],
Gemelli Against COVID-19 Post-Acute Care Study Group

Affiliations + expand

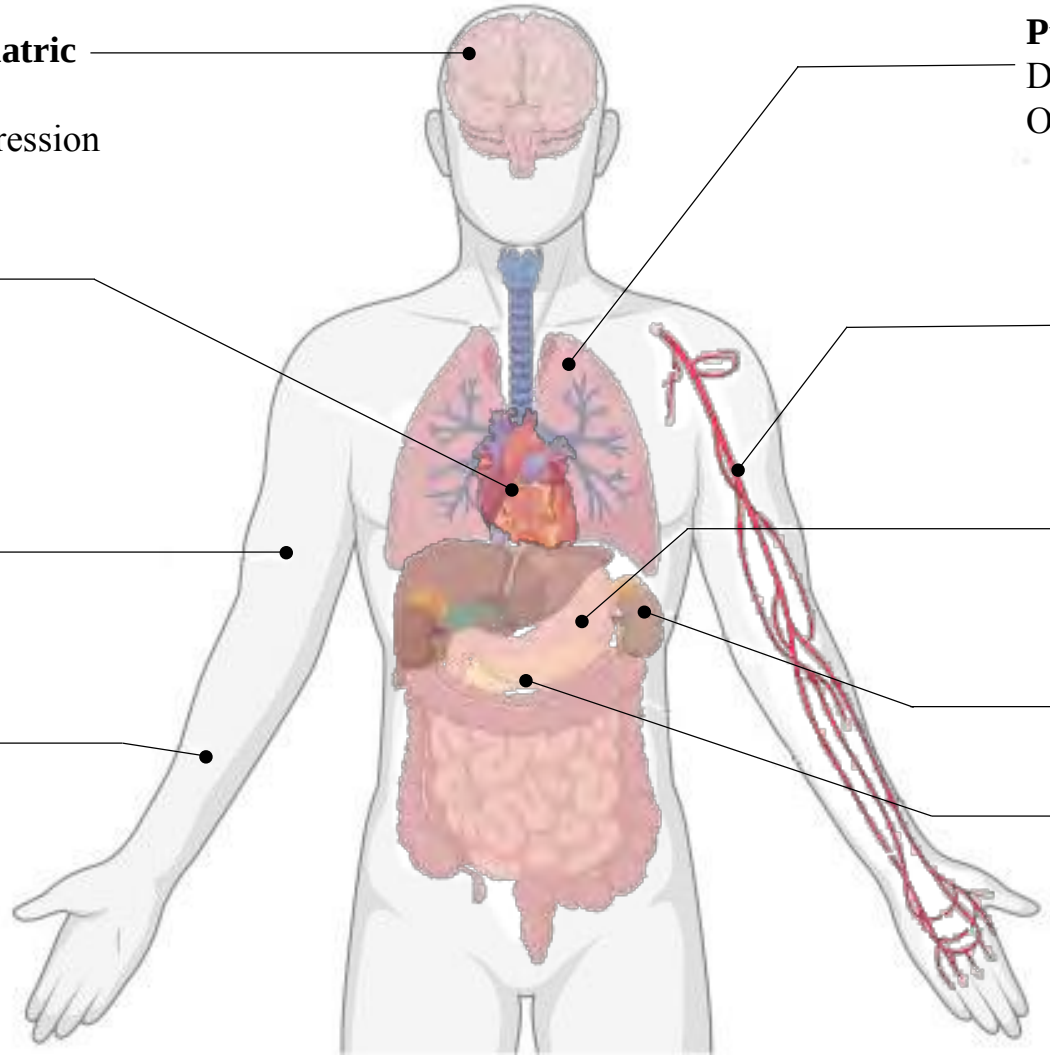
PMID: 32644129 PMCID: PMC7349096 DOI: 10.1001/jama.2020.12603

Lancet. 2021 Jan 16;397(10270):220-232. doi: 10.1016/S0140-6736(20)32656-8. Epub 2021 Jan 8.

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Chaolin Huang [1], Lixue Huang [2], Yeming Wang [3], Xia Li [4], Lili Ren [5], Xiaoying Gu [6], Liang Kang [1], Li Guo [5], Min Liu [7], Xing Zhou [4], Jianfeng Luo [4], Zhenghui Huang [4], Shengjin Tu [4], Yue Zhao [8], Li Chen [8], Decui Xu [8], Yanping Li [8], Caihong Li [8], Lu Peng [8], Yong Li [3], Wuxiang Xie [9], Dan Cui [10], Lianhan Shang [11], Guohui Fan [6], Jiuyang Xu [12], Geng Wang [13], Ying Wang [5], Jingchuan Zhong [5], Chen Wang [14], Jianwei Wang [5], Dingyu Zhang [1], Bin Cao [15]

Long Term Complications of Covid-19



Neuropsychiatric
”Brain Fog”
Anxiety/Depression
PTSD

Cardiovascular
Myocardits
Heart Failure
Arrhythmias

Musculoskeletal
Myalgia
Arthalgia

Dermatologic
Rash
Alopecia
Urticaria

Pulmonary
Dyspnea
Oxygen Depandence

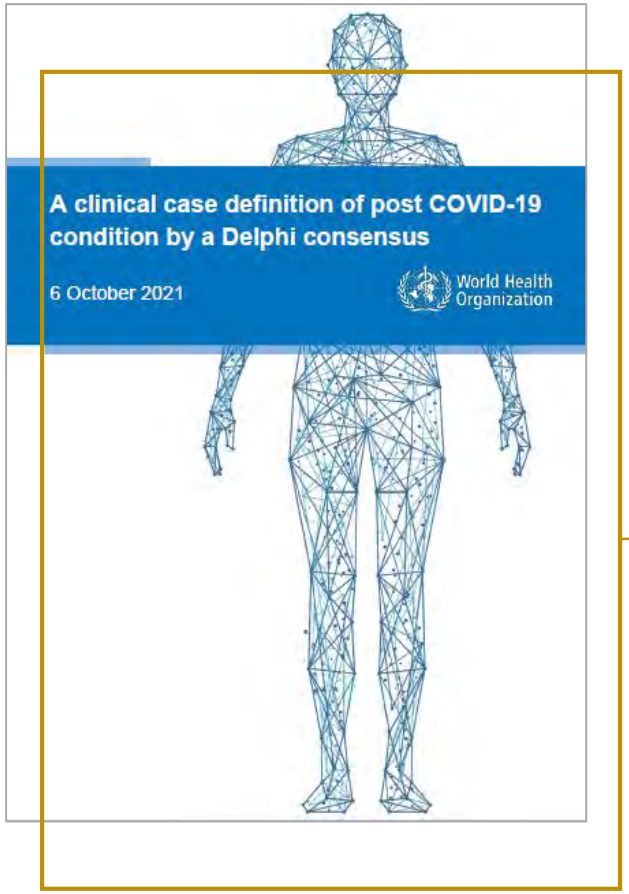
Hematologic
Venous Thromboembolism

Gastrointestinal
Diarrea
Nausea/Vomiting
Abdominal pain

Renal
Kidney Injury

Endocrine
Diabetes Mellitus

Desai AD, Lavelle M, Boursiquot BC, Wan EY. Long-term complications of COVID-19. Am J Physiol Cell Physiol. 2022 Jan 1;322(1):C1-C11. doi: 10.1152/ajpcell.00375.2021. Epub 2021 Nov 24. PMID: 34817268; PMCID: PMC8721906.



CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

NICE National Institute for Health and Care Excellence

NIH National Institutes of Health
COVID-19 Research

"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 which 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. A separate definition may be applicable for children."*

Kids?

ACTA PÆDIATRICA
NURTURING THE CHILD

BRIEF REPORT | Free Access

Preliminary evidence on long COVID in children

First published: 09 April 2021 | https://doi.org/10.1111/apa.15870 |

nature › scientific reports › articles › article

Article | Open Access | Published: 23 June 2022

Long-COVID in children and adolescents: a systematic review and meta-analyses

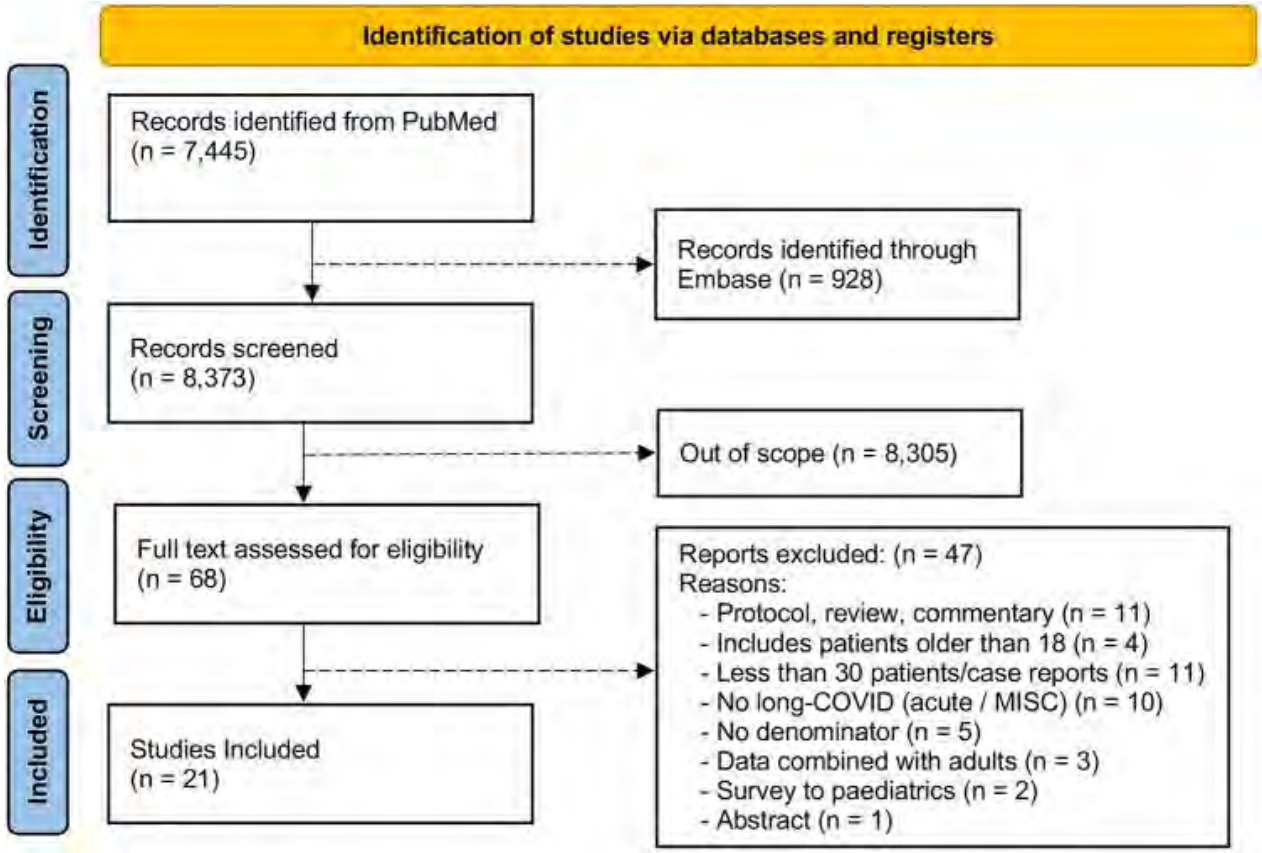
Sandra Lopez-Leon, Talia Wegman-Ostrosky, Norma Cipatli Ayuzo del Valle, Carol Perelman, Rosalinda Sepulveda, Paulina A. Rebolledo, Angelica Cuapio & Sonia Villapol

Scientific Reports **12**, Article number: 9950 (2022) | Cite this article

69k Accesses | **31** Citations | **3596** Altmetric | Metrics

Rate : **25%**

Used definition: " Presence of one or more symptoms more than 4 weeks following a SARS-CoV-2 infection "



Limitations of current studies

- Different study designs
- **Different definitions of Long Covid**
- **Different time of follow-up**
- Diff population (outpatient vs admitted)
- **Data collectins (mostly self collected)**
- Lack of long-term follow-up

Little information about:

- Prevalence
- **Risk Factors**
- **Temporal evolutions**
- **Preventive/Therapeutic strategies**

PEDIATRIC DEFINITION

Arch Dis Child. 2022 Jul;107(7):674-680. doi: 10.1136/archdischild-2021-323624. Epub 2022 Apr 1.

Long COVID (post-COVID-19 condition) in children: a modified Delphi process

Terence Stephenson [1], Benjamin Allin [2], Manjula D Nugawela [3], Natalia Rojas [3], Emma Dalrymple [3], Snehal Pinto Pereira [4], Manas Soni [5], Marian Knight [2], Emily Y Cheung [3], Isobel Heyman [3], CLoCk Consortium; Roz Shafran [3]

"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"

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

NICE National Institute for Health and Care Excellence

NIH National Institutes of Health
COVID-19 Research

‘‘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’’

Update from our Cohort in Rome

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Primary Aim

Risk Factors of

Long Covid

Seconday Aims

- Evolution
- Variants
- Vaccines

Materials and Methods

Type of study: Prospective Cohort, follow-up at 3-6-12-18 months

Setting: In presence at Out-patient Post-Covid Unit Policlinico A. Gemelli, Roma, Italia

Period: April 2020 - October 2022

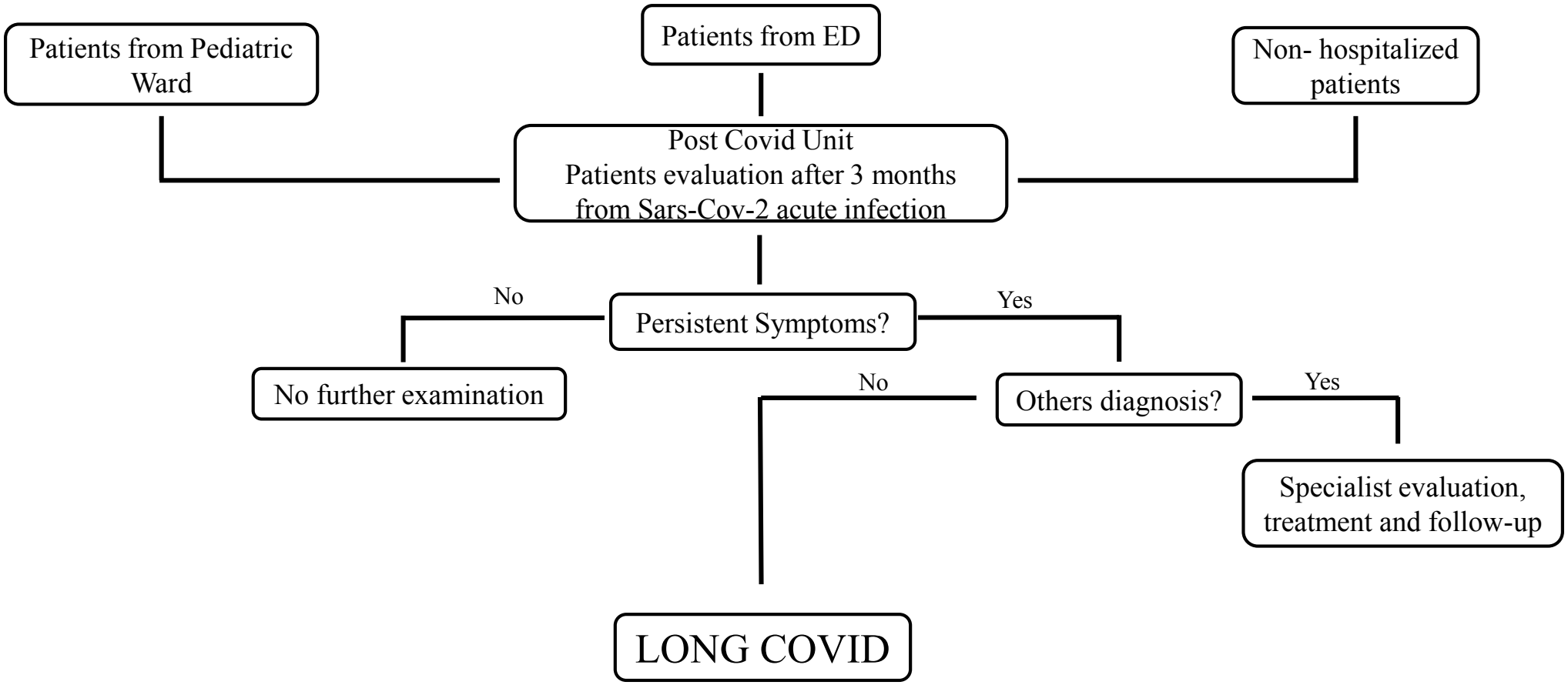
Inclusion Criteria: Children 0 a 18 years

First assessment in the outpatient Post Covid

Confirmed Sars-Cov-2 infection

Informed consent

Materiali e Metodi

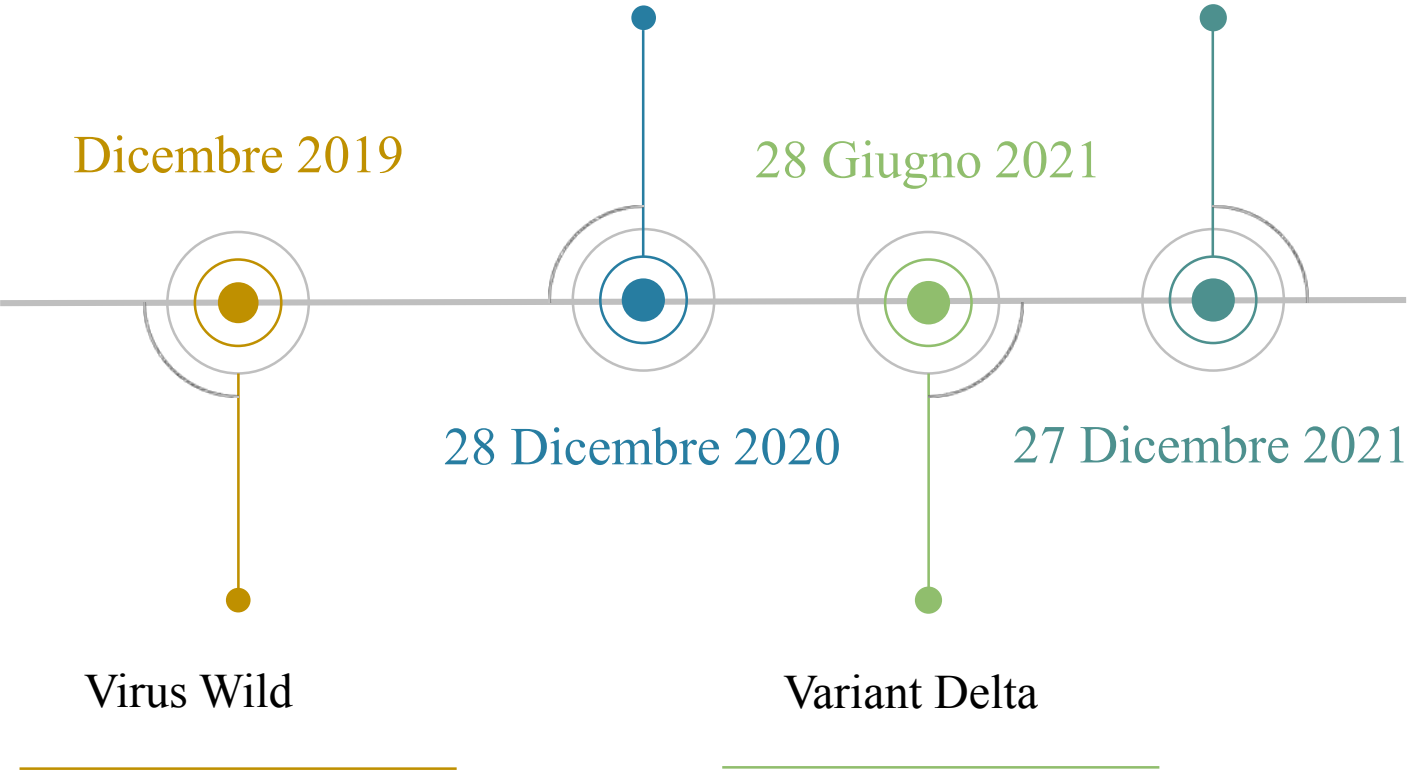


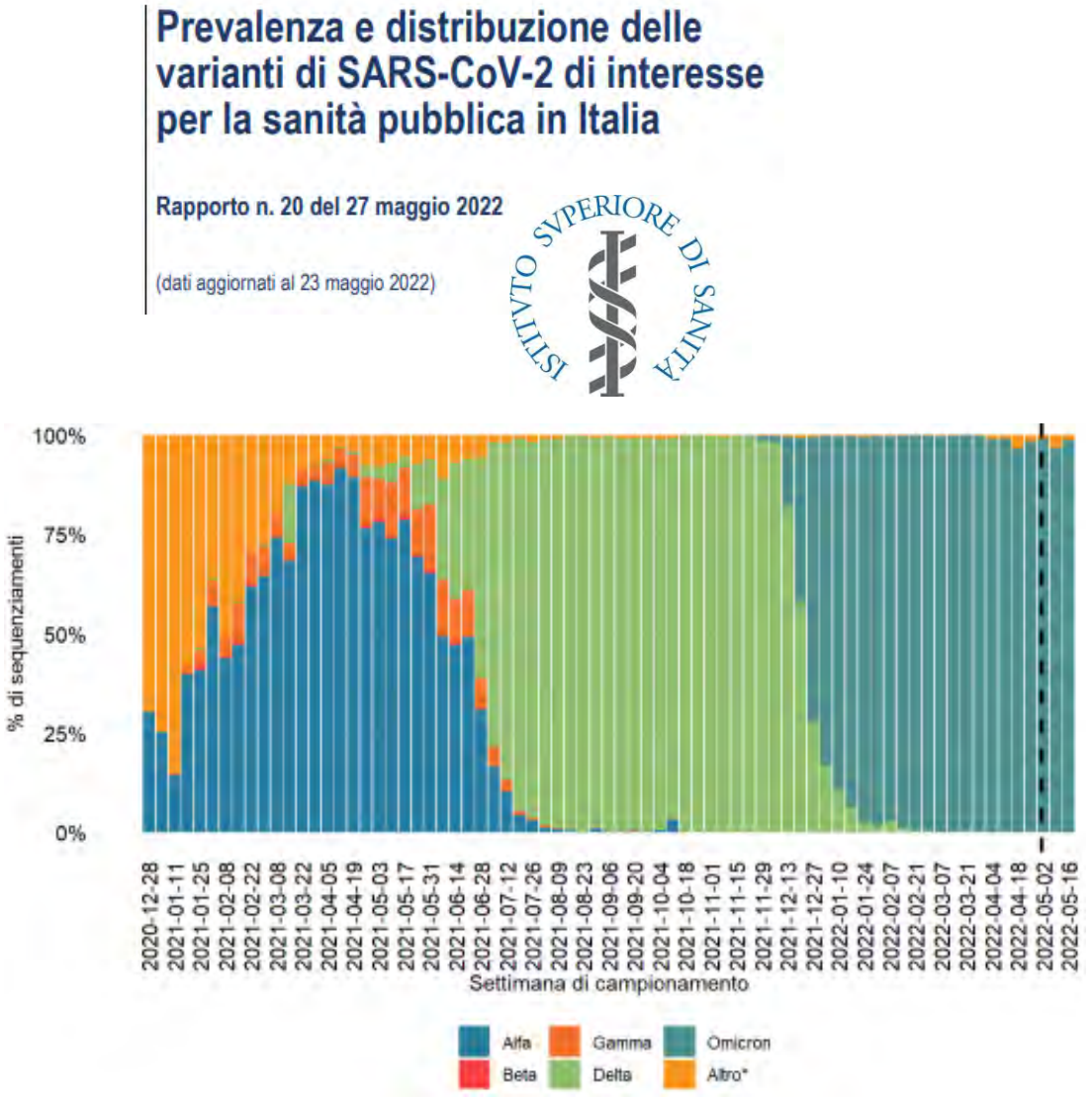
Materiali e Metodi

Informazioni raccolte

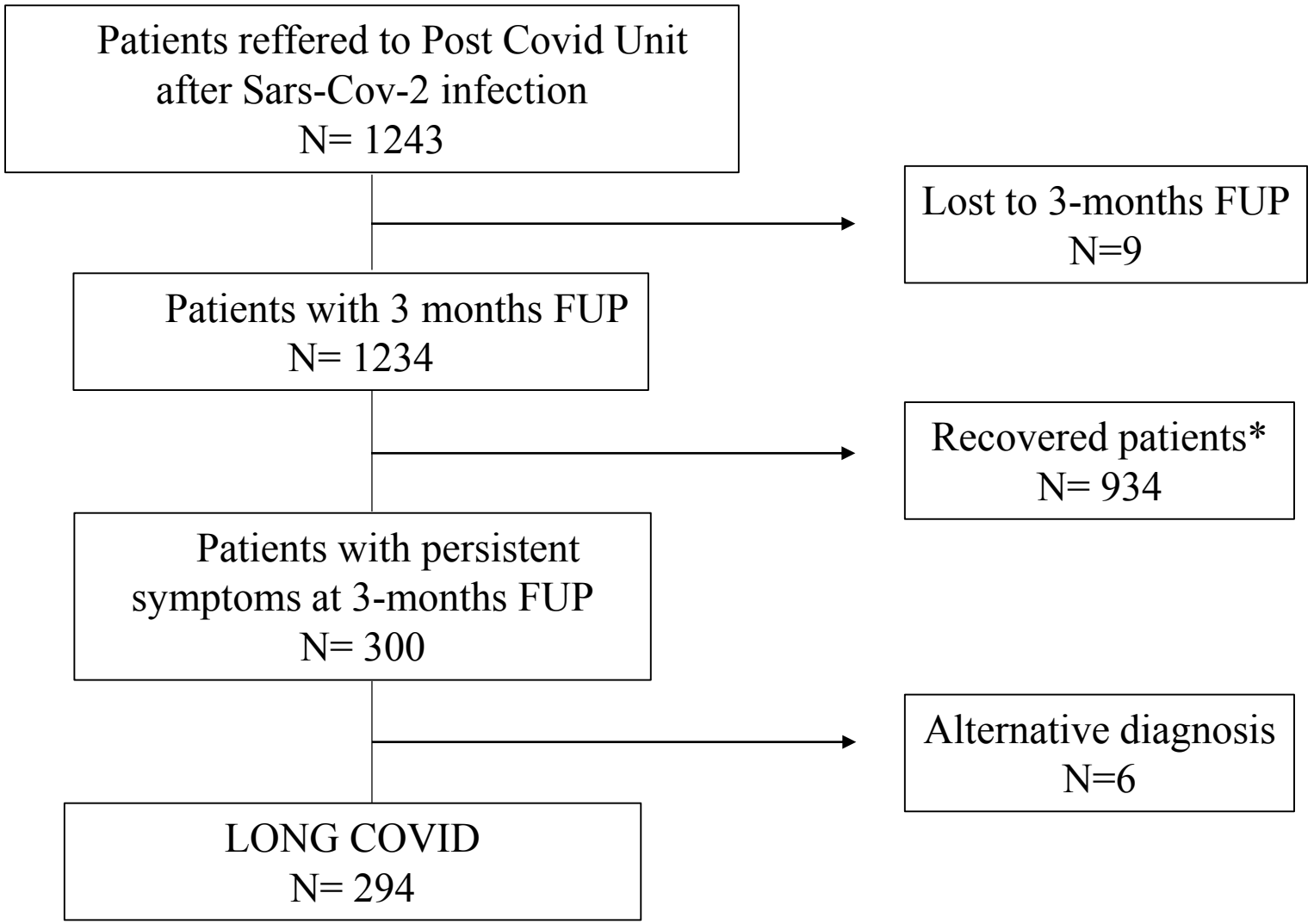
- Age
- Gender
- Comorbidities
- Date of infection and circulating variants
- Symptoms during acute infection
- Severity/Need of admission
- Outcome acute infection (recovery vs persistence)
- Covid-19 vaccines
- Therapy

Materiali e Metodi





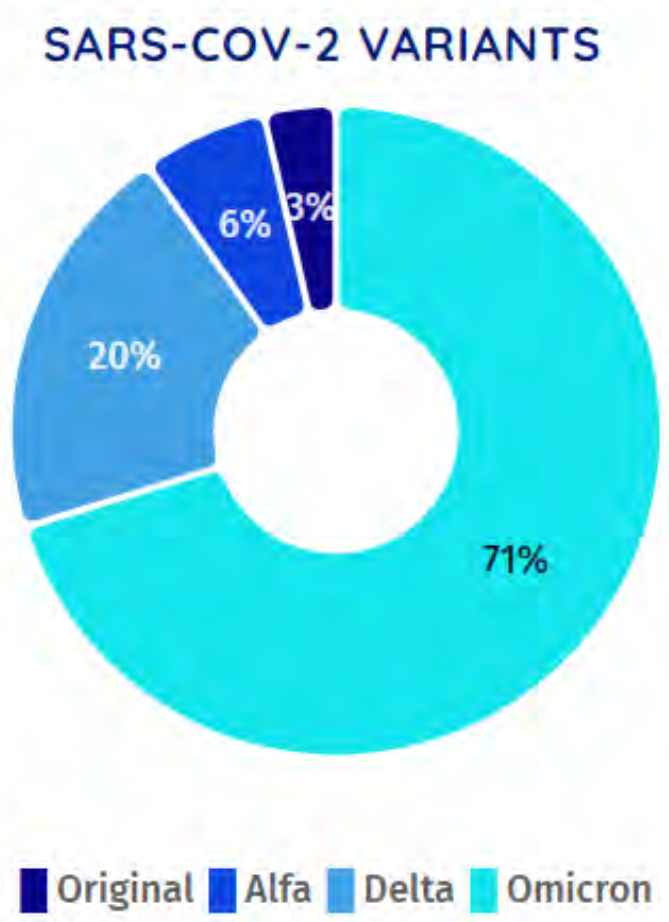
Risultati

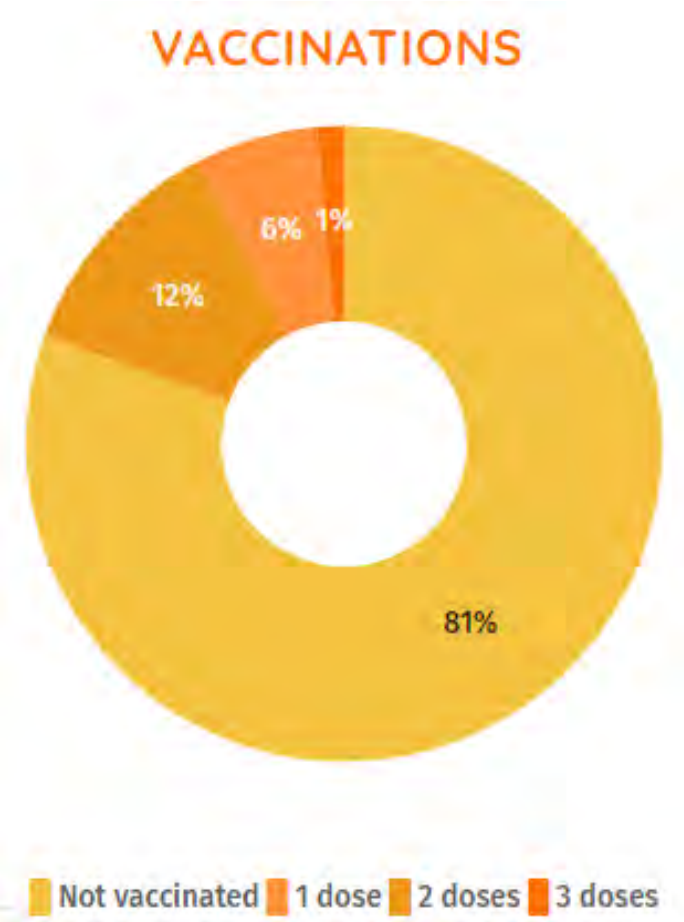


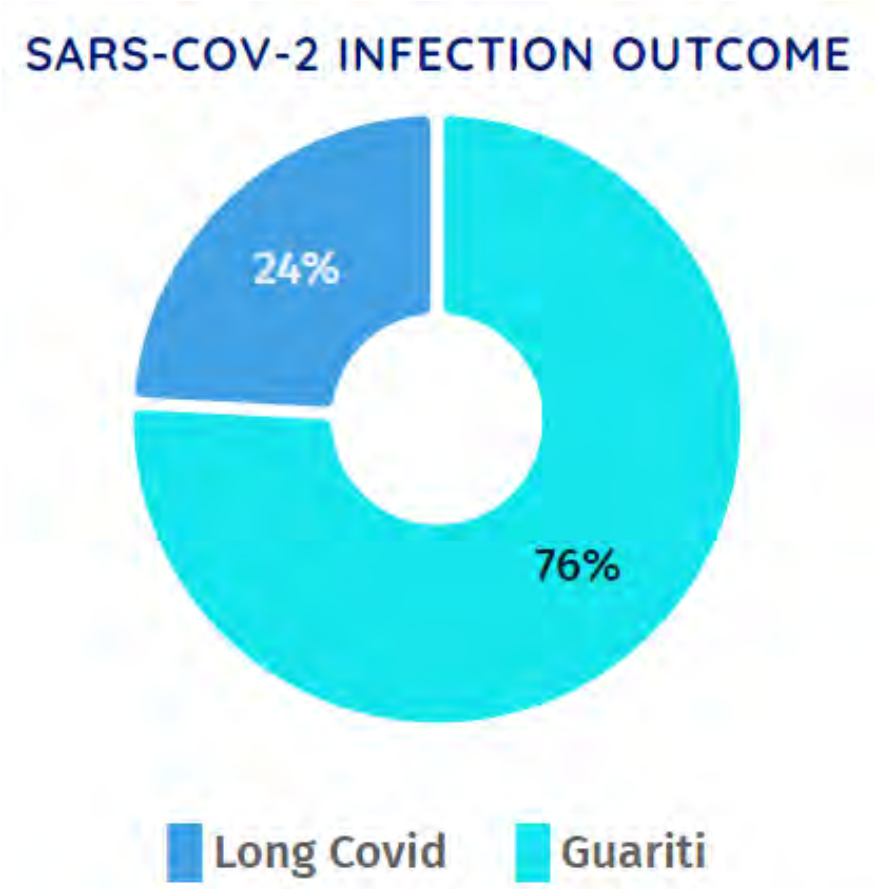
*Definition= disappearance of symptoms or persistence of mild symptoms not limiting daily activities, school or sports

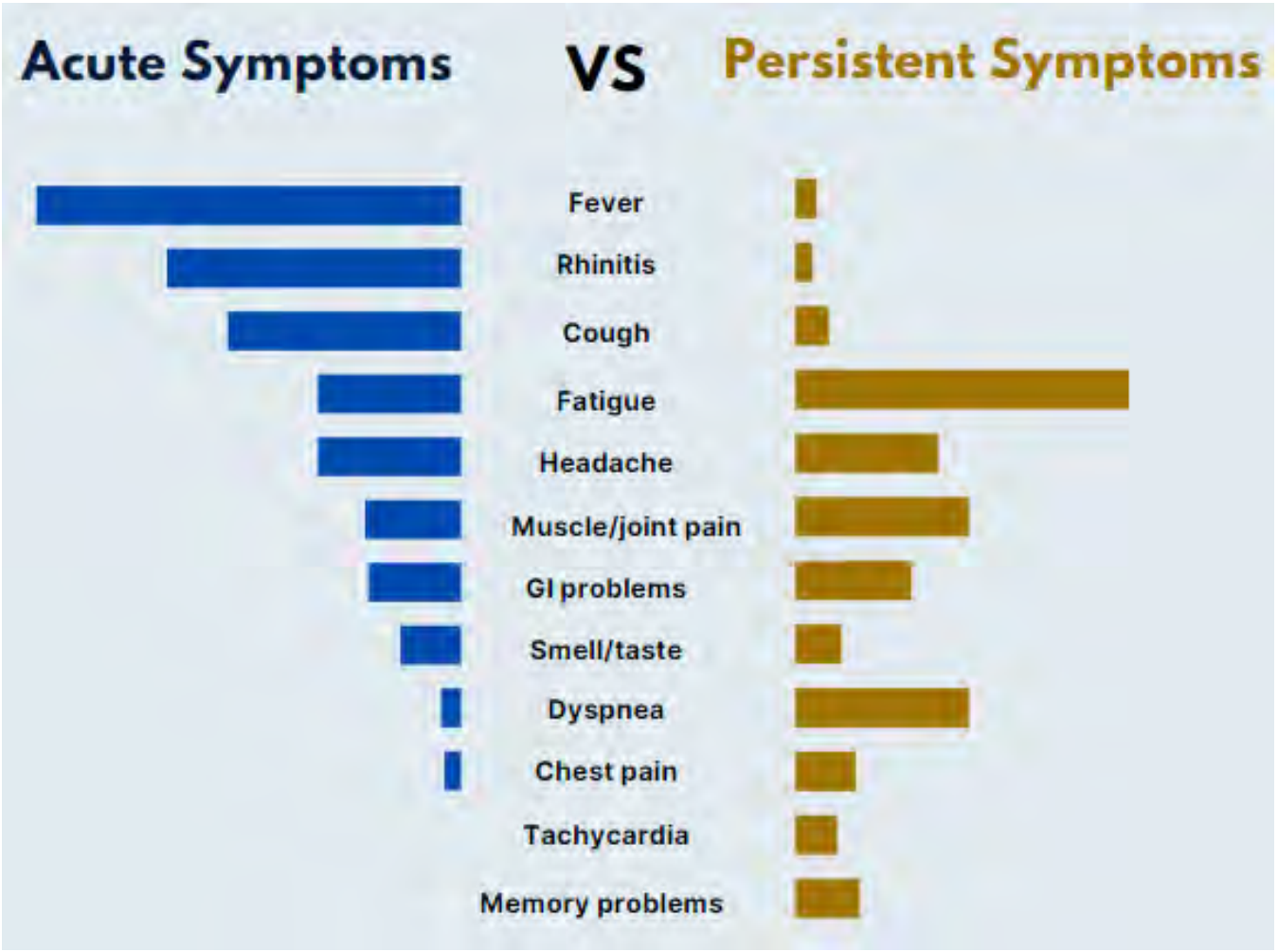
Results

	Entire Cohort (N=1243)
Age (years), median	7,25
Female, n (%)	575 (46,3%)
Comorbidities, n (%)	164 (13,2%)
Asymptomatic, n (%)	109 (8,8%)
Hospitalized, n (%)	28 (2,2%)






SARS-COV-2 INFECTION OUTCOME
24%
76%
Long Covid
Guariti


Acute Symptoms
VS
Persistent Symptoms
Fever
Rhinitis
Cough
Fatigue
Headache
Muscle/joint pain
GI problems
Smell/taste
Dyspnea
Chest pain
Tachycardia
Memory problems

	Univariate OR (95% CI)	P	*R2 di Nagelkerke*	Multivariable OR (95% CI)	p
Female*	1,24 (0,96 - 1,62)	0,100	0,003		
Age (years)	1,24 (1,19 – 1,28)	<0,001	0,176	1,23 (1,18 – 1,28)	<0,001
Age higher than 10 years	3,79 (2,87 - 5,01)	<0,001	0,103		
Comorbidities	1,73 (1,21 - 2,48)	0,003	0,011	1,68 (1,14 – 2,50)	0,09
Asymptomatic	0,40 (0,22 - 0,73)	0,003	0,013	0,46 (0,24 – 0,85)	0,013
Original COVID variant	3,37 (1,81 - 6,26)	<0,001	0,017		
Alfa COVID variant	3,73 (2,32 - 6,00)	<0,001	0,034		
Delta COVID variant	1,18 (0,86 - 1,63)	0,310	0,001		
Omicron COVID variant	0,47 (0,36 – 0,62)	<0,001	0,035	0,60 (0,45 – 0,81)	0,001
Vaccination performed	1,96 (1,44 – 2,67)	<0,001	0,022		
Vaccination completed	1,87 (1,31 – 2,67)	0,001	0,014		
Hospitalization during the acute phase	2,62 (1,21 – 5,67)	0,014	0,007	4,80 (1,91 – 12,1)	0,001

Risultati: Varianti

	Multivariable OR (95% CI) for 3 months follow-up	p	Multivariable OR (95% CI) for 6 months follow-up	p
Omicron SARS-Cov2 variant	-	-	-	-
Wild SARS-Cov2 variant	4,12 (2,20-7,72)	<0,001	8,59 (4,31-17,11)	<0,001
Alfa SARS-Cov2 variant	4,35 (2,68-7,07)	<0,001	9,88 (5,80-16,83)	<0,001
Delta SARS-Cov2 variant	1,47 (1,06-2,05)	0,0219	1,98 (1,27-3,09)	0,003

In multivariate logistic regression, compared to the Omicron variant, all other variants were significantly associated with higher rate of persistence of symptoms at 3 and 6 months.

Risultati: Vaccini

FUP 3 months

	Healed patients (n=464)	Long Covid patients *(n=149)*	OR*** (95% CI)	p
Vaccination performed*	110 (23,7%)	32 (21,5%)	0,88 (0,56 - 1,37)	0,575
Vaccination completed**	68 (14,7%)	14 (9,4%)	0,60 (0,33 - 1,11)	0,104

	Healed patients (n=127)	Long Covid patients *(n=112)*	OR*** (95% CI)	p
Vaccination performed*	46 (36,2%)	49 (43,8%)	1,37 (0,81 - 2,30)	0,236
Vaccination completed**	36 (28,3%)	40 (35,7%)	1,40 (0,81 - 2,43)	0,223

FUP 6 months

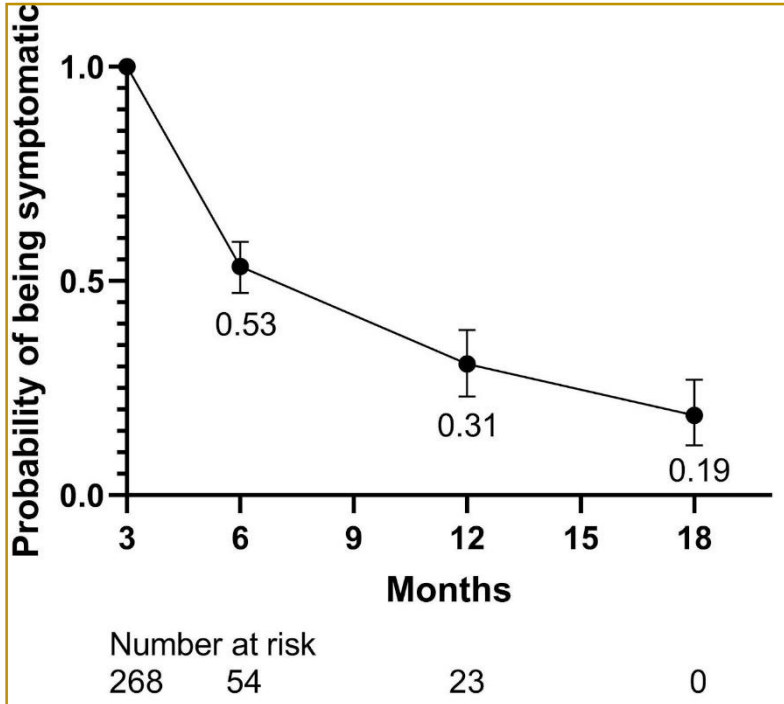
	Healed patients (n=523)	Patients with persistence of symptoms at 6 months *(n=68)*	OR*** (95% CI)	p
Vaccination performed*	125 (23,9%)	10 (14,7%)	0,55 (0,27 - 1,11)	0,093
Vaccination completed**	70 (13,4%)	5 (7,4%)	0,51 (0,20 - 1,32)	0,167

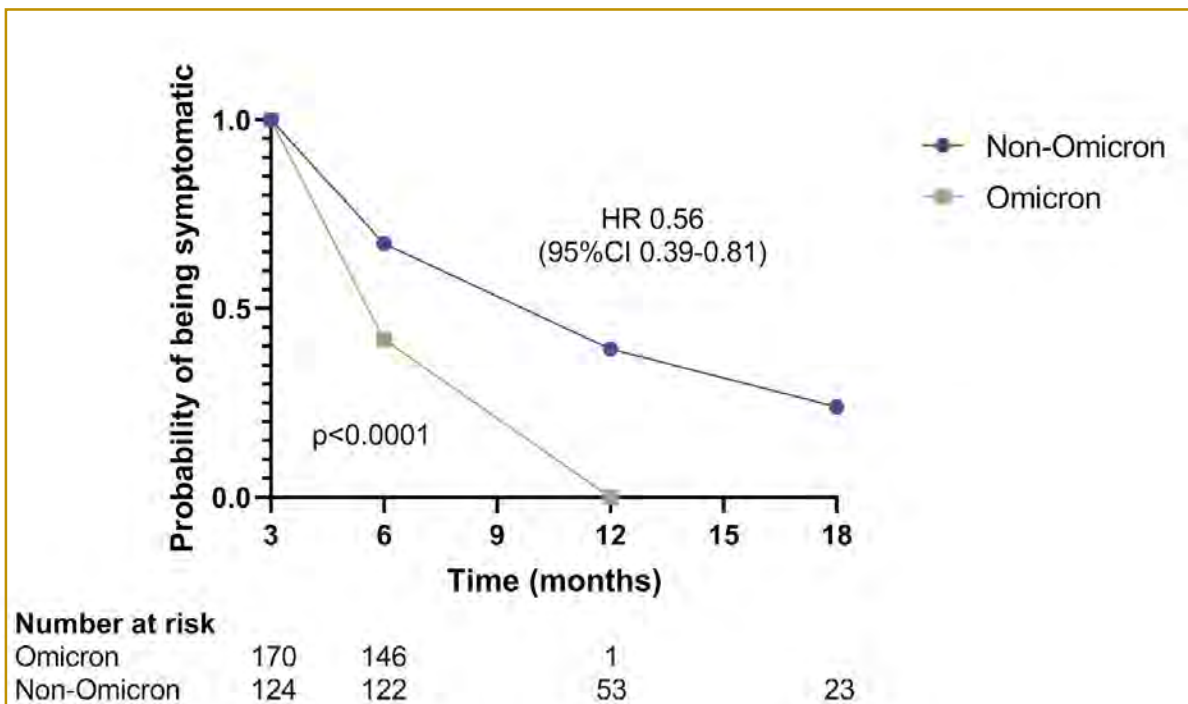
	Healed patients (n=156)	Patients with persistence of symptoms at 6 months *(n=63)*	OR*** (95% CI)	p
Vaccination performed*	63 (40,4%)	19 (30,2%)	0,64 (0,34 - 1,19)	0,159
Vaccination completed**	49 (31,4%)	14 (22,2%)	0,62 (0,32 - 1,24)	0,176

5-11 anni

> 11 anni

Risultati: Evoluzione temporale





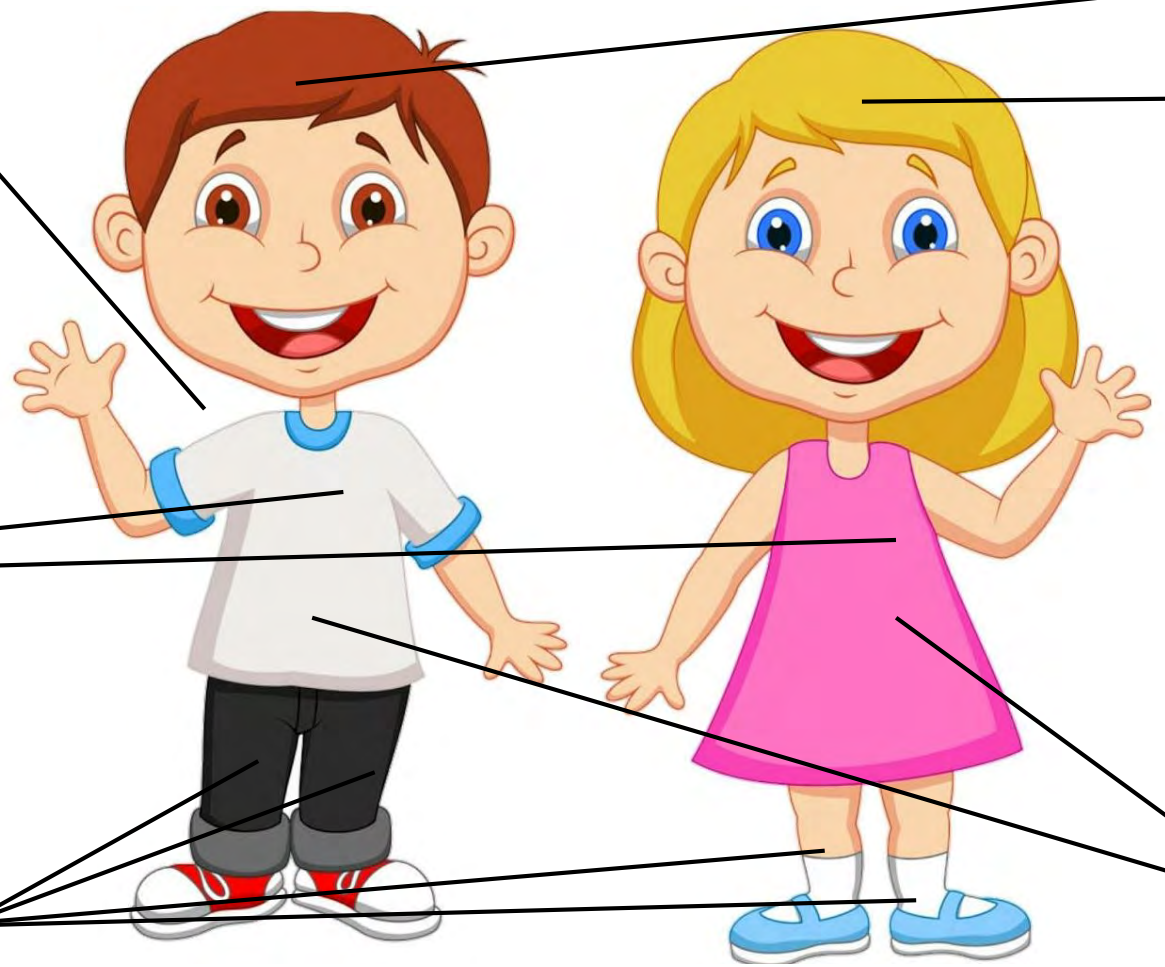
Conclusions (part 1)

- Confirmed long-term impact of Long Covid in children
- Clinical symptoms in line with literature
- Some patients have symptoms for more than a year
- Risk factors (age, comorbidities, hospitalization) and variants (alfa>wild>delta)
- Partial effect of 2 doses of vaccination, need of other strategies
- Need of biomarkers and diagnostic tests (follow this space…)

Fatigue
PEM
Tachycardia
Chest pain

Myopericarditis

Arthalgias and muscle pain



Neuropsychiatric Symptoms

Chronic headache
Difficult concentrating
Brain Fog

New onset subacute neuropsychiatric disease

Gastrointestinal Symptoms

(recurrent abdominal pain,
Nausea
Irregular alvus)

What to do for these children!?!?!?!

1- Don’t know (yet)!!

2- Recognize the problem and offer CARE to the family

3- Establish health services and partnerships FAMILY DOCTORS / HOSPITAL / FAMILIES

4- Develop local guidelines to be implemented regularly as new advances are achieved

5- Open-minded international collaborations to advance knowledge in the field

What to do for these children!?!?!?!

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VIEWPOINT: COVID-19

The road to addressing Long Covid

Reporting, recognizing, and researching the chronic effects of COVID-19 will help those affected

By **Nisreen A. Alwan**[1,2]

Meeting the need of Long Covid

The public health response to the COVID-19 pandemic needs to adequately address the direct long-term effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the context of the ongoing pandemic. An adequate response should incorporate the 4 Rs: Reporting, Recognition (including Rehabilitation), and Research.

- Universal and frequently updated case definitions
- Disease registries
- Follow-up after infection to assess recovery
- Pandemic and postpandemic morbidity surveillance systems
- Direct link to prevention policy decisions
- Informing health and social care planning

- Listening, believing, and avoiding stereotypes.
- Thorough clinical assessment and investigations
- Inclusive diagnostic criteria
- Personalized treatment and rehabilitation
- Equitable care pathways
- Multidisciplinary care
- Employment rights and occupational health

- Risk factors
- Prognosis and progression
- Predictors of recovery
- Pathophysiology
- Therapeutics
- Role of vaccination
- Reinfection
- Inequalities and stigma
- Economic and services burden
- Long Covid in children

What to do for these children!?!?!?!

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A conceptual framework to accelerate the clinical impact of evolving research into long COVID

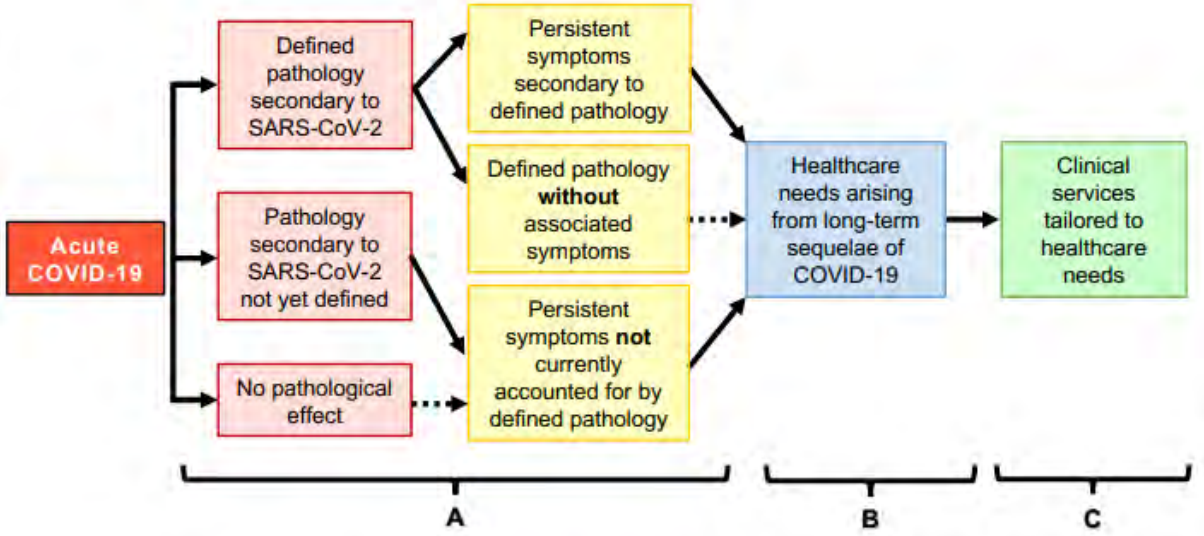

Figure 1. The relationship between symptoms and pathology after acute COVID-19 and how this can inform research and healthcare planning.

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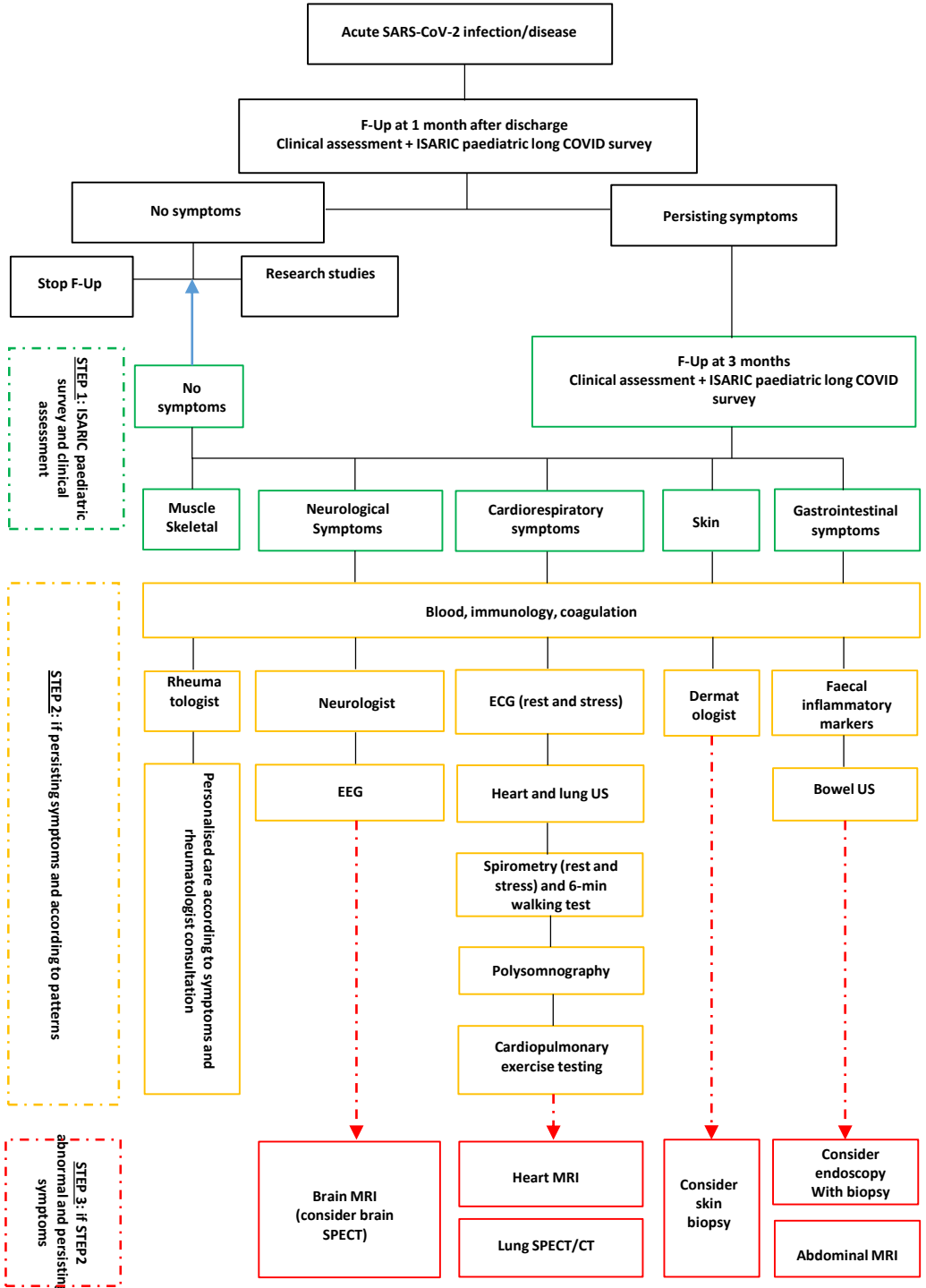
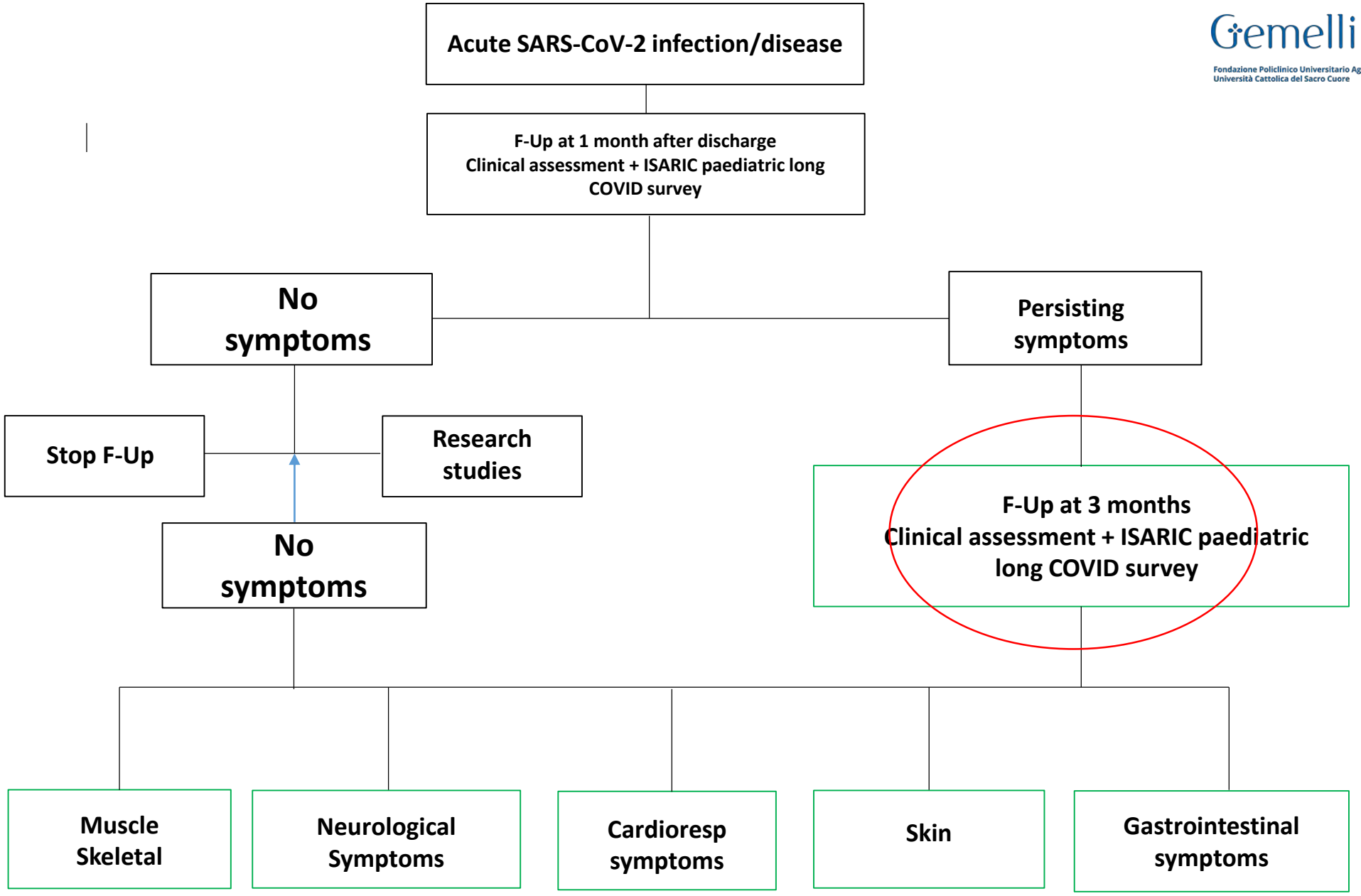


Wait and see up to 3 months (self recover?), but showing the family your support in the meantine, and that a team will take care of their needs

Personalized approach, investigating

- Either other causes
- Organ / immune damage related to SARS-CoV-2 infection

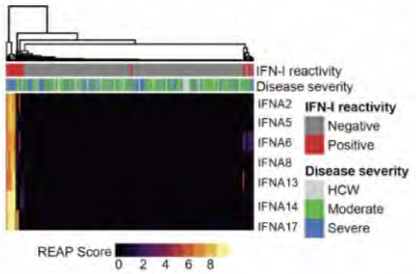
STEP 1: ISARIC paediatric survey and clinical assessment

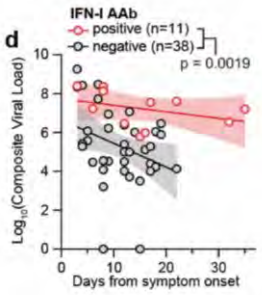


Immune profile of children with post-acute sequelae of SARS-CoV-2 infection (Long Covid)

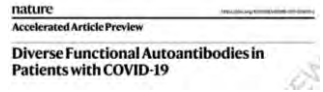
Why Post Covid-19 Condition?

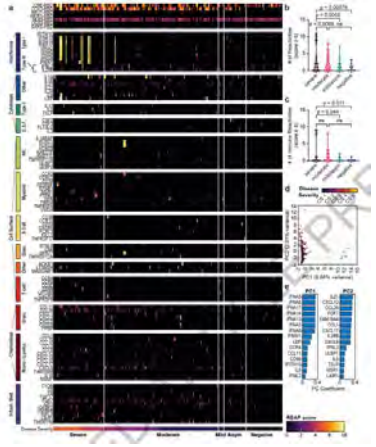
Autoantibodies to IFN-I leads to failure to control virus

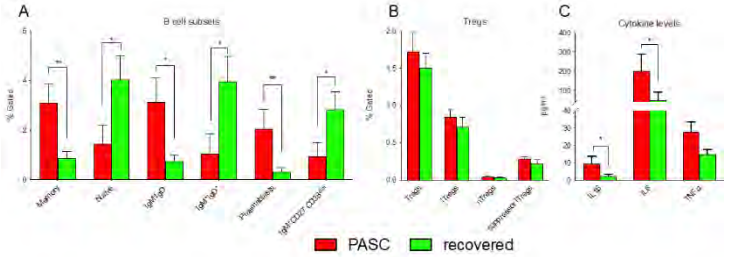




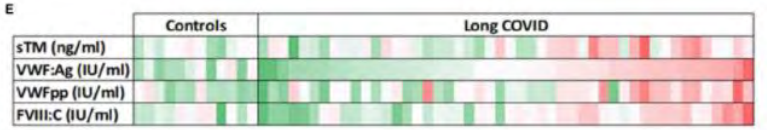
Iwasaki et al


nature
Accelerated Article Preview
Diverse Functional Autoantibodies in Patients with COVID-19

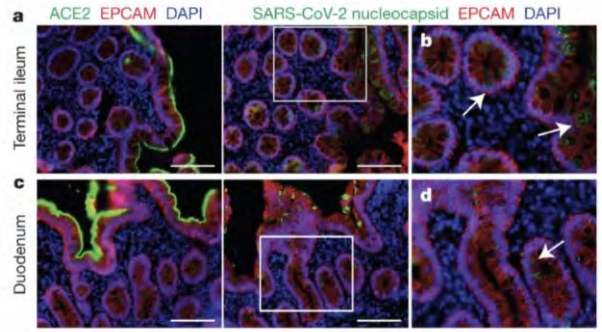




Persistent endotheliopathy in the pathogenesis of long COVID syndrome

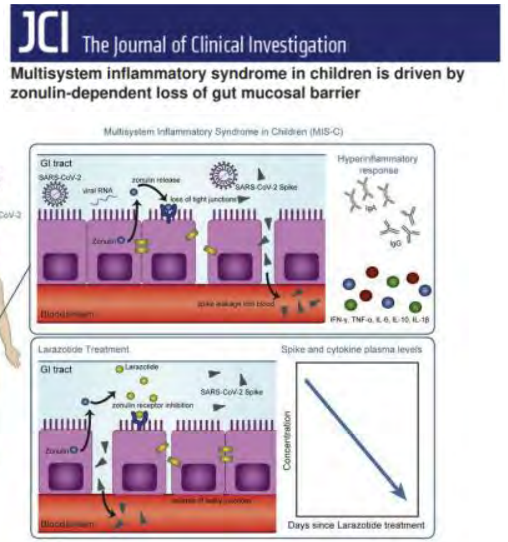


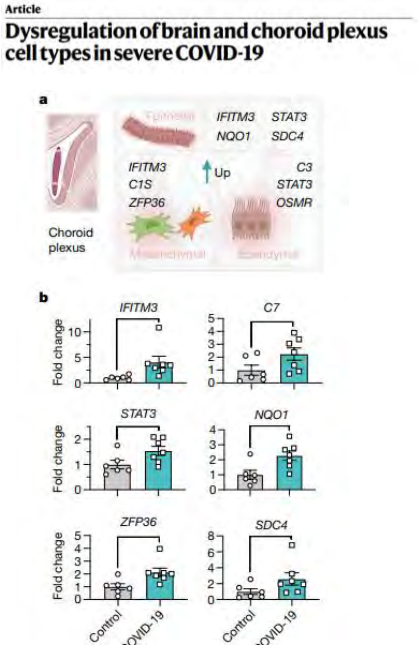
Viral reservoirs have been seen in COVID



Intestinal biopsy 92 days from symptom onset
(5/14 patients had positive staining after 3 months)

Gaebler, C., Wang, Z., Lorenzi, J.C.C. *et al.* Evolution of antibody immunity to SARS-CoV-2. *Nature* **591**, 639–644 (2021).


JCI The Journal of Clinical Investigation
Multisystem inflammatory syndrome in children is driven by zonulin-dependent loss of gut mucosal barrier


Article
Dysregulation of brain and choroid plexus cell types in severe COVID-19

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Muscle Skeletal | Neurological Symptoms | Cardioresp symptoms | Skin | Gastrointestinal symptoms

Blood, immunology, coagulation

Rheumatologist | **Neurologist** | ECG (rest and stress) | Dermatologist | Faecal inflammatory markers

Personalised care according to symptoms and rheumatologist consultation

EEG

Heart and lung US

Spirometry (rest and stress) and 6-min walking test

Polysomnography

Cardiopulmonary exercise testing

Bowel US

Brain MRI (consider brain SPECT) LP?

Heart MRI

Lung SPECT/CT

Consider skin biopsy

Abdominal MRI

Consider endoscopy With biopsy

STEP 2: if persisting symptoms and according to patterns

STEP 3: if STEP2 abnormal and persisting symptoms

These steps requires a few months!!!!!

Challenges in younger children!!!!!

Cardiopulmonary exercise testing (CPET)

- on a cycloergometer with a WATT Ramp protocol
- Functional global cardiorespiratory capacity (VO2 peak)
- **Signs of cardiac limitation** (VO2 / work - HR max - VO2 / HR)
- **Locomotor muscle dysfunction**
- Anaerobic threshold (AT)
- Signs of **pulmonary vascular disease with or whitout pulmonary hypertension** (VE / VCO2 slope - PETCO2 teleinspiratory pressure for CO2)
- Signs of **inefficient ventilation** (BR breathing reserve - Basal and peak SatO2)
- Arrhythmias and signs of **reduced coronary reserve** (ECG)
- Blood pressure
- Signs and symptoms of dyspnoea, muscle fatigue and reduced coronary reserve

P	SPECT: Details of abnormal Distribution pattern	CPET: muscolar deconditioning and fatigue	CPET: Likehood of pulmonary vasculopathy (VE/VCO2 slope)	CPET: cardiogenic efficiency (pulse of O2)	functional capacity (VO2 peak)
1	non homogeneous distribution with localized perfusion defect	Mild	likely	Reduced	Moderate reduction
2	normal	moderate	unlikely	Reduced	Normal?
3	non homogeneous distribution with localized perfusion defect	Severe	unlikely	Reduced	Moderate reduction
4	normal	Moderate with desaturation	unlikely	normal	normal
5	non homogeneous distribution	moderate	unlikely	reduced	mild reduction
6	normal	moderate	unlikely	reduced	mild reduction
7	non homogeneous distribution	moderate	unlikely	normal	normal
8	normal	moderate	not evaluable for early fatigue and pains	not evaluable for early fatigue and pains	not evaluable for early fatigue and pains
9	normal	Mild	suspected	normal	normal
10	non homogeneous distribution	Severe	suspected	normal	normal
11	normal	moderate	unlikely	reduced	mild reduction
12	normal	Severe	unlikely	reduced	severe reduction
13	normal	moderate	suspected	normal	normal

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†

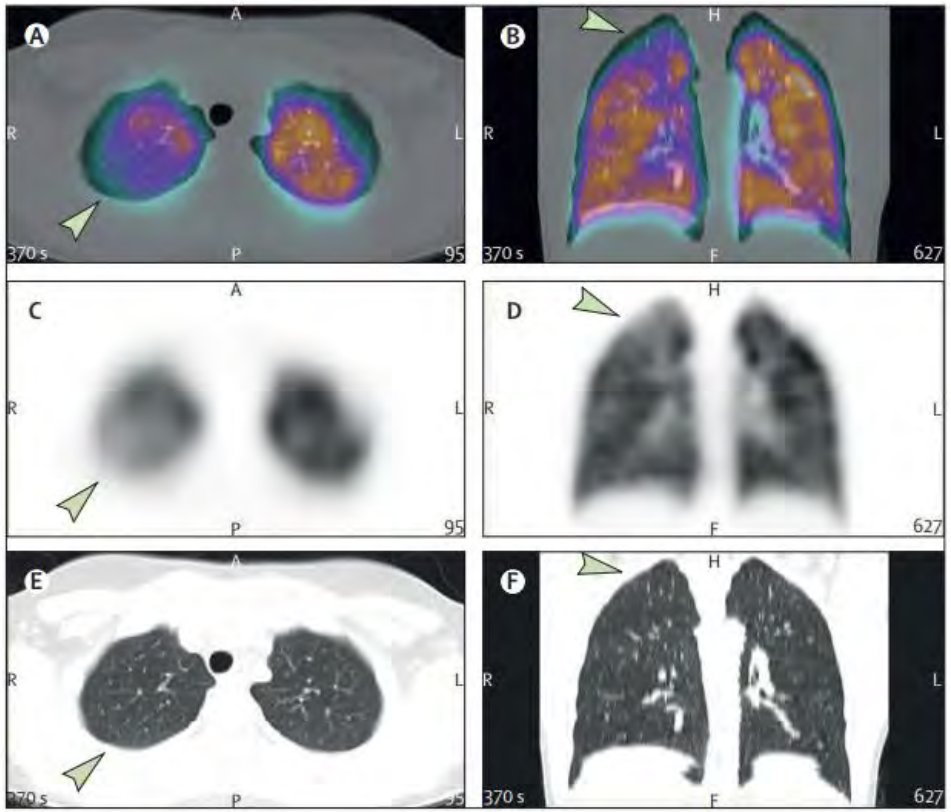
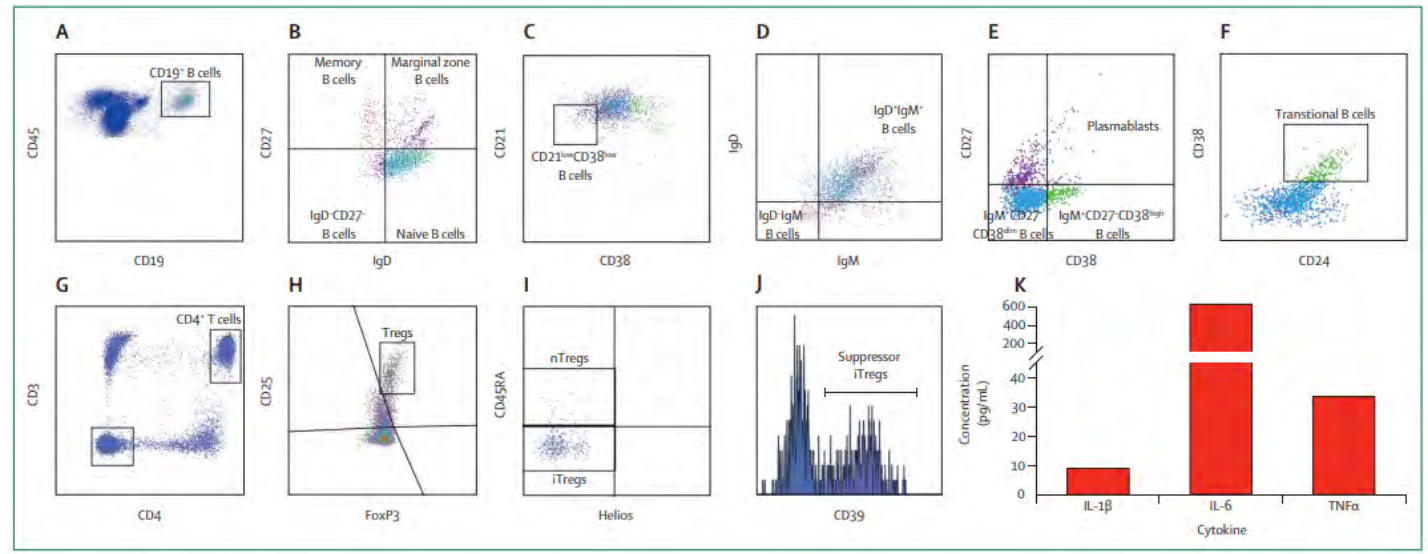
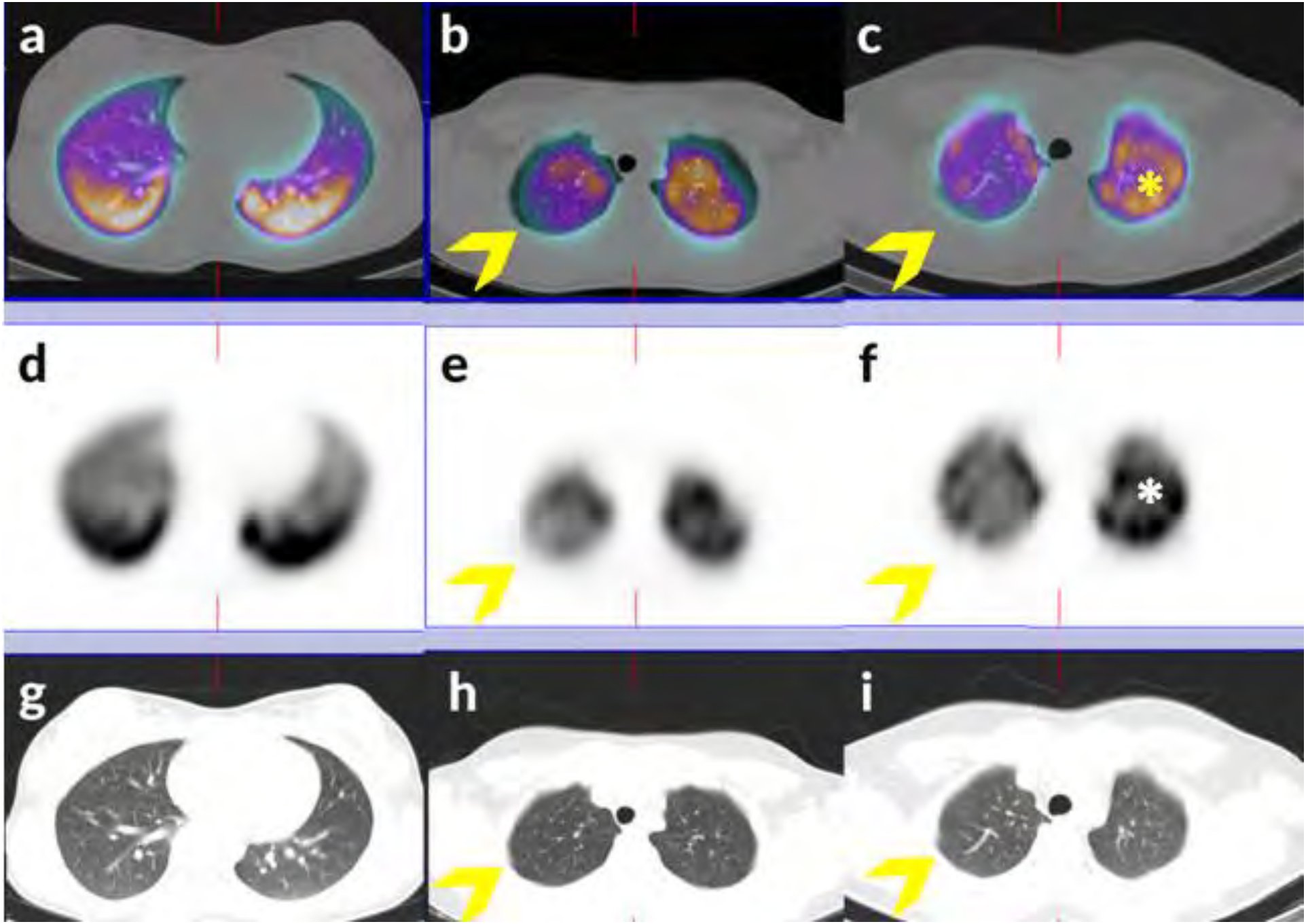


Figure 2: **Lung SPECT/CT**
Lung SPECT/CT scan with ^{99m}Tc-macroaggregated albumin showed hypoperfusion in the apical segment of the right upper lobe, clearly evident on axial and coronal hybrid images (A, B; arrow) as well as on functional slices (C, D; arrow). This finding did not correspond to parenchymal alterations on co-registered CT images (E, F; arrow). SPECT/CT=single photon emission computed tomography with co-registered CT.





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European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05528-4

ORIGINAL ARTICLE

Similar patterns of [^{18}F]-FDG brain PET hypometabolism in paediatric and adult patients with long COVID: a paediatric case series

Aurelie Morand[1,2] · Jacques-Yves Campion[3] · Anne Lepine[1] · Emmanuelle Bosdure[1] · Léa Luciani[4] · Serge Cammilleri[3] · Brigitte Chabrol[1] · Eric Guedj[3]

Received: 15 July 2021 / Accepted: 6 August 2021

Abstract

Purpose Several weeks after COVID-19 infection, some children report the persistence or recurrence of functional complaints. This clinical presentation has been referred as "long COVID" in the adult population, and an [^{18}F]-FDG brain PET hypometabolic pattern has recently been suggested as a biomarker. Herein, we present a retrospective analysis of 7 paediatric patients with suspected long COVID who were explored by [^{18}F]-FDG brain PET exam. Metabolic brain findings were confronted to those obtained in adult patients with long COVID, in comparison to their respective age-matched control groups.

Methods Review of clinical examination and whole-brain voxel-based analysis of [^{18}F]-FDG PET metabolism of the 7 children in comparison to 21 paediatric controls, 35 adult patients with long COVID and 44 healthy adult subjects.

Results Despite lower initial severity at the acute stage of the infection, paediatric patients demonstrated on average 5 months later a similar brain hypometabolic pattern as that found in adult long COVID patients, involving bilateral medial temporal lobes, brainstem and cerebellum (p-voxel < 0.001, p-cluster < 0.05 FWE-corrected), and also the right olfactory gyrus after small volume correction (p-voxel = 0.010 FWE-corrected), with partial PET recovery in two children at follow-up.

Conclusion These results provide arguments in favour of possible long COVID in children, with a similar functional brain involvement to those found in adults, regardless of age and initial severity.

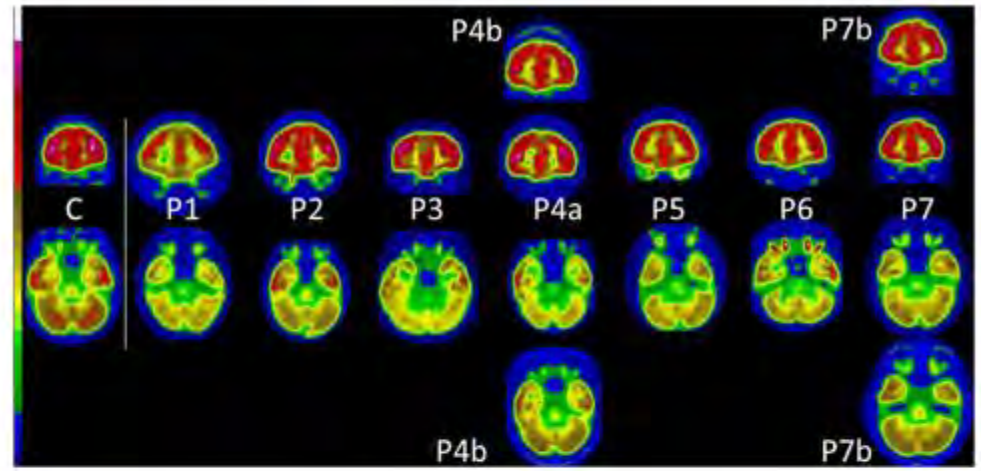


Fig. 1 Individual [^{18}F]-FDG PET of each of the seven children patients (P1 to P7), including the follow-up of two of them (P4b and P7b). *An example of normal PET metabolism in a child of 10 years old is also presented (C). Hypometabolism is found in olfactory regions for children #1,3,4,5,6; in temporal regions for children #1,3,4,5,6,7; in the brainstem for children #1,3,4,5,6,7; in the cerebellum for all children. At follow-up, the brain metabolism was improved at least for the brainstem*

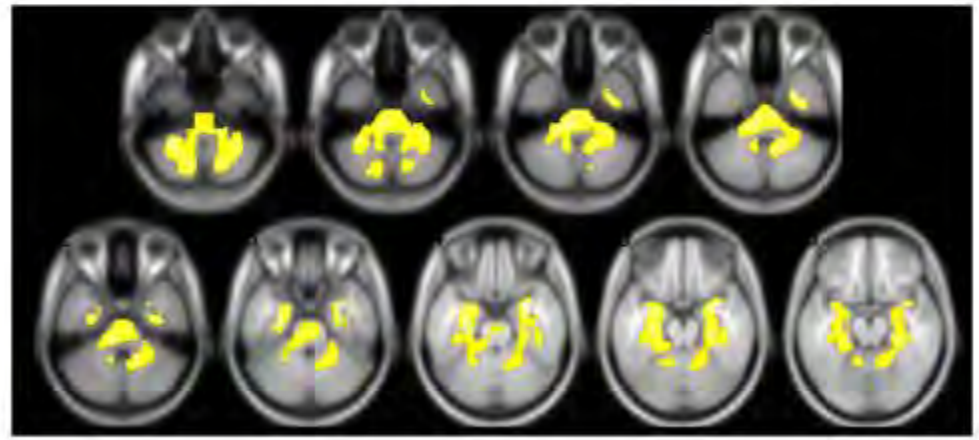


Fig. 2 Brain [^{18}F]-FDG PET hypometabolism in paediatric patients with long COVID. *In comparison to paediatric controls, children with long COVID exhibited hypometabolism in bilateral medial lobes, the pons and cerebellum (p-voxel < 0.001, p-cluster < 0.05 FWE-corrected), and also in the right olfactory gyrus after small volume correction (p-voxel = 0.010 FWE-corrected; not shown in these slices). Findings are presented in axial MR slices (the left hemisphere is on the left side, anatomical convention)*

	Patient 1	Patient 2	Patient 3
Age	**13**	**14**	**13**
Gender	**Female**	**Male**	**Female**
Covid-19 vaccination before infection	**Not vaccinated**	**Not vaccinated**	**Not vaccinated**
Severity of acute disease	**Mild**	**Mild**	**Mild**
Signs and symptoms			
Fever	**Yes**	**Yes**	**Yes**
Days of fever	**7**	**2**	**2**
Cough	No	No	No
Gastrointestinal	No	No	No
Headache	**Yes**	No	No
Anosmia	No	No	**Yes**
Dysgeusia	No	**Yes**	**Yes**
Memory problems	No	No	No
Concentration problems	No	No	No
Fatigue			
Pain (muscle/joints)	**Yes**	No	No
Rash	**Yes**	No	No
	Yes	No	No
Distance from acute infection (days) at PET scan	**100**	**150**	**185**
Time from SARS-CoV-2 infection to onset of neurological symtpoms (weeks)	**0**	**4**	**6**
Persisting symptoms			
Memory Problems	**Yes**	No	No
Concentration problems	**Yes**	No	No
Headache	**Yes**	No	No
Olfactory disfunction	No	**Yes***	**Yes#**
Fatigue	**Yes**	No	No
Pain (muscle/joints)	**Yes**	No	No
Rash	**Yes**	No	No
Other	**Post Exertional Malaise**	**Dysgeusia**	**Dysgeusia#**

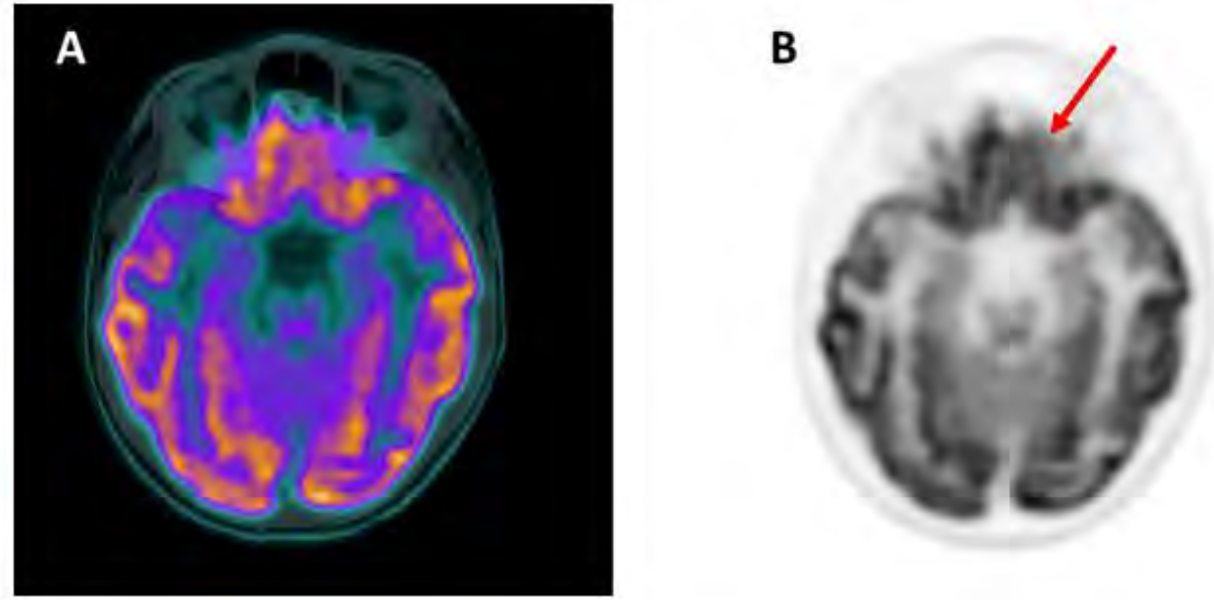
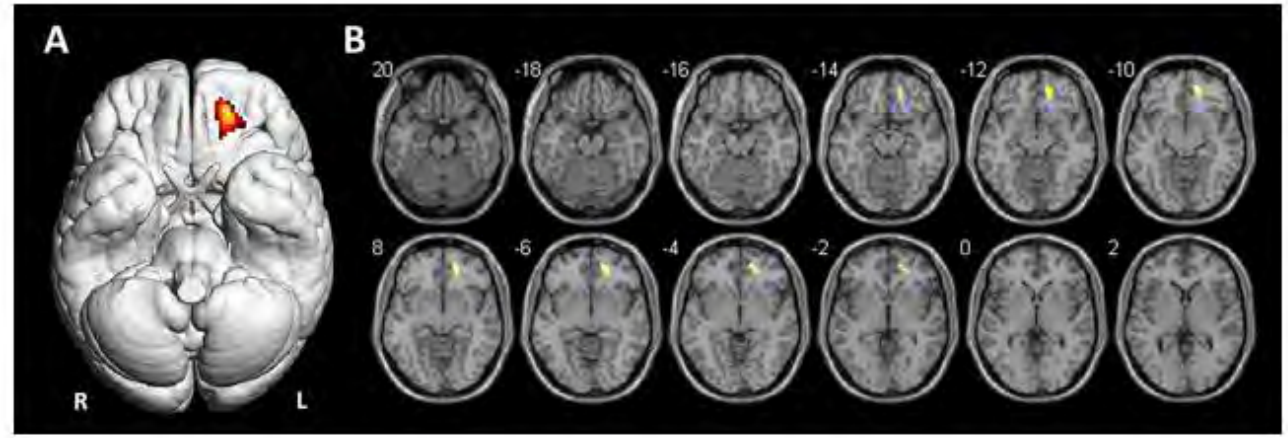
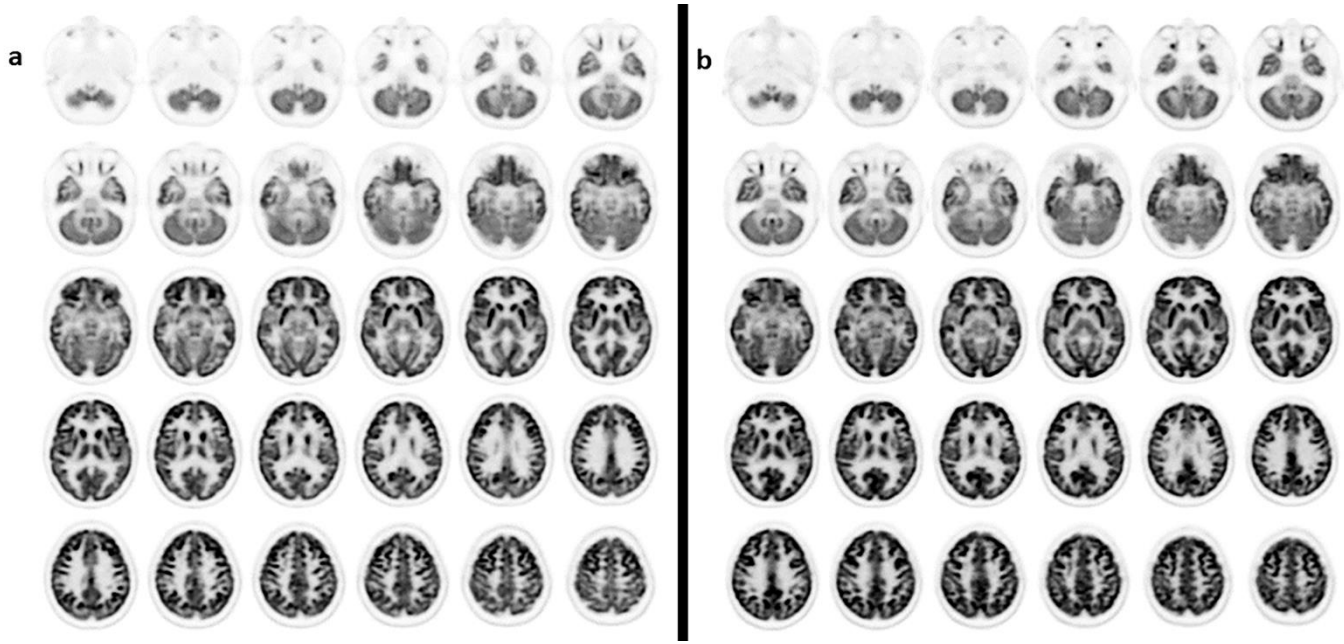
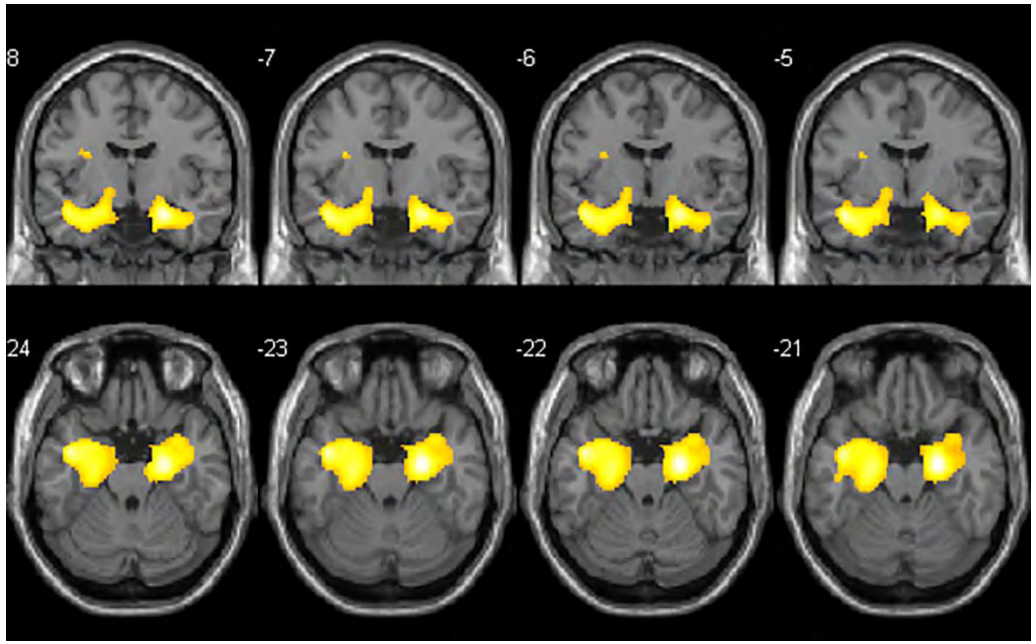


Fig 1. Fused PET-CT (A) and PET (B) axial slices showing a mild hypometabolism in the orbitofrontal left cortex in patient 1.







Visual analysis of PET images showed a moderate reduction in 18F-FDG uptake in bilateral mesio-temporal region (Figure 1); these findings were confirmed by the voxel wise analysis. The SPM8 analysis showed, at a height threshold of $p<0.001$ (uncorrected), a significant hypometabolism ($p<0.001$) in both patients ($n = 2$), as compared to healthy subjects ($n = 19$), in the left and right mesio-temporal regions with a peak in bilateral hippocampus (right: MNI coordinates 22/-12/-20 mm with a T-Score of 6.7; left: MNI coordinates -20/-16/-19 mm with a T-Score of 6.1; Figure 2).

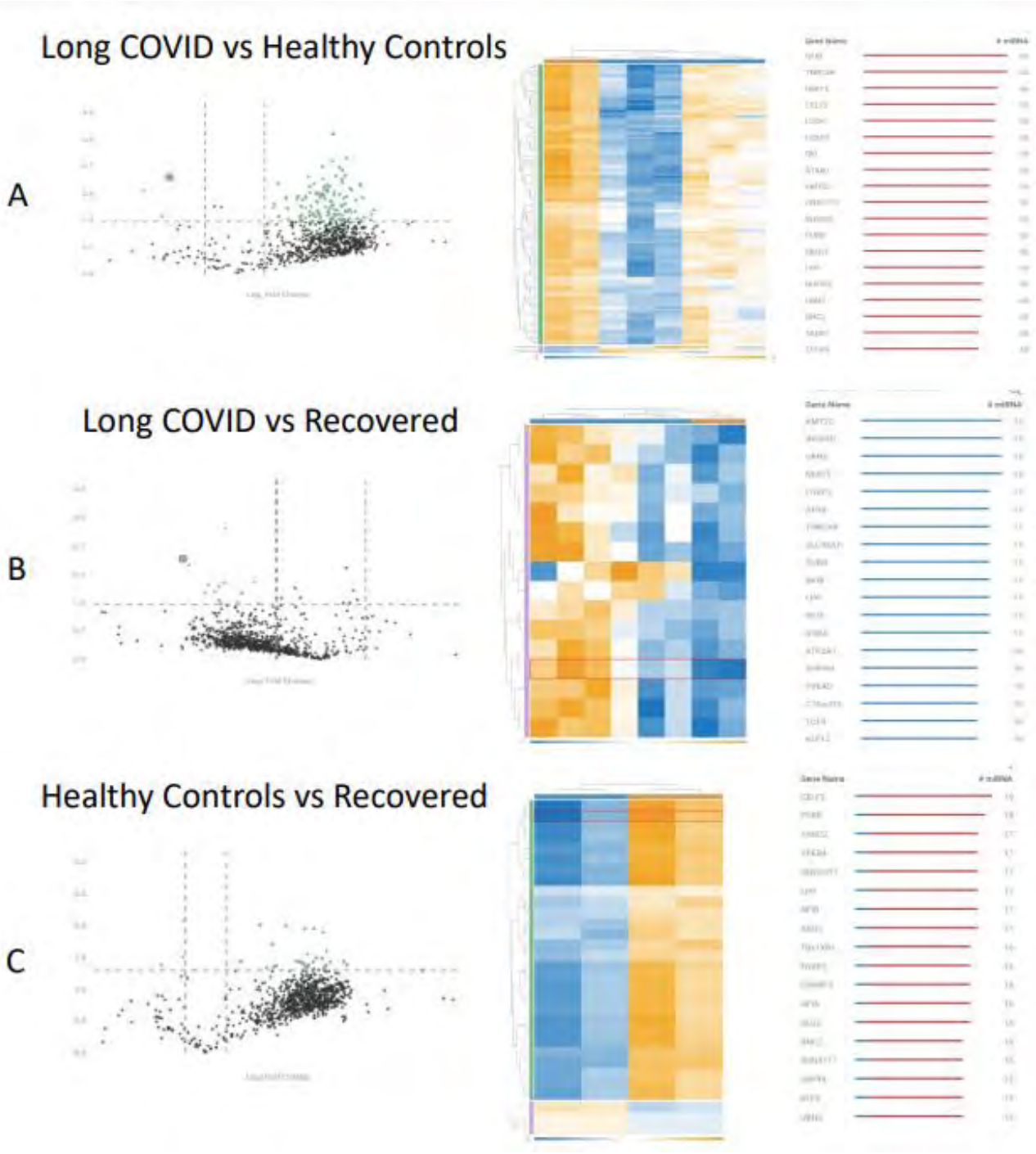


Figure 1. Preliminary results obtained with NanoString nCounter Human Human v3b miRNA Assay (NanoString, Seattle, WA, USA). MicroRNA have been extracted from PBMC dervied from 12 children (6 with Long COVID, 4 who fully recovered from Long COVID and 2 healthy Controls). A) Comparison of Long COVID children with healthy controls: Volcano Plot and array chart show that 119 microRNA were deregulated during the disease and most of them were predicted to impact with inflammation and cell proliferation (e.g. 60 were able to downregulate NFkB pathway). B) Comparison of children affected by Long COVID with the ones who fully recovered: Volcano plot and chart array show a significant different expression of 16 microRNA, most of all involved in the up-regulation of several inflammatory pathways. C) The Volcano plot and the array chart display the expression of micorRNA comparing children who fully recovered from Long COVID with children who never contacted SARS-CoV-2 (2 vs 2), showing significant difference of 31 microRNA, mostly involved in cell proliferation and DNA repair.
Data were analysed with ROSALIND® Nanostring miRNA Expression Methods and software.

What to do for these children!?!?!?!

1- Don’t know (yet)!!

2- Recognize the problem and offer CARE to the family

3- Establish health services and partnerships FAMILY DOCTORS / HOSPITAL / FAMILIES

4- Develop local guidelines to be implemented regularly as new advances are achieved

5- **Open-minded international collaborations to advance knowledge in the field**

Cite this article as: BMJ, doi:10.1136/bmj.38933.585764.AE (published 1 September 2006)

BMJ

Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study

Ian Hickie, Tracey Davenport, Denis Wakefield, Ute Vollmer-Conna, Barbara Cameron, Suzanne D Vernon, William C Reeves, Andrew Lloyd, for the Dubbo Infection Outcomes Study Group

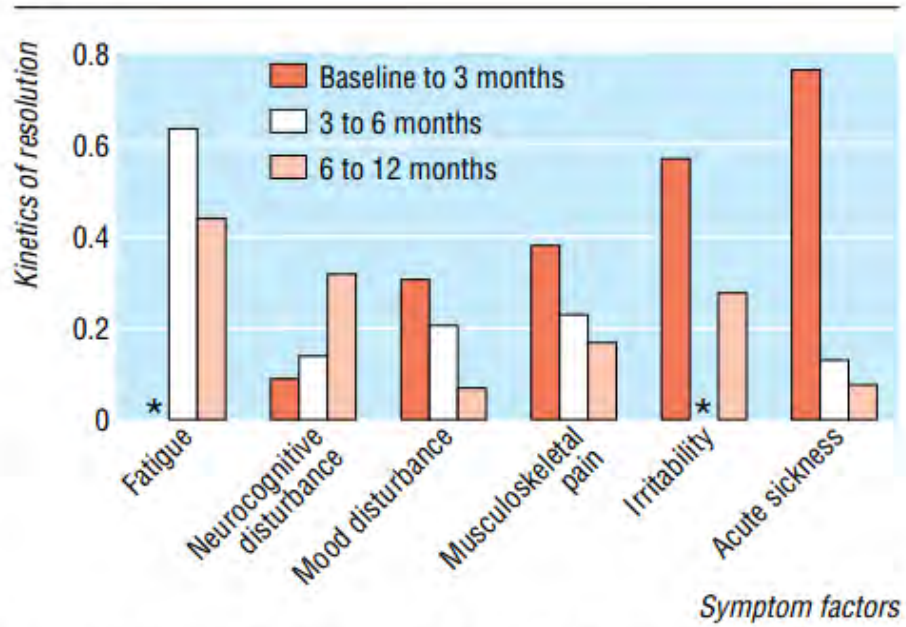


Fig 3 Differential rates of resolution of individual symptom factors after acute infection. Scores on each of six symptom factors for each participant (n=229) over 12 months in three divided time periods, calculated from factor analysis. Mean symptom scores standardised (to ensure comparability) by dividing the mean at each time point for each factor by its mean at baseline. Each bar represents gradient of resolution of factor scores between each time point of assessment. *Period of non-resolution of individual symptom domain between two time points of assessment (that is, gradient=0)

What is already known on this topic

A post-infective fatigue syndrome that meets diagnostic criteria for chronic fatigue syndrome may follow Epstein-Barr virus infection but not common, minor viral infections

What this study adds

Post-infective fatigue syndrome represents a common and stereotyped outcome from several viral and non-viral infections

The key risk factor for post-infective fatigue syndrome is the severity of the acute illness and not age, sex, or psychological factors

Conclusions

- Increasing recognition of pathological events in Long Covid Adults, including those living with children. **This can potentially impact their ability to care for their children**.
- Increasing evidence of children with Long Covid worldwide
- Need of investigate for chronic subtle organ damage in kids as well
- Better partnerships with patients/parents org
- Hopefully, shared protocols worldwide
- Indirect benefits: better understanding of other post-viral/infectious conditions

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Thank You