22 – 23 SETTEMBRE 2023

LONG-COVID: UNA NUOVA PANDEMIA DA GESTIRE PER L'INTERNISTA?
Maria Angela Barletta
UOC MEDICINA INTERNA PO PERRINO

MEDICINA INTERNA 2.0: la quiete dopo la tempesta?

FONDAZIONE SAN RAFFAELE || CEGLIE MESSAPICA (BR)

A Novel Coronavirus Associated
with Severe Acute Respiratory Syndrome

BRIEF REPORT

A Novel Coronavirus from Patients with
Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xinwang Li, M.D.,

NEWS IN FOCUS
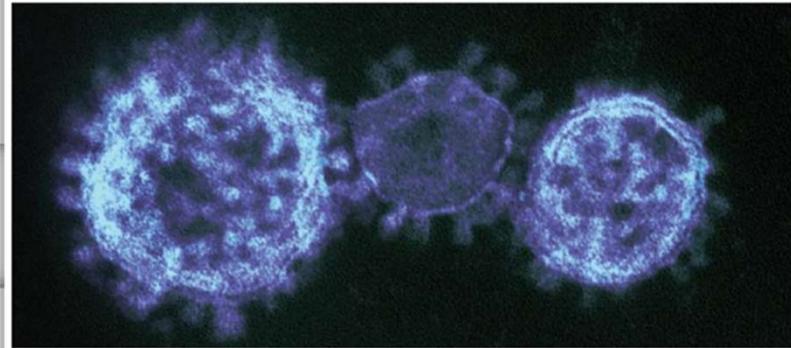
A new coronavirus found in the Middle East is one of a family of viruses named after the corona-like appearance of their surface spikes.

VIROLOGY

Clusters of coronavirus cases put scientists on alert

*Surveillance ramped up after novel virus is identified in three Middle Eastern countries.*

Breve timeline degli eventi

100nm
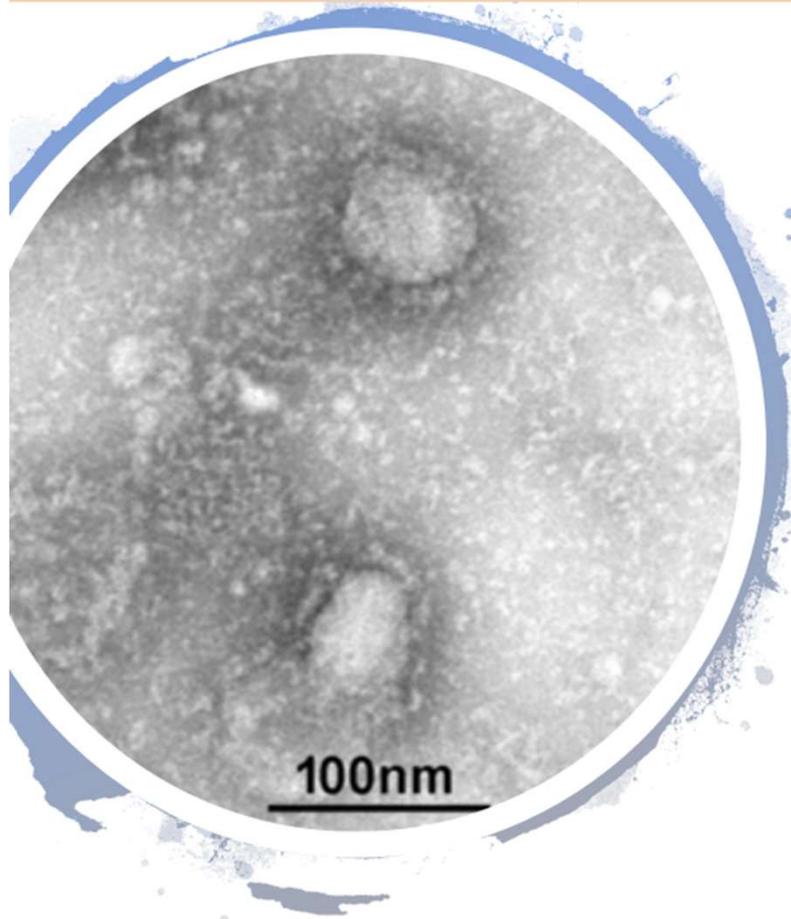
- **Metà dicembre 2019**: compaiono i primi casi di polmonite virale di origine sconosciuta, tra lavoratori e frequentatori del South China Seafood Market di Wuhan;

- **31 Dicembre 2019**: primo report ufficiale da parte delle Autorità Sanitarie Cinesi, che parlano di 27 casi, tra cui 7 gravi, legate alla esposizione comune al South China Seafood Market, che è stato chiuso il 1° Gennaio 2020;

- **9 Gennaio 2020**: primo decesso, in un uomo di 61 anni con numerose co-morbidità. Intanto i casi riportati salgono a 59;

- **9-10 Gennaio 2020**: virologi cinesi comunicano di aver isolato, in numerosi casi sospetti, un nuovo Coronavirus, con un 70% di omologia genetica con il SARS-CoV. Il giorno dopo le sequenze virali vengono rese pubblica sul GISAID e successivamente su GenBank, rendendo possibile lo sviluppo rapido di test diagnostici basati sulla RT-PCR;

Breve timeline degli eventi

- **25 Gennaio 2020:** primo caso sospetto (vero) ricoverato in Regione Campania, presso il Cotugno. I test escluderanno che si tratta di 2019-nCoV;

- **28 Gennaio 2020:** primi casi confermati in Italia, in due turisti cinesi attualmente ricoverati presso lo Spallanzani di Roma;

- **30 Gennaio:** il WHO dichiara che l'epidemia da 2019-nCoV è un PHEIC (Public Health Emergency of International Concern). L'Italia, intanto, dichiara lo stato di Emergenza Sanitaria per 6 mesi;

- **31 gennaio:** Il Governo italiano dichiara lo stato di emergenza sanitaria;

- **6 febbraio:** primo caso in un Cittadino italiano in uno dei rimpatriati da Wuhan e messo in quarantena alla Cecchignola

Long COVID-19 as defined:

"Signs and symptoms that develop during or following an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis."

NICE, SIGN and RCGP, 'COVID-19 guideline scope: management of the long-term effects of COVID-19', see Reference [6]

COVID-19 rapid guideline: managing the long-term effects of COVID-19

NICE guideline

Published: 18 December 2020

www.nice.org.uk/guidance/ng188

Acute infection (acute COVID-19)
- Active viral replication and initial host response

4 weeks

On going symptomatic COVID
- Postacute hyperinflammatory illness
- Immune-mediated response
- Persistant viral replication
- Organ disfunction

12 weeks

Post-COVID-19 syndromes
- The pathophysiology is not know, nor have the viral or inmunological responses been defined in this phase

PROLONGED COVID-19

'long COVID'
- **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 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.

NICE guideline on long COVID

LONG COVID
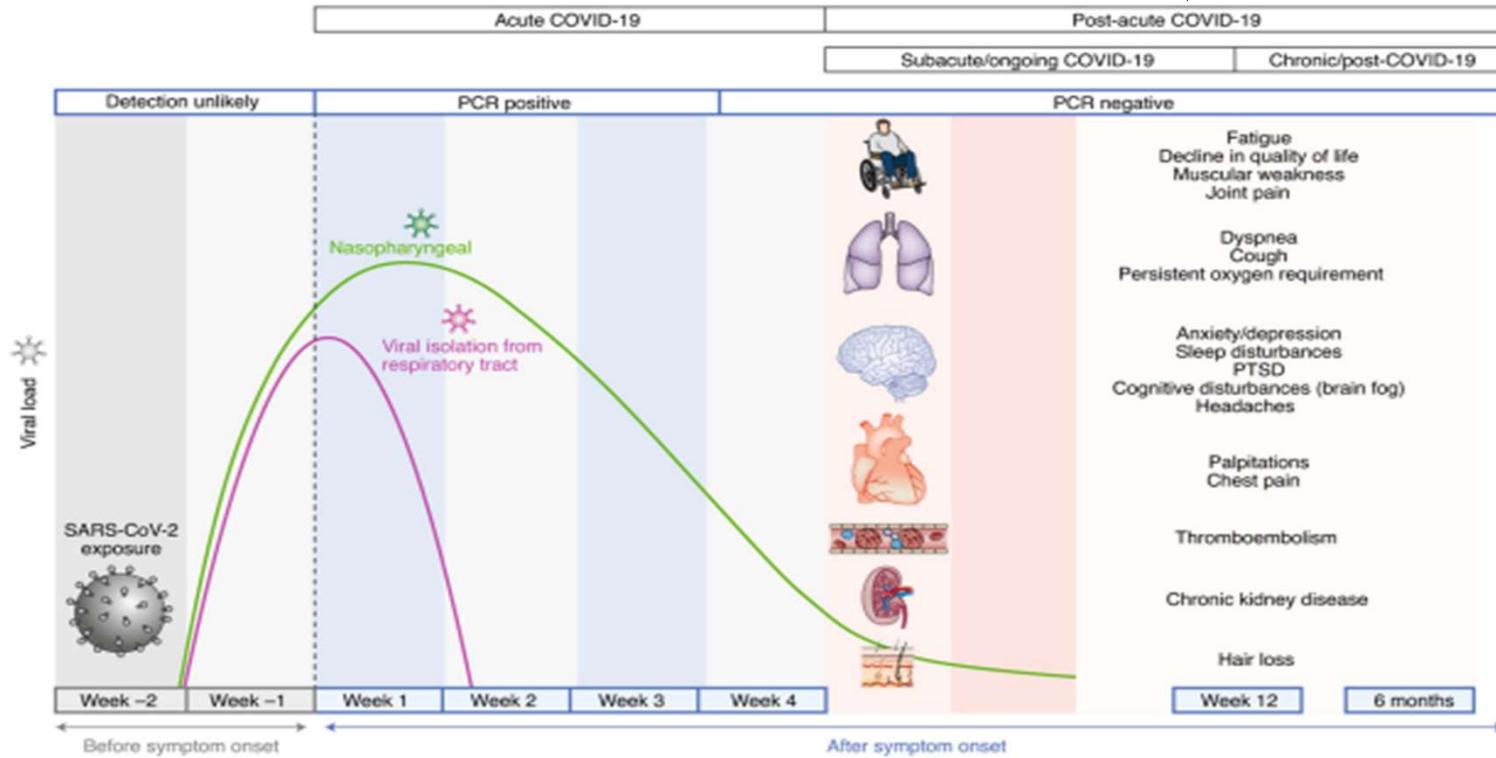
COVID: DECORSO CLINICO

- *Acute COVID*: guarigione in 2-3 settimane (la maggior parte dei pazienti)

- *Ongoing symptomatic COVID-19*: sintomi >4 settimane (1:5 paz.)

- *Post-COVID-19*: sintomi >12 settimane (1:10 paz.)

National Institute for Health and Care Excellence (NICE) (2021) COVID-19 rapid guideline: managing the long-term effects of COVID-19. https://www.nice.org.uk/guidance/ng188.

LONG-COVID 19

Long covid—mechanisms, risk factors, and management

Harry Crook,[1] Sanara Raza,[1] Joseph Nowell,[1] Megan Young,[1] Paul Edison[1,2]

COVID 19: PATOGENESI

Heart
- Chest pains
- Myocardial inflammation
- ↑ Serum troponin
- Palpitations

Lungs
- Dyspnea
- Chest pain
- Cough

Brain
- 'Brain fog'
- Delirium
- Fatigue
- Sleep disturbances
- Depression/anxiety/PTSD/OCS

Pancreas
- Pancreatic injury
- Pancreatitis

Spleen
- ↓ T & B lymphocyte
- Atrophy of lymphoid follicles

Kidney
- Renal impairment
- Acute kidney injury

Liver
- Liver injury
- ↑ Aspartate aminotransferase
- ↑ Alanine aminotransferase

Gastrointestinal tract
- Diarrhea
- Nausea
- Sore throat

Blood vessels
- Inflammation
- Vessel damage
- Coagulopathy
- Microangiopathy

ACE2

Long covid—mechanisms, risk factors, and management, Bmj, 2021

Check for updates

Long COVID: major findings, mechanisms and recommendations

january 2023

Hannah E. Davis [1], Lisa McCorkell [2], Julia Moore Vogel [3] & Eric J. Topol [3]
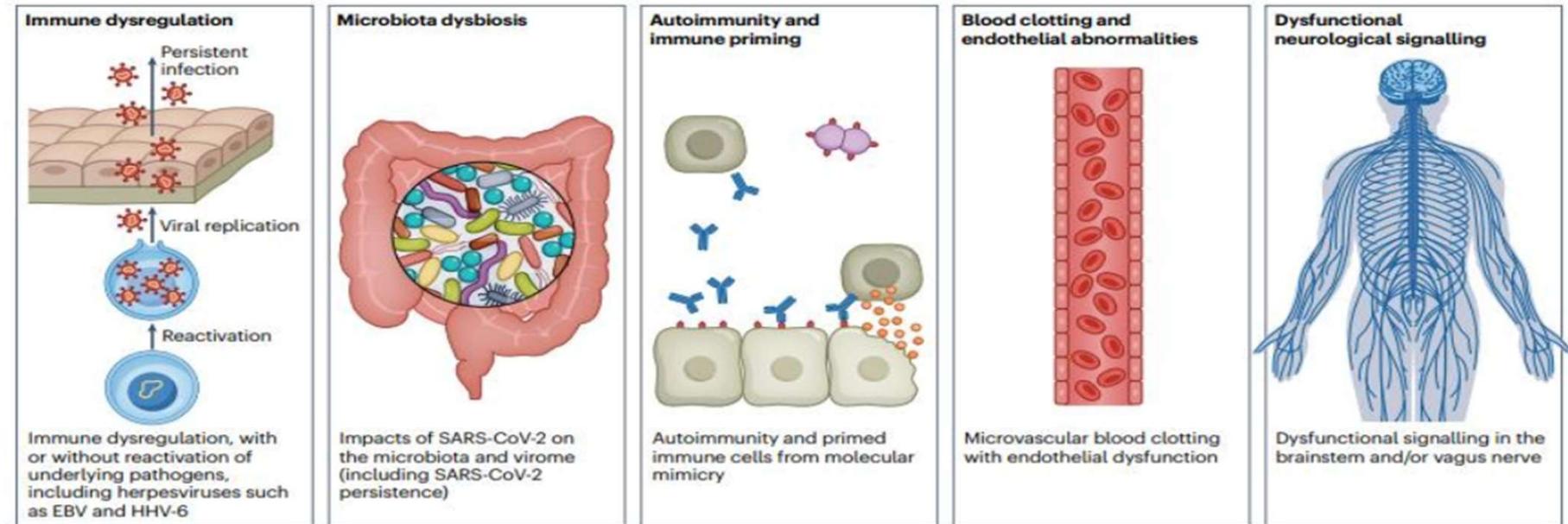

Fig. 3 | Hypothesized mechanisms of long COVID pathogenesis. There are several hypothesized mechanisms for long COVID pathogenesis, including immune dysregulation, microbiota disruption, autoimmunity, clotting and endothelial abnormality, and dysfunctional neurological signalling. EBV, Epstein–Barr virus; HHV-6, human herpesvirus 6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

LONG COVID: PATOGENESI
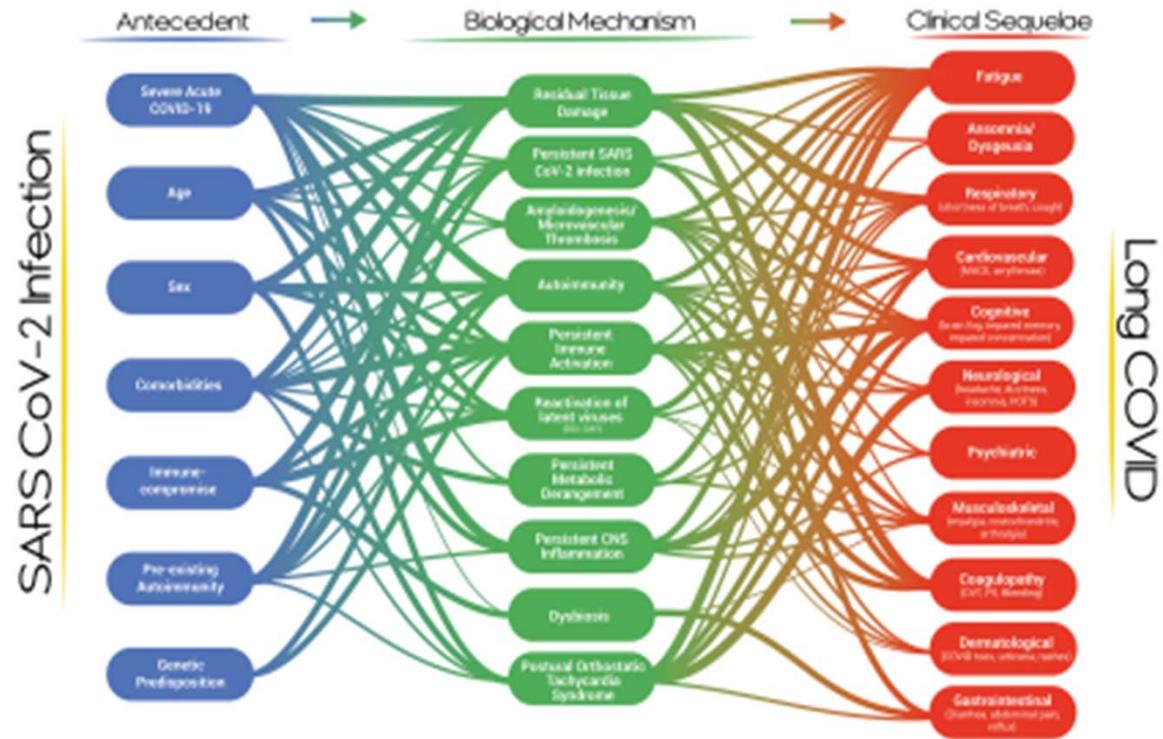
FIGURE 1

A systems-level visualization of the complexity of Long COVID and its pathogenesis.

Inflammation Research

Potential roles of mitochondrial cofactors in the adjuvant mitigation of proinflammatory acute infections, as in the case of sepsis and COVID-19 pneumonia

Giovanni Pagano[1] · Carla Manfredi[1] · Federico V. Pallardó[2] · Alex Lyakhovich[3,4] · Luca Tiano[5] · Marco Trifuoggi[1]

ELSEVIER

Mitochondria and microbiota dysfunction in COVID-19 pathogenesis

Jumana Saleh[a], Carole Peyssonnaux[b,c], Keshav K Singh[d], Marvin Edeas[b,c,*]

[a] College of Medicine, Sultan Qaboos University, Oman
[b] Université de Paris, INSERM U1016, Institut Cochin, CNRS UMR8104, Faculté de médecine Cochin-Port Royal, Paris, France
[c] Laboratory of Excellence GR-Ex, Paris, France
[d] Integrated Center for Aging Research, Department of Genetics, University of Alabama at Birmingham, Birmingham, AL 35294, USA

frontiers in Pharmacology

Mitochondria Targeted Viral Replication and Survival Strategies—Prospective on SARS-CoV-2

Priya Gatti[1,2†], Hema Saranya Ilamathi[1,2†], Kiran Todkar[1,2] and Marc Germain[1,2*]

[1] Groupe de Recherche en Signalisation Cellulaire et Département de Biologie, Médicale, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada, [2] Centre d'Excellence en Recherche sur les Maladies Orphelines - Fondation Courtois, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada

DISFUNZIONE MITOCONDRIALE E COVID

LONG-COVID: PATOGENESI

IL COVID OGGI

Canada

4.697.504 Confirmed cases

53.147 Deaths

Cases

Total

17.576
new cases last 7 days

770.563.467
cumulative cases

6.957.216
cumulative deaths

Cases - Total ×

> 5.000.000

500.001 − 5.000.000

50.001 − 500.000

5.001 − 50.000

1 − 5.000

0

Not applicable

Download Map Data
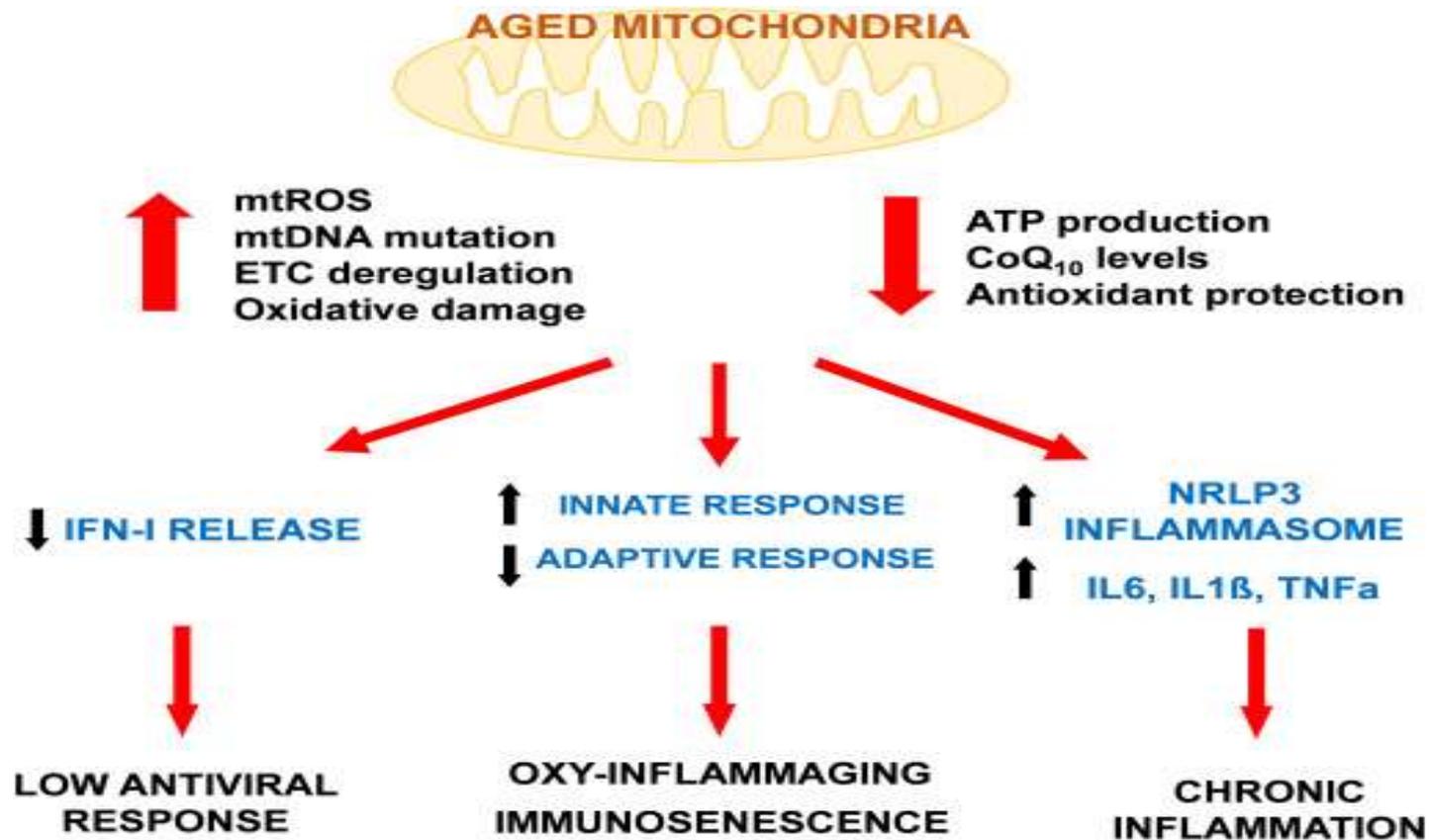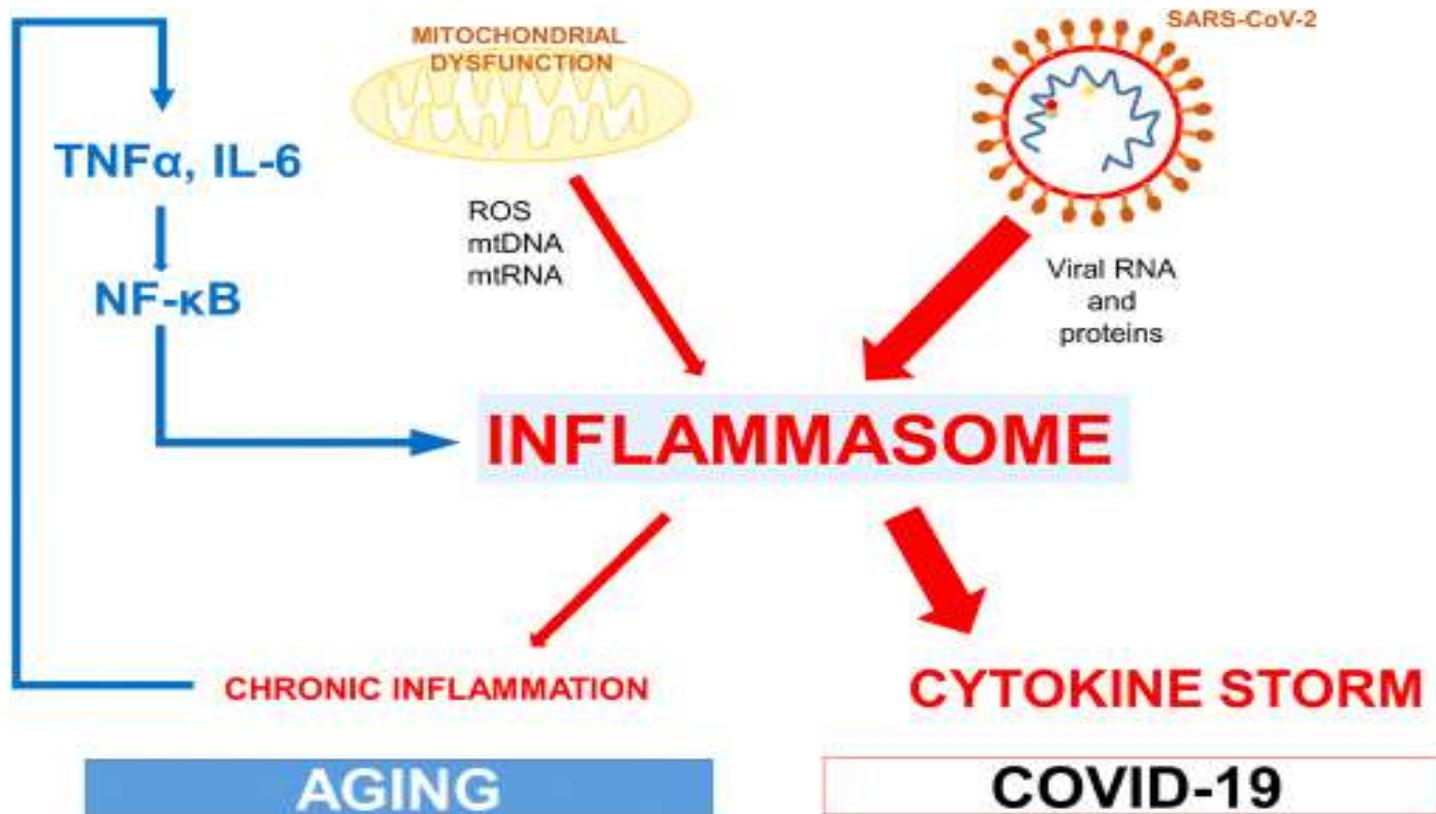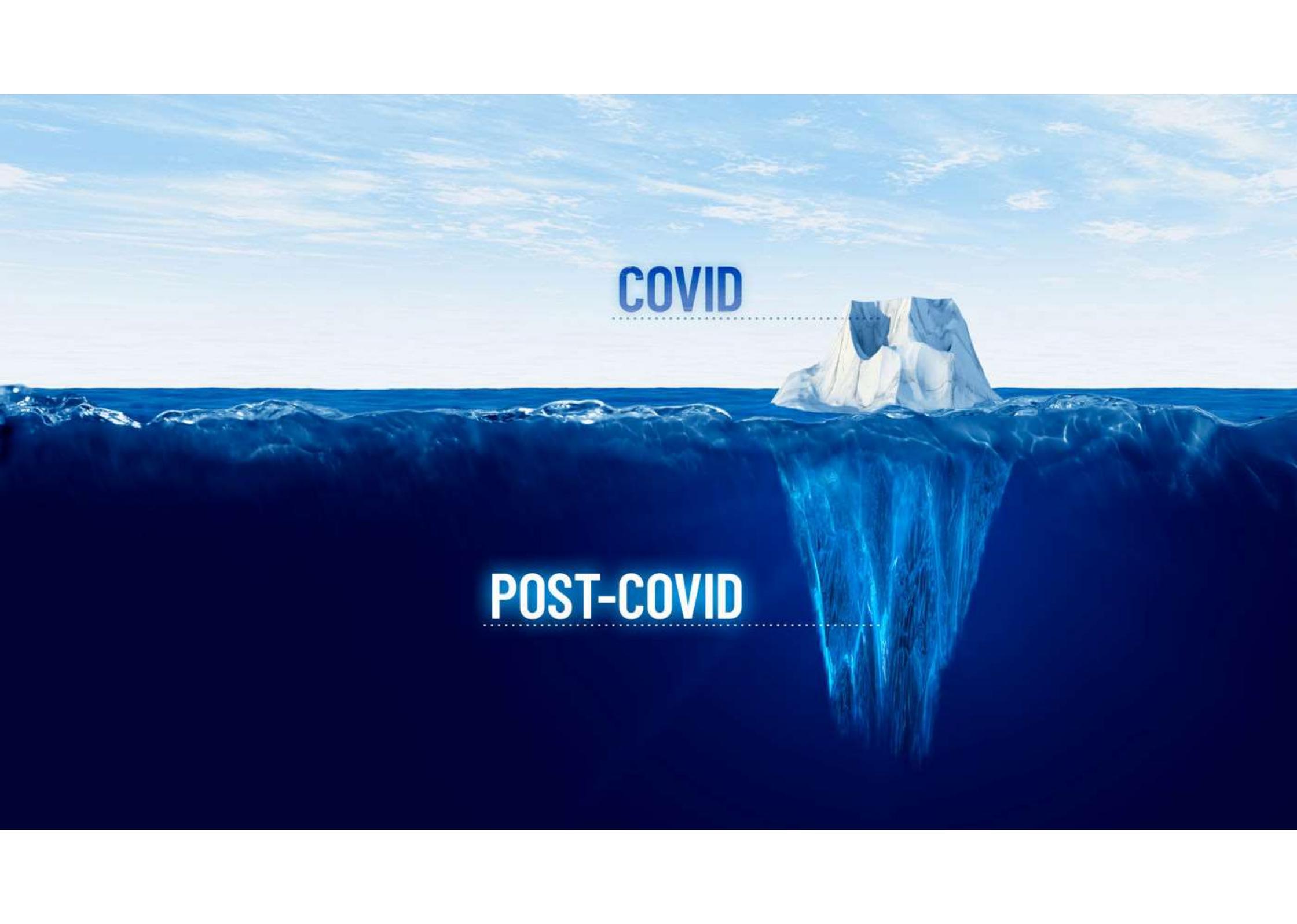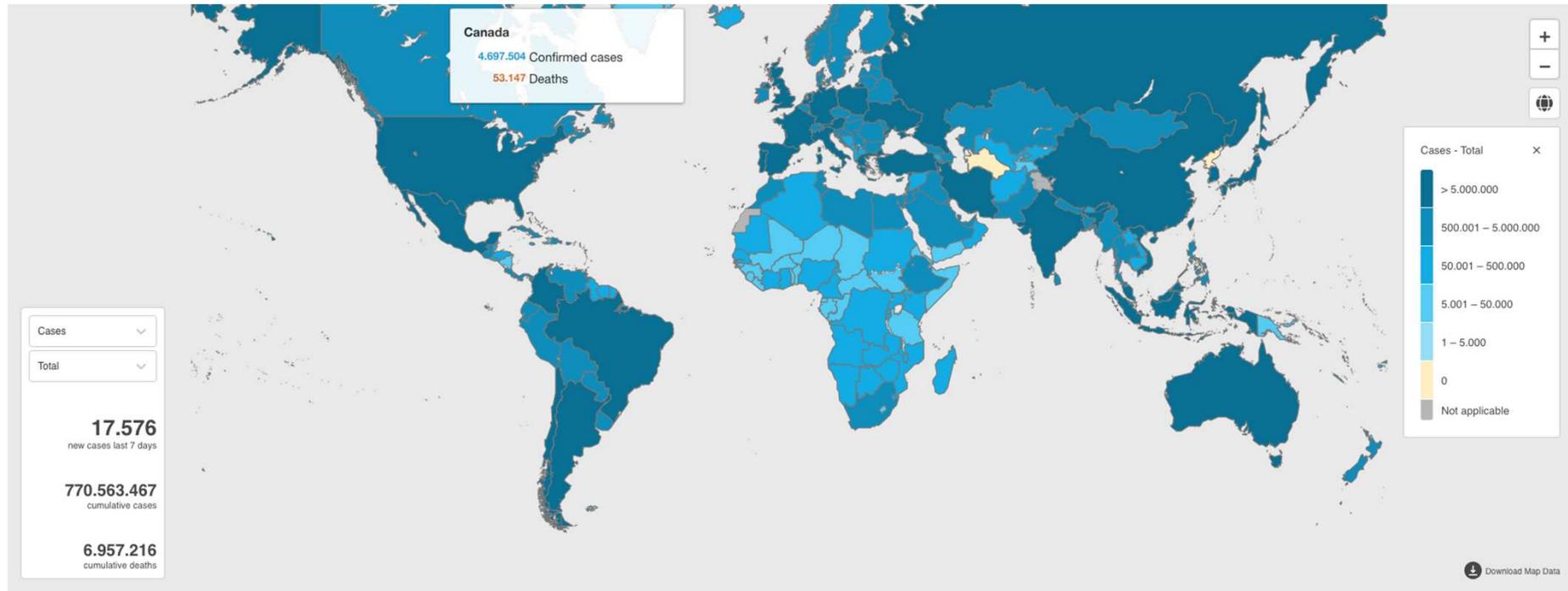
Globally, as of **7:25pm CEST, 13 September 2023**, there have been **770.563.467 confirmed cases** of COVID-19, including **6.957.216 deaths**, reported to WHO. As of **7 September 2023**, a total of **13.501.166.968 vaccine doses** have been administered.

LONG COVID: I NUMERI

World Health Organization

Health topics ∨ · Our work ∨ · Newsroom ∨ · Data ∨ · Emergencies ∨ · About us ∨

Français · Русский · Deutsch

At least 17 million people in the WHO European Region experienced long COVID in the first two years of the pandemic; millions may have to live with it for years to come

WHO/Europe urges countries to take post COVID-19 condition seriously by urgently investing in research, recovery, and rehabilitation

13 September 2022 | Media release | Reading time: 4 min (1072 words)

Media Contacts
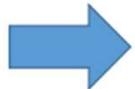
➡ approx. 20 mio people in European Region in march 2023

LONG COVID: PREVALENCE 15-30% PATIENTS <u>4-6</u> MONTHS AFTER AN INITIAL COVID EPISODE

The **UK Office for National Statistics** tracked 20,000 people following a positive COVID test to determine how long symptoms lasted: 14 at 12 weeks

2.8% of the population i.e 1,8 million people in UK
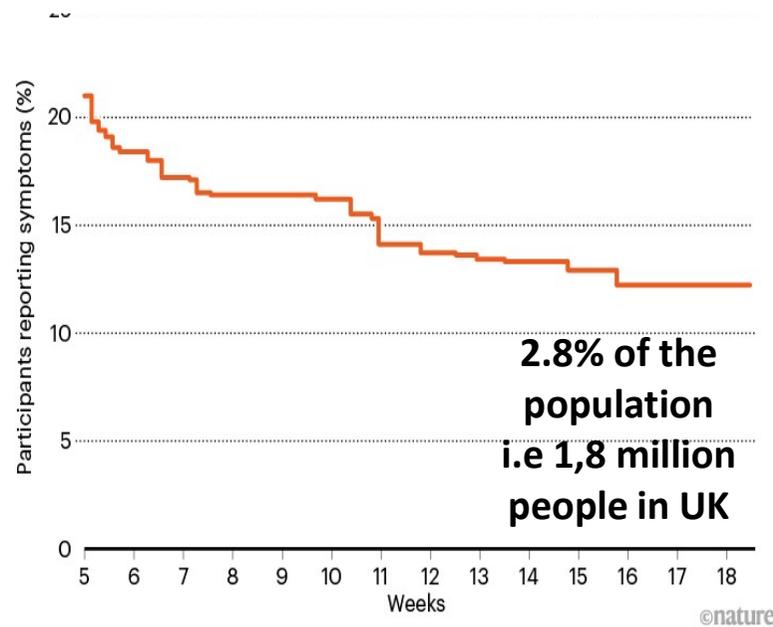
National Office for Statistics (UK). Prevalence of ongoing symptoms following COVID-19 infection in the UK: 2 Sep 2021.

A 2022 **French Survey** tracked 25,537 adult volunteers. On those infected > 3 months and 18 months, 30 % and still 20% had prolonged symptoms

4% of the adult population

(IC 95: 3,7- 4,2 %)

2,06 million people in France

Santé Publique France. Results of post-COVID affection survey in France, 21 July 2022.

BUSINESS · FEATURED

Long Covid Will Have a Massive Impact on the U.S. Economy

An estimated 15 million Americans could have the lingering symptoms of long Covid, potentially costing the economy more than $2.6 trillion.

By Linda Carroll · 05/26/22 12:53pm

Living with long Covid

Dr Anthony Fauci: long Covid is an 'insidious'
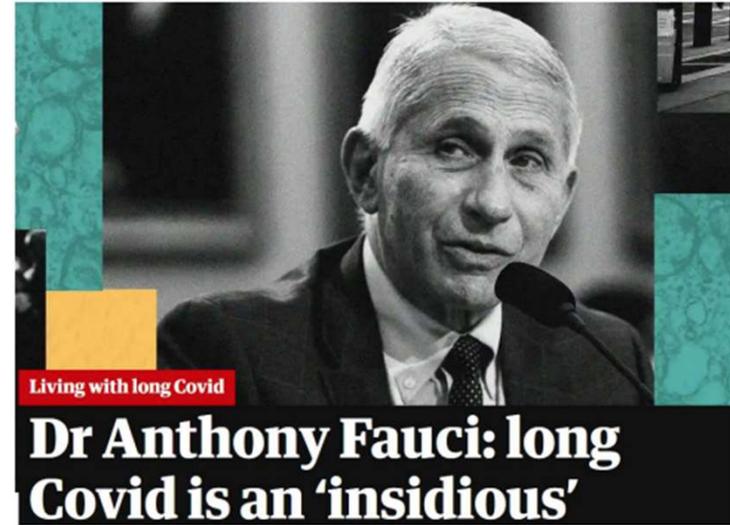
The great gaslighting: how Covid longhaulers are still fighting for recognition

People with long Covid face an uphill battle convincing skeptics their malady is real – but discrediting uncommon conditions is hardly a new phenomenon

JAMA Health Forum™

2022

The Costs of Long COVID

David M. Cutler, PhD

More than 6 million people have died from COVID-19 worldwide, including nearly 1 million in the US. But mortality is not the only adverse consequence of COVID-19. Many survivors suffer long-term impairment, officially termed *post-acute sequelae of SARS-CoV-2 infection* and commonly called *long COVID*.

……..If 1 million people are out of the labor force because of long COVID, the lost income would be more than $50 billion annually………

LONG-COVID: COSA SAPPIAMO

- **Over 65 million people worldwide** are estimated to be suffering from long Covid (Davis et al. 2023 *Nature Rev Micro*); **17m** in **WHO European** region

- Prevalence highest in people aged **35 to 69**, **women**, residents in **deprived areas**, **economically inactive**, and those with **activity-limited health conditions** (UK ONS)

- **Economic cost: Estimated $3.7tn** (Cutler 2022) **to US and an estimated £2.5 billion a year for UK economy**

- **Pressure on labour market:** In the US **up to 4m people** estimated to be **out of work** due to long Covid with an annual cost of **lost wages at $170bn a year** (Brookings 2022).

- Initial lack of an **agreed definition** and use of **different study populations and designs** led to highly estimates from **5 to 50% after Covid-19,** but most around **10%**

- **Vaccination seems to reduce the risk of long Covid** by 15% and 50% , and possibly treatment such as with ensiltrelvir (Shionogi)

LONG-COVID: COSA SAPPIAMO

- **Female sex: OR= 1.21-2**

  Augustin et al, 2021 Sudre et al 2021; Evans et al 2021; Mirfazeli et al 2021; Ford et al,2022; Marra et al.   2022, Wynberg et al, 2022; Han et al, 2022..

- **Severity at initial COVID and number of symptoms: OR = 1.29-3.53**

  Augustin et al, 2021; Sudre et al, 2021; Mirfazeli et al, 2021; Durstenfeld et al; Ford et al, 2022: Han et al, 2022

- **Neuropsychological symptoms at the initial phase**

  Mirfazeli et al 2021

- **Low anti-SARS CoV-2 antibody: OR=2**

  Augustin et al 2021, OR: 2.05; Wynberg et al, 2022

- **Body Mass-Index (BMI): OR=3.5**

  Sudre et al 2021 OR: 3.53

- **Age OR=3.5**

  Sudre et al 2021 OR: 3.53

Augustin M et al. Lancet Reg Health Eur. 2021 Jul;6:100122. Sudre C et al.. Nat Med. 2021 Apr;27(4):626-631; Mirfazeli et al, Pychiatry and Clinical Psychology, 2021; Evans et al, Infectious Diseases, 2021; Durstenfeld M et al, MefdRxiv 2022; Ford E et al. MedRxiv 2022; Wynberg E, et al. Clin Infect Dis. 2022 Aug 24;75(1):e482-e490.; Han, Q.et al.. Pathogens 2022, 11, 269.

LONG-COVID: COSA SAPPIAMO

- **Pre-Delta variants (OR = 0.30-0.49 for Delta and Omicron)**

  Durstenfeld et al, 2022 (OR 0.37 Omicron vs souches ancestrales); Marra et al, 2022 (OR = 0,30 pour Delta et 0,49 pour Omicron vs souches ancestrales)

- **No vaccination before getting COVID**

  Byambasuren O et al. BMJ 2022 (OR: 0.16 if 3 doses); Brannock et al, 2022 (HR: 0.66 if vaccination), Marra et al. 2022 (OR=0.05 if 4 vaccine doses before getting COVID

Durstenfeld M et al, Factors Associated with Long Covid Symptoms in an Online Cohort Study , MefdRxiv 2022; Marra AR et al. Risk factors for long COVID among healthcare workers, Brazil, 2020–2022. medRxiv 2022; Brannock MD et al. Long COVID Risk and Pre-COVID Vaccination: An EHR-Based Cohort Study from the RECOVER Program, MedRxiv 2022.; Byambasuren O et al. BMJ Medicine 2023

FATTORI DI RISCHIO/PREDITTIVI DEL LONG COVID
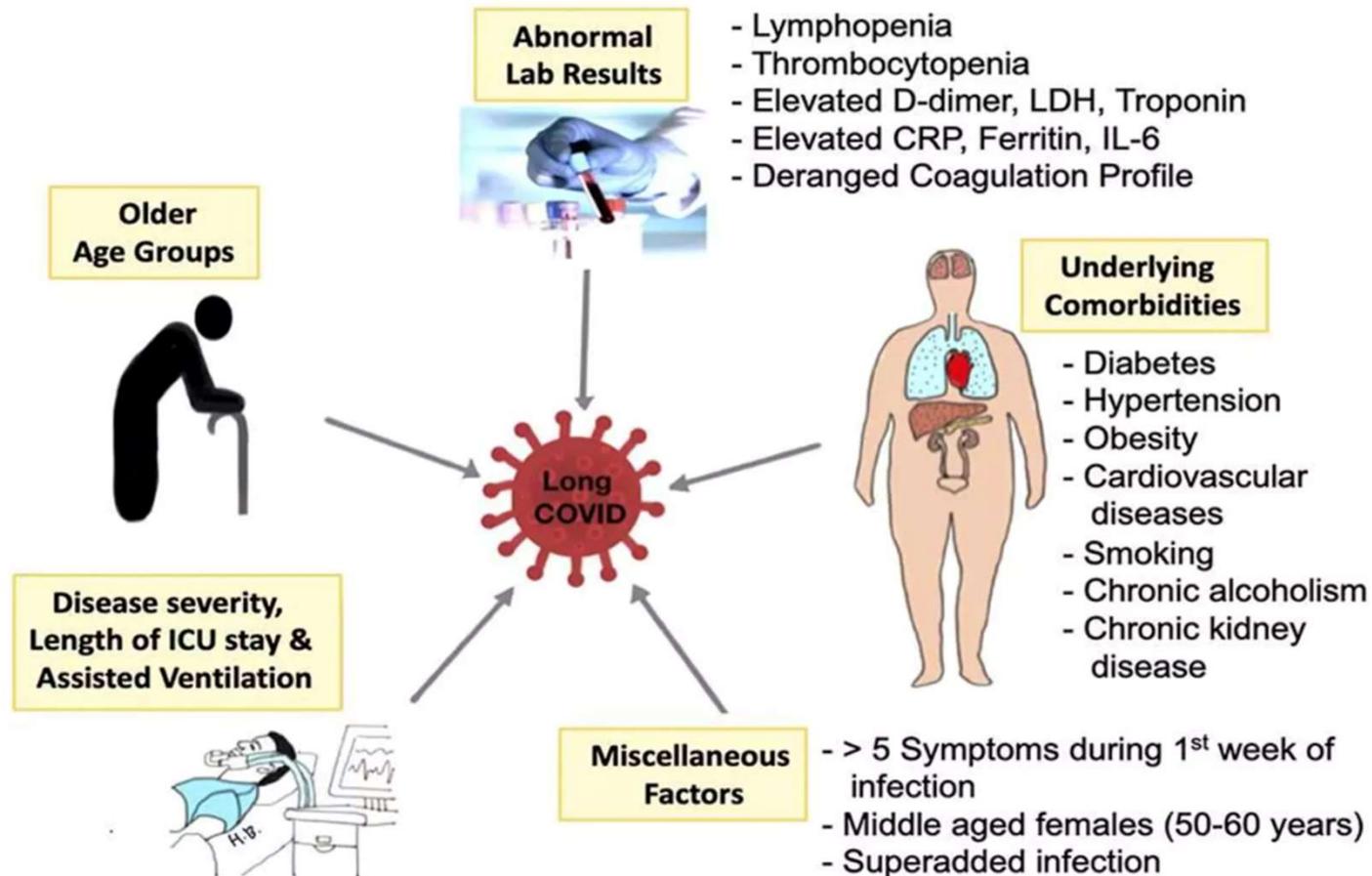
RESEARCH ARTICLE

Characteristics and predictors of Long COVID among diagnosed cases of COVID-19

M. C. Arjun[1], Arvind Kumar Singh[1,*], Debkumar Pal[1], Kajal Das[1], Alekhya G.[1], Mahalingam Venkateshan[2], Baijayantimala Mishra[3], Binod Kumar Patro[1], Prasanta Raghab Mohapatra[4], Sonu Hangma Subba[1]

1 Department of Community Medicine and Family Medicine, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, 2 College of Nursing, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, 3 Department of Microbiology, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India, 4 Department of Pulmonary Medicine and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India

Table 4. Predictors of self-reported Long COVID symptoms at four weeks follow-up.

Variable		Univariable logistic regression		Multivariable logistic regression	
		Odds Ratio (95% CI)	p value	Adjusted Odds Ratio (95% CI)	p value
Age Categories	18 to 45 years	Reference	-	Reference	-
	46 to 59 years	1.46 (0.91,2.36)	0.12	1.24 (0.68,2.29)	0.48
	60 years & above	1.46 (0.79,2.67)	0.22	1.08 (0.48,2.43)	0.86
Sex	Male	Reference	-	Reference	-
	Female	1.33 (0.89,1.97)	0.16	1.29 (0.74,2.25)	0.36
Occupation	Unemployed/Student/Homemaker	Reference		Reference	
	Professional/Technical/ Administrative/ Managerial	1.32 (0.84,2.08)	0.23	1.79 (0.96,3.33)	0.06
	Skilled/Unskilled manual	0.65 (0.31,1.34)	0.24	0.82 (0.32,2.09)	0.68
	Other	0.98 (0.55,1.74)	0.94	1.15 (0.53,2.48)	0.73
BMI	Underweight (<18.5)	Reference	-	Reference	-
	Normal or lean (18.5–24.9)	2.13 (0.71,6.44)	0.18	1.58 (0.39,6.47)	0.52
	Overweight (25.0–29.9)	2.35 (0.76,7.26)	0.14	1.49 (0.35,6.26)	0.58
	Obese (>30.0)	1.05 (0.23,4.82)	0.95	0.56 (0.09,3.44)	0.53
History of substance use		0.75 (0.39,1.44)	0.38	0.95 (0.41,2.16)	0.89
Past history of COVID-19		0.93 (0.33,2.66)	0.90	0.66 (0.20,2.15)	0.49
Pre-existing medical condition		1.69 (1.12,2.55)	**0.01**	2.00 (1.16,3.44)	**0.01**
COVID-19 vaccination	Not vaccinated	Reference	-	Reference	-
	Completed 1 dose	1.30 (0.66,2.55)	0.45	1.88 (0.84,4.22)	0.13
	Completed 2 doses	2.05 (1.23,3.42)	**0.01**	2.32 (1.17,4.58)	**0.01**
Number of COVID-19 symptoms	No symptoms	Reference	-	Reference	-
	1 to 4 symptoms	9.40 (3.99,22.09)	<0.001	6.88 (2.74,17.23)	<0.001
	5 or more symptoms	12.77 (4.89,33.37)	<0.001	11.24 (4.00,31.51)	<0.001
Severity of COVID-19 disease	Mild/Moderate	Reference	-	Reference	
	Severe/Critical	5.46 (3.22,9.27)	<0.001	5.71 (3.00,10.89)	<0.001
Care received during COVID-19 disease	Home Isolation	Reference	-	-	
	Admitted to hospital	3.89 (2.49,6.08)	<0.001	-	
Cycle threshold	E Gene/N Gene (n = 442)	0.98 (0.94,1.02)	0.38	-	
	ORF1a/ORF1b/N/N2 Gene (n = 378)	0.99 (0.95,1.03)	0.53	-	

More Than 100 Persistent Symptoms of SARS-CoV-2 (Long COVID): A Scoping Review

Lawrence D. Hayes [1]*, Joanne Ingram [2] and Nicholas F. Sculthorpe [1]

[1] *School of Health and Life Sciences, Institute of Clinical Exercise and Health Science, University of the West of Scotland, Hamilton, United Kingdom,* [2] *School of Education and Social Sciences, University of the West of Scotland, Paisley, United Kingdom*

LONG COVID IMPACTS

Mental Health
- Anxiety
- Depression
- Sleep problems
- Substance abuse

Respiratory System
- Cough
- Low blood oxygen
- Shortness of breath

Kidney
- Acute kidney injury
- Chronic kidney disease

Gastrointestinal
- Diarrhea
- Acid reflux
- Constipation

Skin Disorders
- Rash
- Hair loss

Blood Disorders
- Anemia
- Blood clots
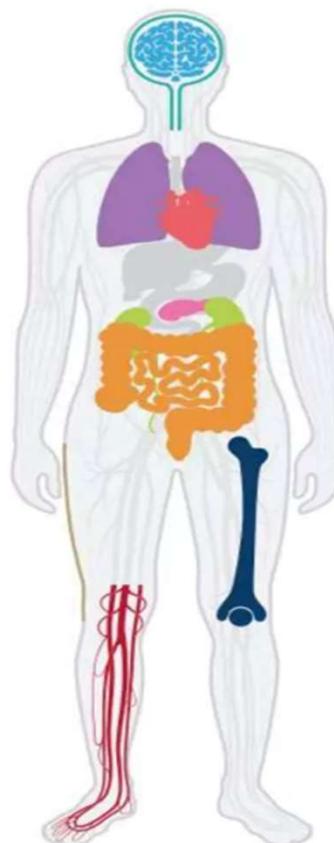
Nervous System
- Stroke
- Headaches
- Memory problems
- Loss of smell and taste

Cardiovascular
- Arrhythmia
- Palpitations
- Heart failure
- Acute coronary disease

Metabolic/Endocrine
- Obesity
- Diabetes
- High cholesterol

Musculoskeletal
- Joint pain
- Muscle weakness

General
- Fatigue
- Malaise
- Mitochondrial dysfunction

Cayman
CHEMICAL

SINTOMI DA LONG COVID

Long-term effects of COVID-19
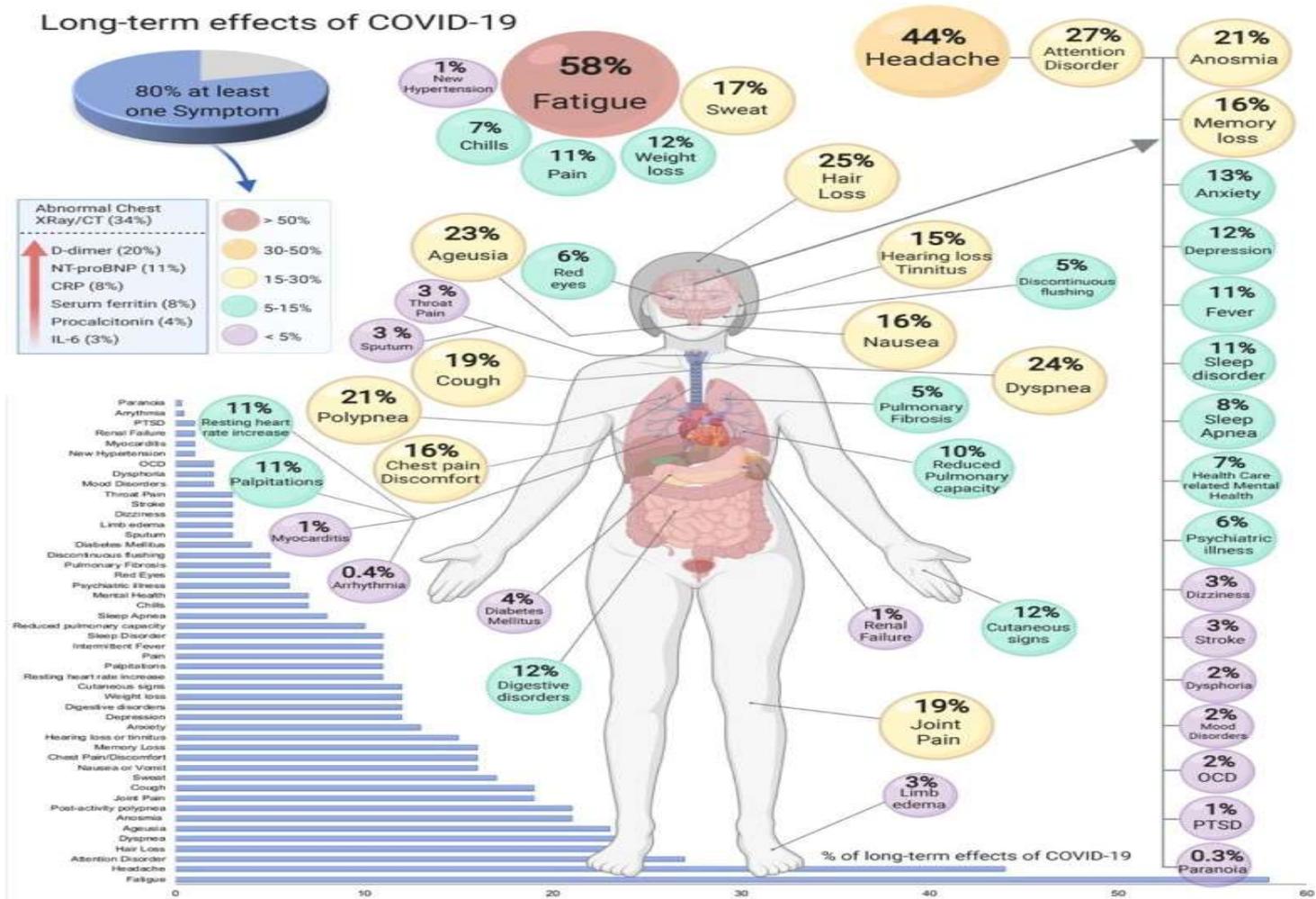
COVID VS LONG COVID

Percentage of participants who reported COVID-19 symptoms during acute illness and at follow-up
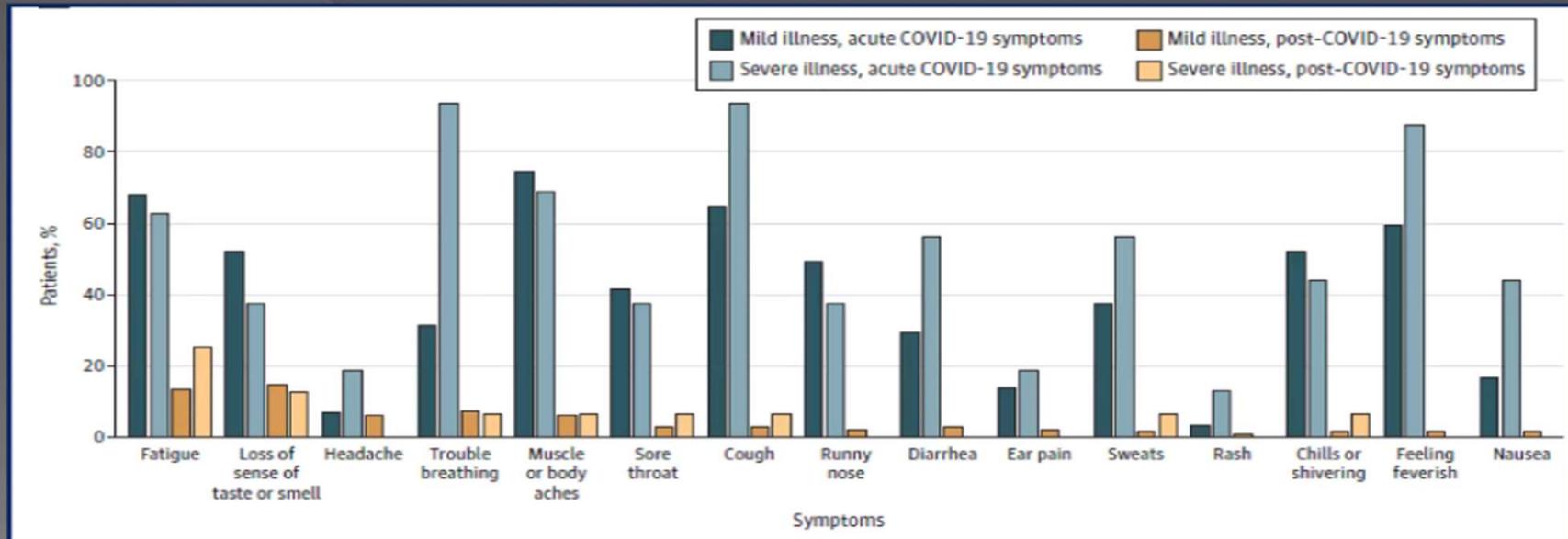
JAMA Network Open. 2021;4(2):

From: Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies
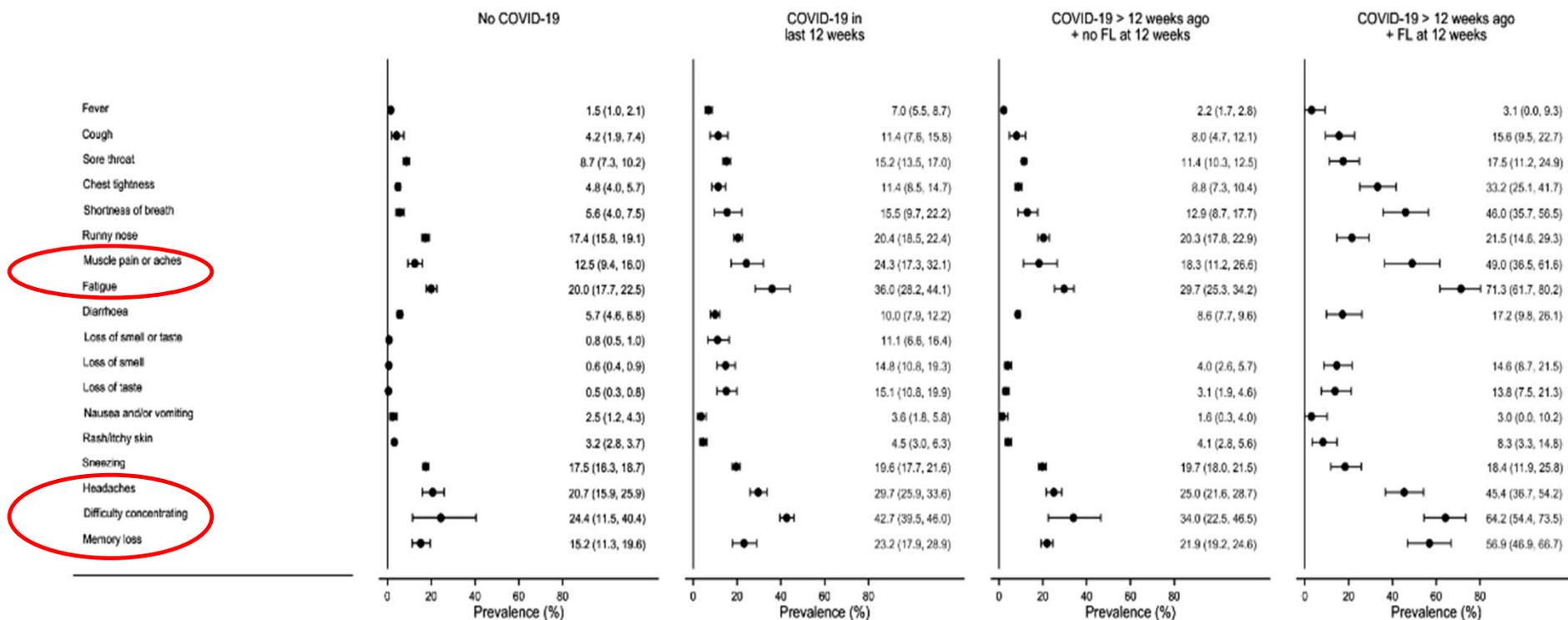
Meta-analysis of prevalence of each symptom for each COVID-19 group. Bars represent 95% confidence intervals. Estimates are from random effects meta-analyses of study-specific estimates. FL: function limitation

LONG COVID: SINTOMI APPARATO SPECIFICI
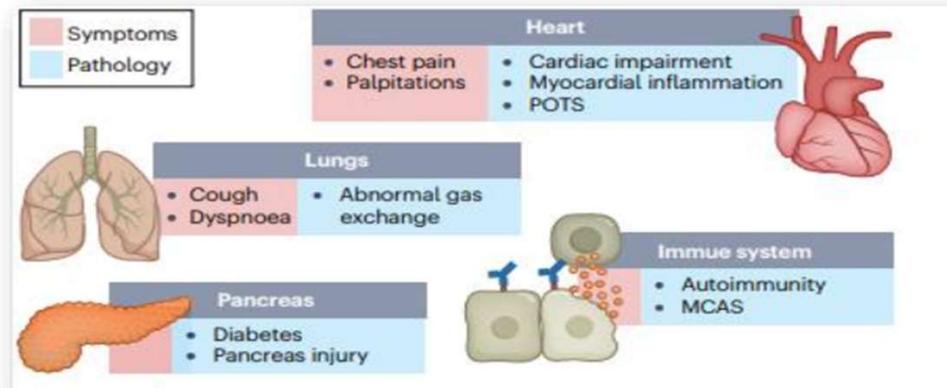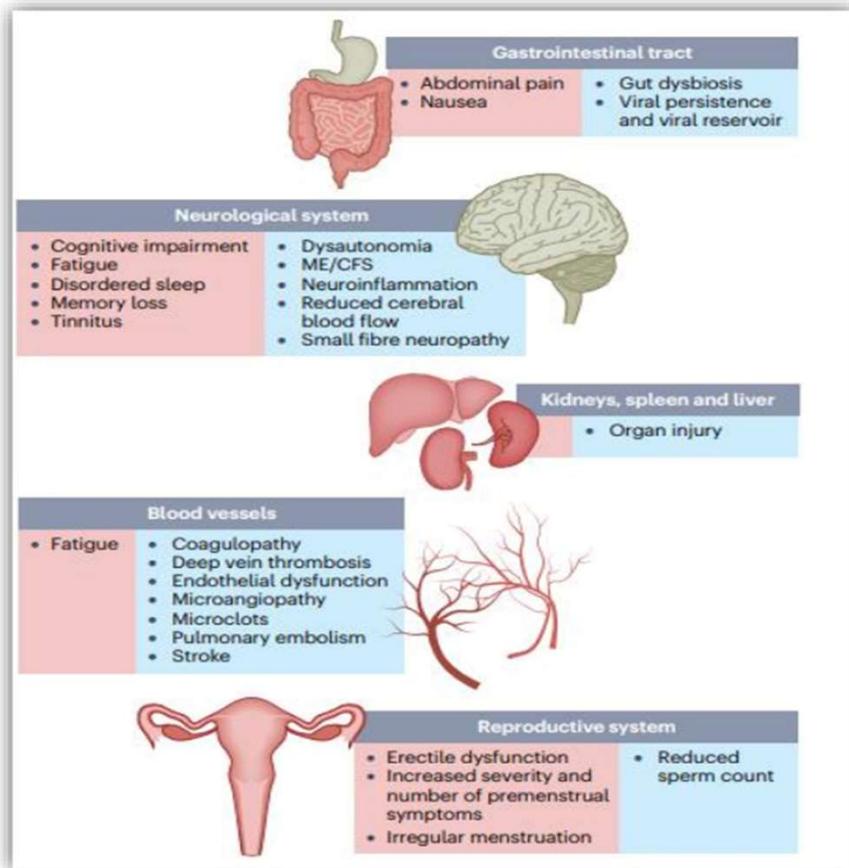
LONG-COVID: SINDROMI CLINICHE

| Post COVID syndrome	Predominant clinical features	Remarks
Post COVID fatigue syndrome	Profound fatigue	Rule out causes like anaemia, hypothyroidism, electrolyte imbalance
Post COVID cardio-respiratory syndrome	Cough, low grade fever, shortness of breath, chest pain,	Sudden increase in dyspnoea can be due to tension pneumothorax, pulmonary embolism, coronary artery disease or heart failure in patients recovered from COVID-19
Post COVID neuro-psychiatric syndrome	Headaches, anosmia, neurocognitive difficulties, insomnia, depression and other mental health conditions	In patients with acute onset neurological symptoms consider vasculitis, thrombosis or demyelination. Post COVID psychological issues have to be addressed properly.
Post COVID gastro-intestinal syndrome	Abdominal discomfort, diarrhea, constipation, vomiting,	GI symptoms can be a sequelae of the disease. Various drugs used during acute COVID, especially lopinavir/ritonavir produces GI symptoms
Post COVID hepato-biliary syndrome	Nausea, jaundice, deranged LFT	Drugs used in the treatment of COVID-19 like remdesivir, favipiravir, lopinavir/ritonavir and tocilizumab can cause hepatic impairment.
Post COVID musculo-skeletal syndrome	Muscle pains and weakness, arthralgia	May be due to disease, prolonged ICU care, neurological problems, myopathy or electrolyte imbalance. Usually subside during follow up. Inflammatory arthralgia has to be differentiated from other causes like RA, SLE
Post COVID thromboembolic syndrome	Depending upon the vascular territory of involvement breathlessness in PE, chest pain in CAD and limb weakness and neurological deficit in CVA	Early diagnosis and treatment is life saving. Follow the standard treatment protocol.
Post COVID multisystem inflammatory syndrome/post COVID autoimmune syndrome	Fever, gastrointestinal symptoms, rash, chest pain, palpitations	Elevated levels of markers of inflammation.
Post COVID genito-urinary symptoms	Proteinuria, haematuria, development of kidney injury	Endothelial dysfunction, coagulopathy, complement activation, direct effect of virus on kidney, sepsis and multi-organ dysfunction contribute to the development
Post COVID dermatological syndrome	Vesicular, maculopapular, urticarial, or chilblain-like lesions on the extremities (COVID toe)	

SINTOMI SISTEMICI
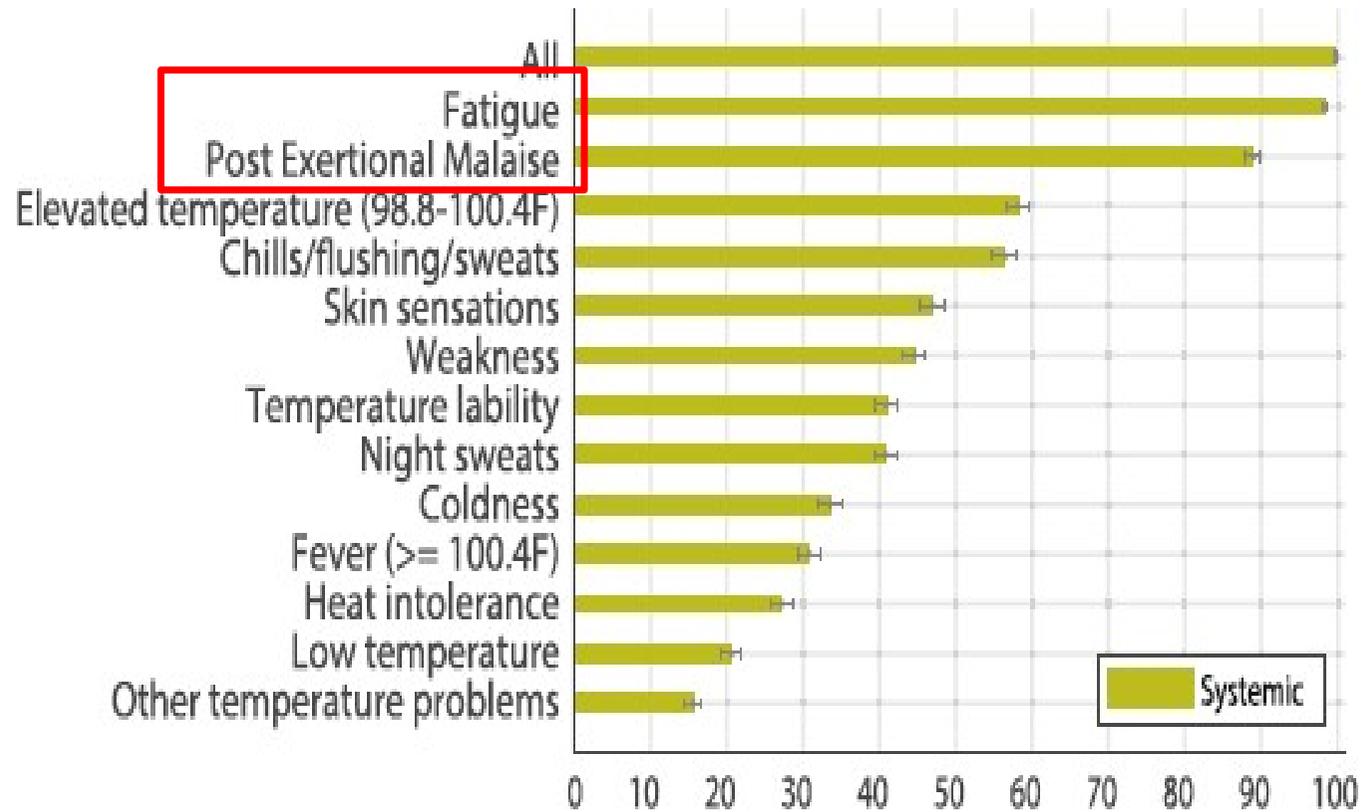
SINTOMI RESPIRATORI
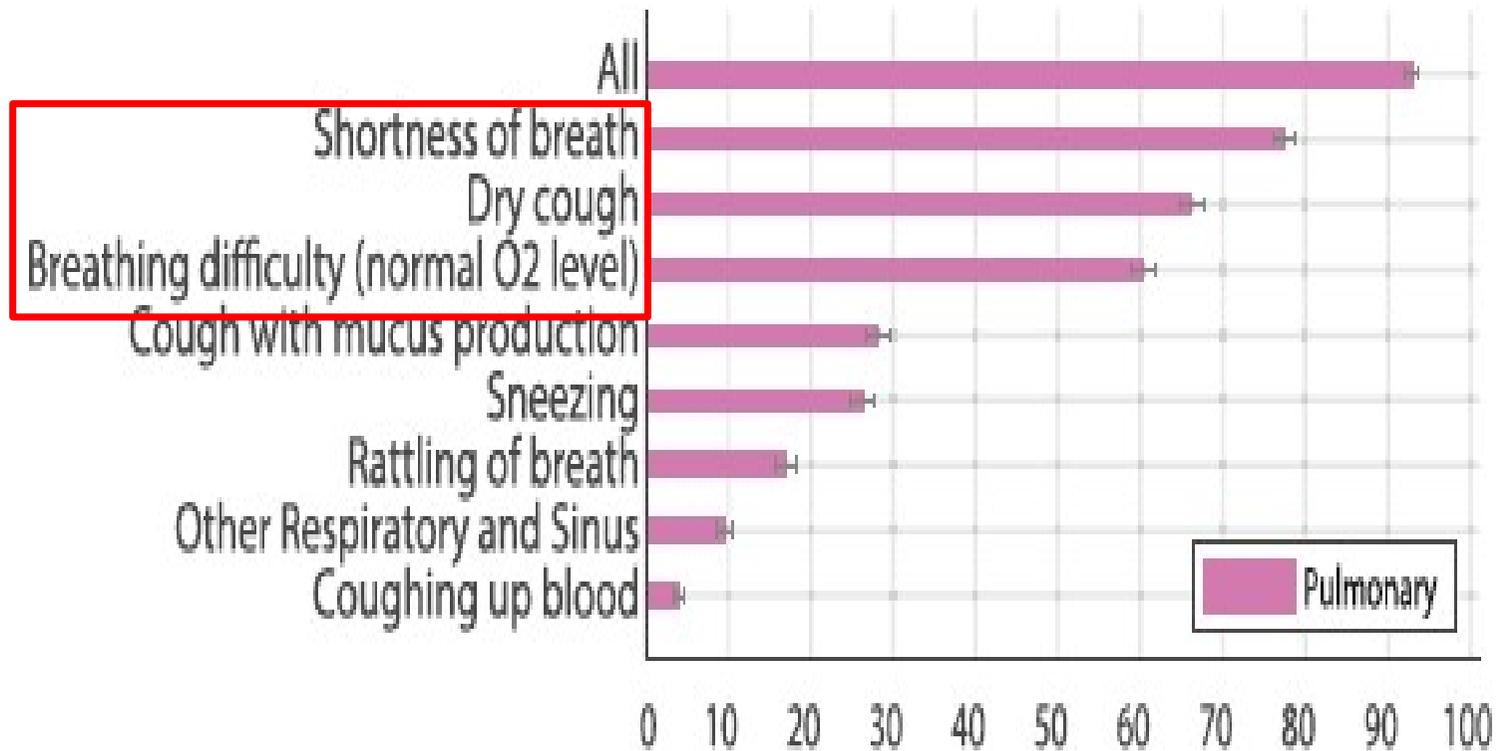
SINTOMI CARDIO-VASCOLARI
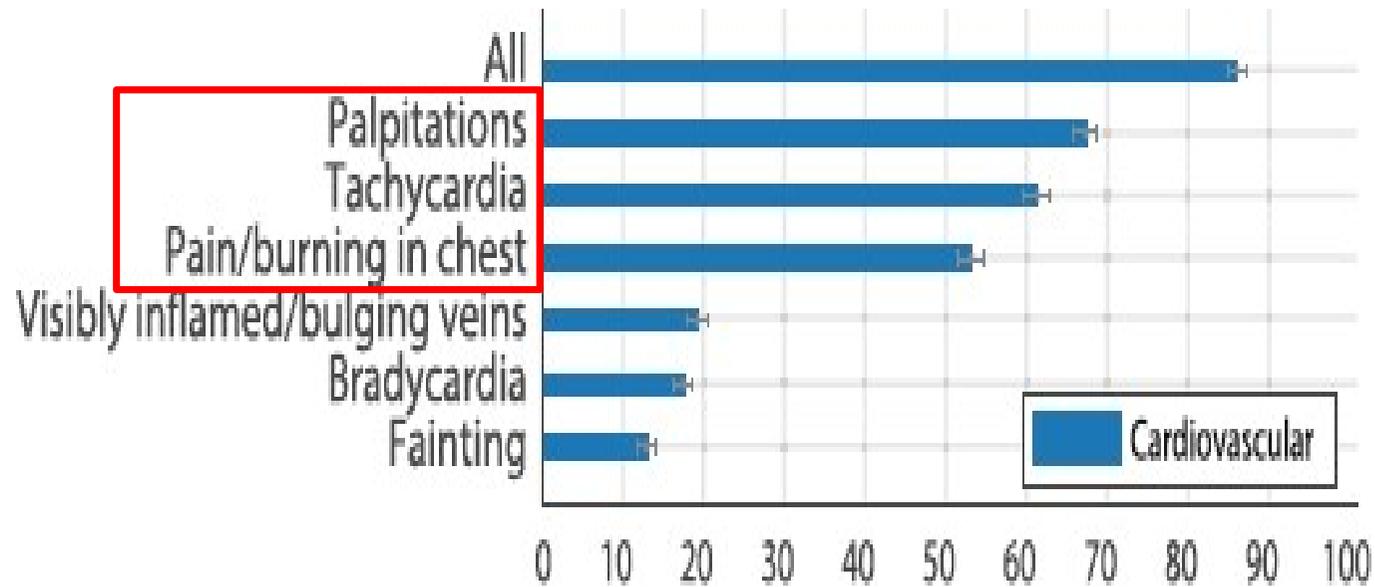
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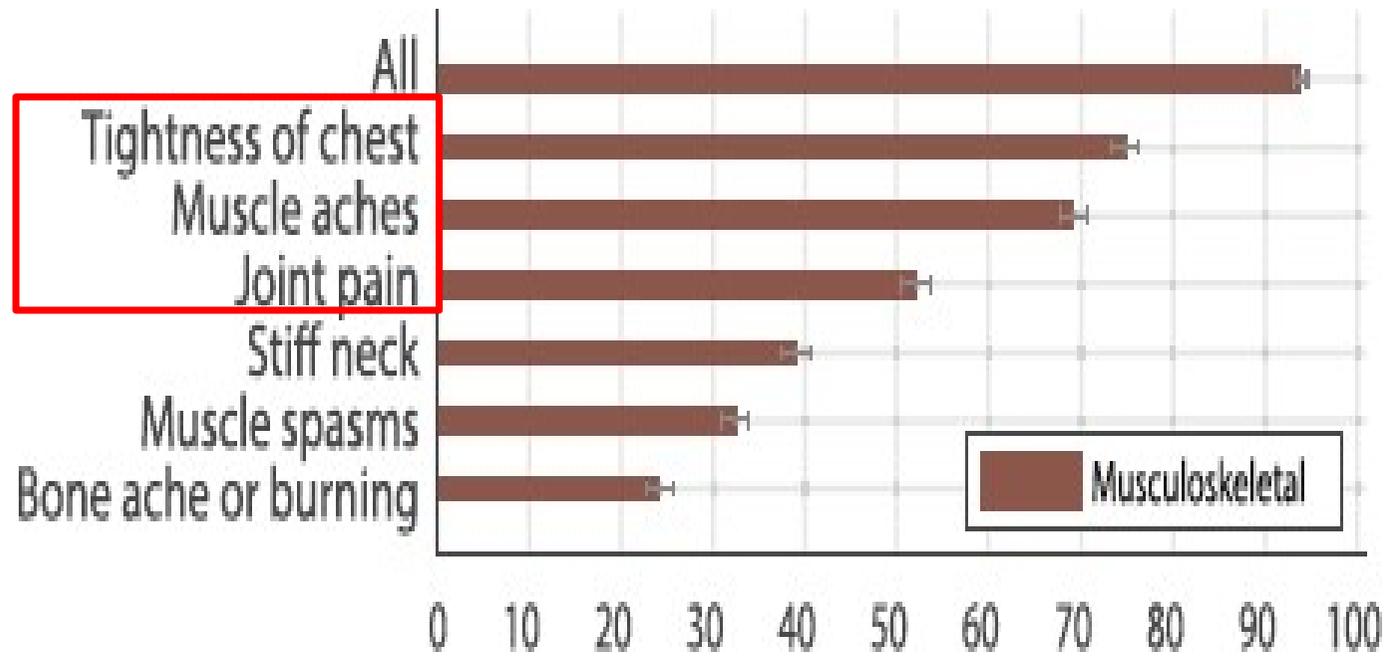
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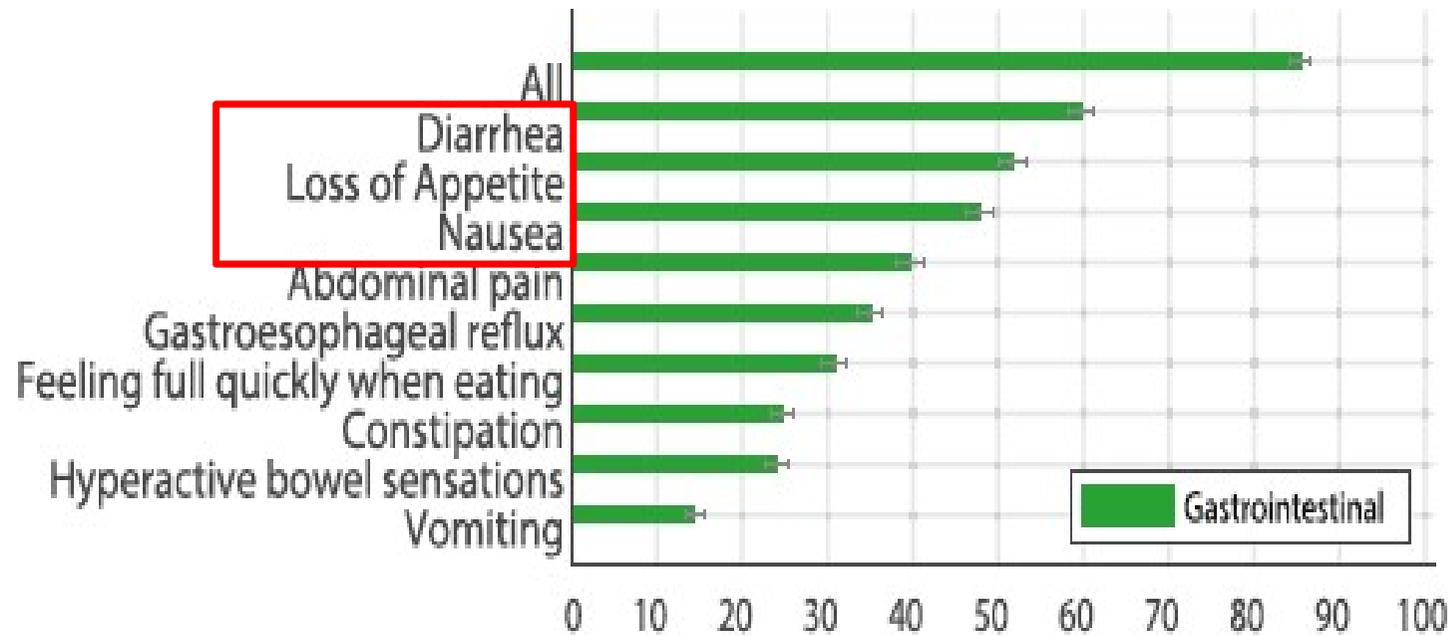
SINTOMI DERMATOLOGICI
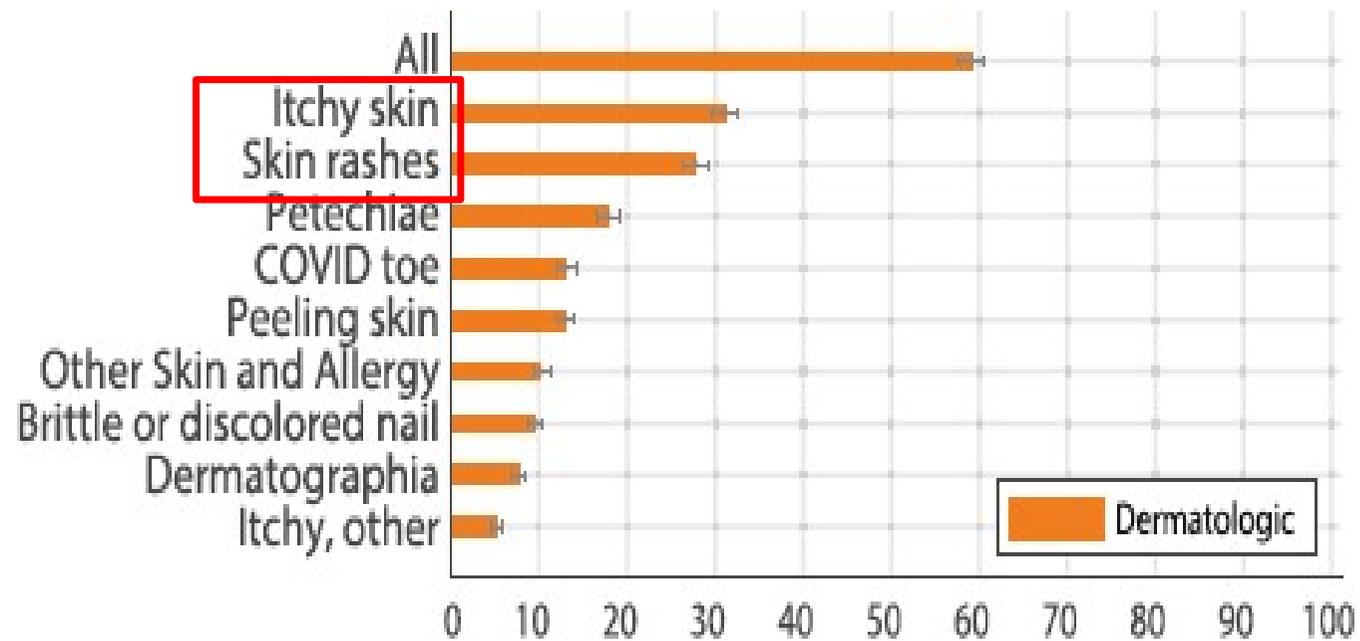
SINTOMI NEURO-PSICHIATRICI
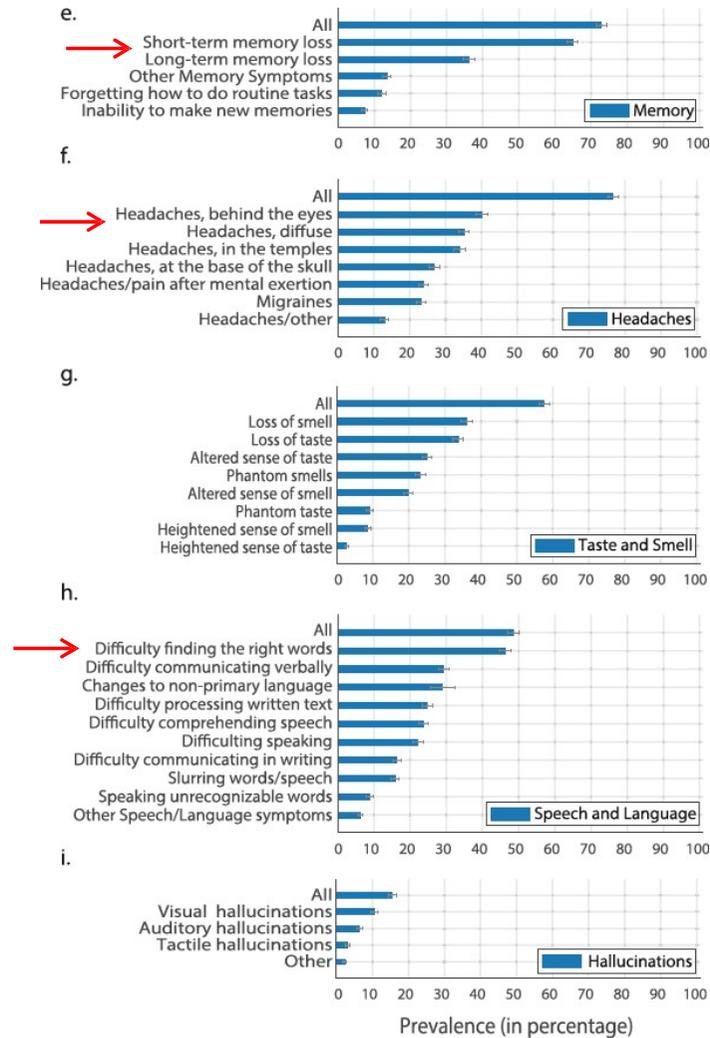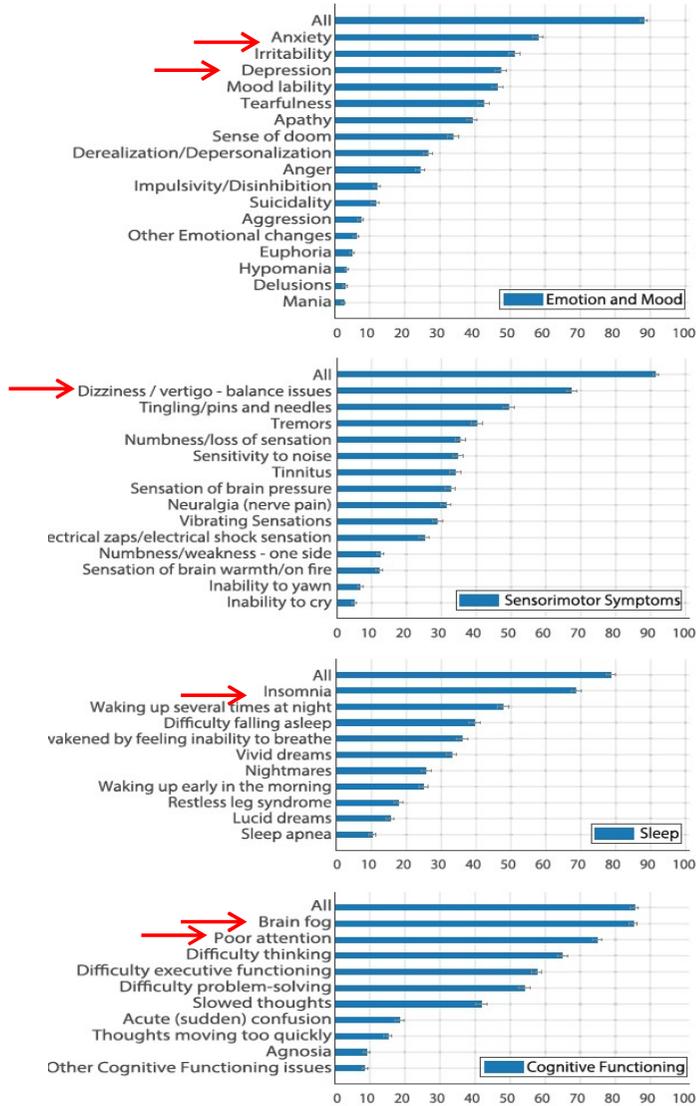
H.E. Davis et al. / EClinicalMedicine 38 (2021) 101019

SINTOMI DA LONG COVID

Low vision – 17%
Red eyes – 10%
Vertigo - 6%
Fatigue – 53%
Muscle pain – 6%
Lack of appetite – 8%
Diarrhoea – 3%
Skin lesions – 7%
Joint pain – 27%

Headache – 9%
Rhinitis – 13%
Loss of/changed sense of smell – 15%
Sjögren's syndrome – 14%
Loss of/changed sense of taste – 10%
Sore throat – 7%
Cough – 16%
Chest pain – 22%
Shortness of breath – 43%

LONG-TERM EFFECTS OF COVID-19

58% FATIGUE
27% ATTENTION LOSS
24% DYSPNEA
21% ANOSMIA
19% COUGH
13% ANXIETY
11% SLEEP DISORDER
3% DIZZINESS

JAMA 2020;324(6):603-605.
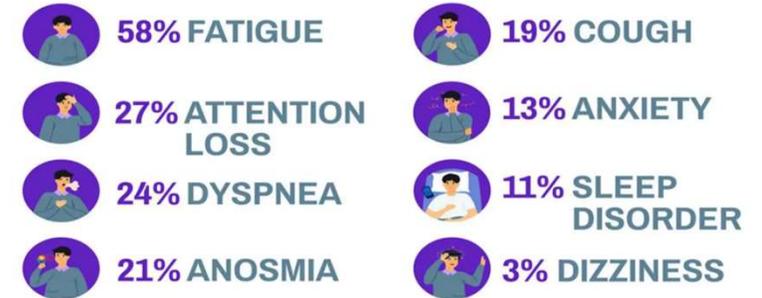
PERSISTENZA DEI SINTOMI DOPO 6 MESI

H.E. Davis et al. / EClinicalMedicine 38 (2021) 101019
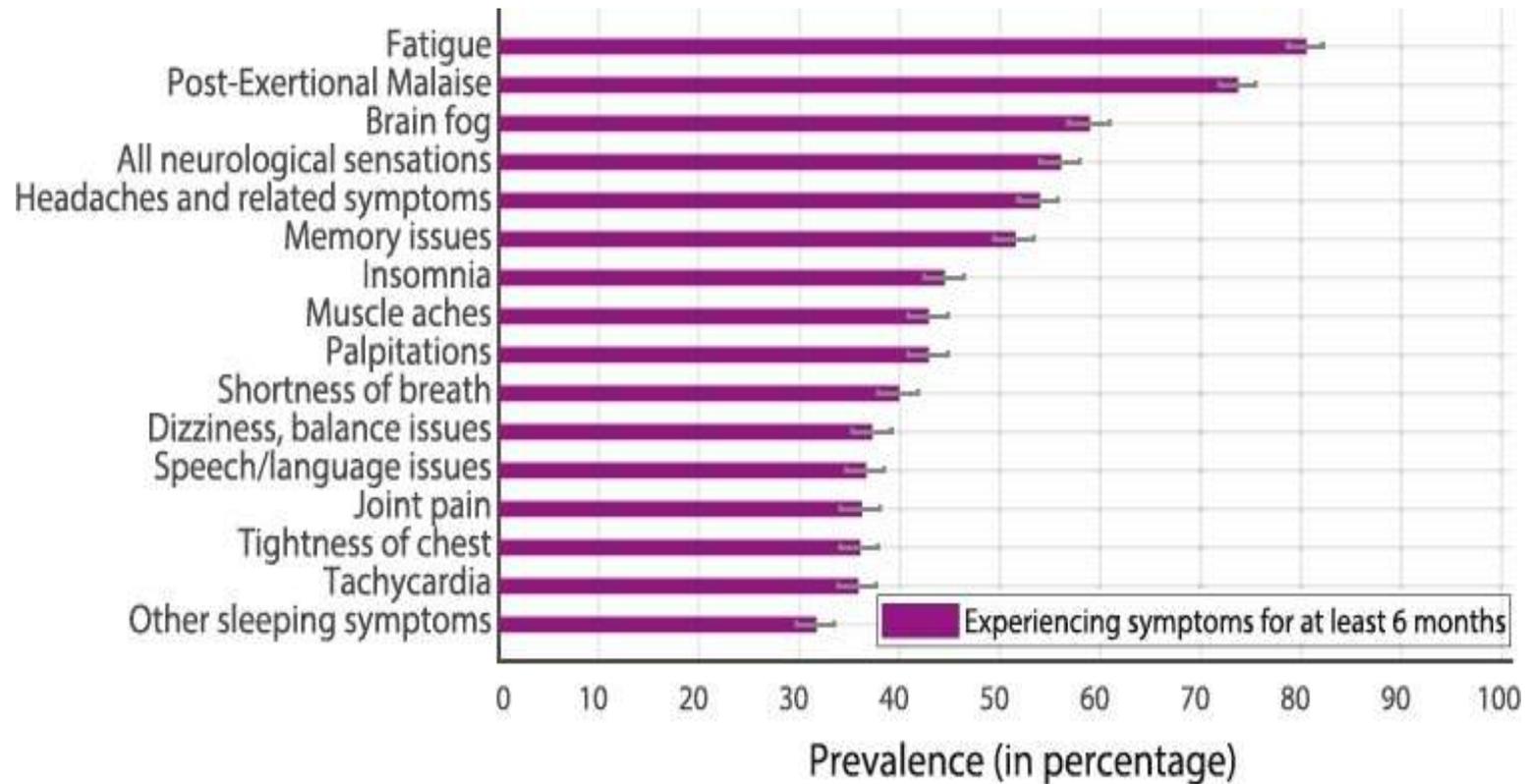
COURSE OF POST COVID-19 SYMPTOMS AT ONE YEAR
COMPARE E-COHORT

One year after COVID onset, **84.9% patients still report persistence of symptoms,** with a progressively lower prevalence
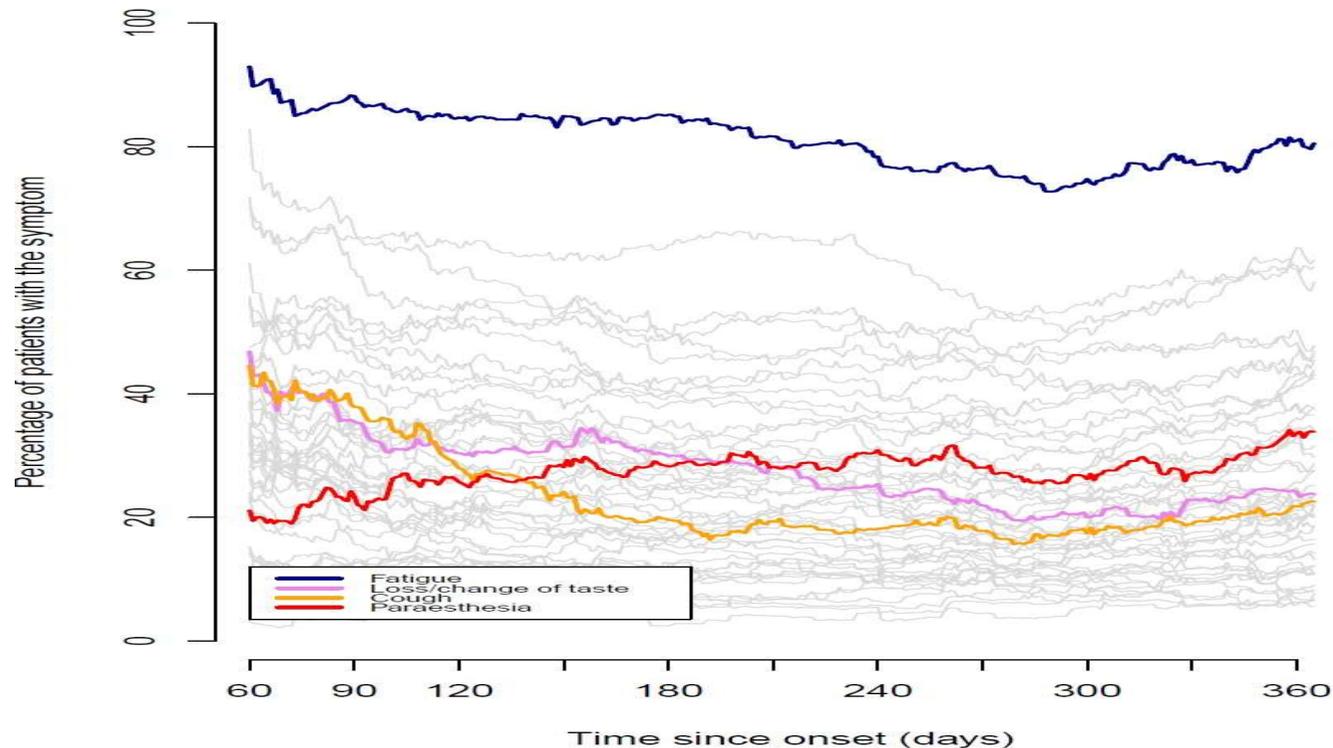
Tran VT, et al. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun. 2022 Apr 5;13(1):1812.

Long-COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic Review of the Literature

César Fernández-de-las-Peñas [1,2,*], Kin Israel Notarte [3], Princess Juneire Peligro [4], Jacqueline Veronica Velasco [4], Miguel Joaquín Ocampo [4], Brandon Michael Henry [5], Lars Arendt-Nielsen [2,6], Juan Torres-Macho [7,8] and Gustavo Plaza-Manzano [9]

Author	Variant	Country Study Period	Design Sample	Age	Symptoms Assessment	Prevalence of Long-COVID by Variant	Long-COVID Definition
Morioka et al., 2022 [24]	Omicron	Japan Omicron (n = 53) 1 December 2021–9 February 2022 Follow-up: 3 months after Other variants (n = 502) February 2020–November 2021	Cross-sectional n = 555 Female n = 314 Hospitalized n = 53	Omicron age 56 (35–69) Other variants age 48 (42–55)	Telephone interviews Self-reporting questionnaire survey	Omicron group At least one post-COVID symptom 5.6% Other variants group At least one post-COVID symptom 55.6%	Symptoms that persisted for at least 2 months within 3 months of COVID-19 onset
Azzolini et al., 2022 [25]	Historical Alpha Delta–Omicron	Italy March 2020 to April 2022	Longitudinal observational cohort n = 739 Female n = 551	NR	Survey questionnaire	OR (95% CI) Wave 1 NR Wave 2 0.72 (0.48–1.08) Wave 3 1.34 (0.26–7.01)	At least one symptom with a duration of more than 4 weeks after the infection
Qasmieh et al., 2022 [28]	Omicron	United States June 2022–July 2022	Cross-sectional n = 1036 Female n = 528 Hospitalized NR	Range 18–65 y	Survey via landlines (IVR) and mobile phones (SMS text)	Prevalence (95% CI) 21.5% (18.2–24.7) Men: 15.5 (11.6–19.4) Women: 27.3 (22.2–32.4) Fully vaccinated 25.1% (16.9–33.4) Not vaccinated 22.2% (16.6–27.9) Boosted 19.2% (14.8–23.5)	Symptoms more than 4 weeks after the start of COVID-19 that are not explained by something else
Antonelli et al., 2022 [23]	Omicron Delta	United Kingdom June 2021–March 2022	Case-control n = 97,364 Delta (n = 41,361) Omicron (n = 56,003) Female n = 55,205 Hospitalized NR	53 years	Self-reported data from the COVID Symptom Study app	OR (95% CI) Omicron vs. Delta >6 m post-vaccination 0.26 (0.20–0.32) 3–6 m post-vaccination 0.24 (0.19–0.32) <3 m post-vaccination 0.50 (0.43–0.59)	New or ongoing symptoms 4 weeks or more after acute COVID-19
Arjun et al., 2022 [27]	Omicron	India First week of January–middle of February 2022	Retrospective cohort n = 524 Female n = 212 Hospitalized n = 27	Age Mean (SD) 36 (14);	Telephone interviews	Prevalence (95% CI) 8.2% (6% to 10.9%)	Post-COVID-19 condition defined as signs and symptoms that develop during or after COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis
Fernández-de-las-Peñas et al., 2022 [26]	Historical (n = 201) Alpha (n = 211) Delta (n = 202)	Spain March 2020–August 2021	Cross-sectional cohort n = 614 Female n = 327 Hospitalized n = 614	Mean (SD) Historical 60.5 (15.5) Alpha 70.0 (15.5) Delta 56.5 (21.0)	Telephone interviews	Historical variant Number symptoms: 2.7 ± 1.3 Fatigue 68.2% Dyspnea 29.35% Alpha variant Number symptoms: 1.8 ± 1.1 Fatigue 71.5% Dyspnea 13.75% Delta variant Number symptoms: 2.1 ± 1.5 Fatigue 76.35% Dyspnea 12.8%	Development of symptoms 6 months after the acute phase of the infection

NR: not reported

Fernández-de-Las-Peñas C, G. Long-COVID Symptoms in Individuals Infected with Different SARS-CoV-2 Variants of Concern: A Systematic Review of the Literature. Viruses. 2022 Nov 25;14(12):2629.

LONG COVID: E LA DIAGNOSI?

At this time, no laboratory test can definitively distinguish post-COVID conditions from other etiologies

- A positive viral test is not required to establish a diagnosis of post-COVID conditions
- Lab testing should be guided by clinical findings
- A basic panel of lab tests might be considered between 4 and 12 weeks
- Consider additional testing if symptoms persist for 12 weeks or longer

Maurizio G. Abrignani[1], Alessandro Maloberti[2], Pier Luigi Temporelli[3], Giulio Binaghi[4], Arturo Cesaro[5,6], Francesco Ciccirillo[7], Fabrizio Oliva[8], Domenico Gabrielli[9], Carmine Riccio[10], Michele Massimo Gulizia[11,12], Furio Colivicchi[13], a nome dell'Area Cronicità Cardiologica ANMCO

[1] U.O. Cardiologia, P.O. S. Antonio Abate, Asp Trapani

Table 2. Comprehensive evaluation of long COVID-19. (a). Laboratory tests. (b). Other diagnostic tests. Tests for each symptom are not mandatory but depend on individualized medical assessment.

(a)

LABORATORY TESTS	Fatigue	Arthralgia	Myalgia	Chest Pain	Cough	Dyspnea	Anosmia	Dysgeusia	Headache	Digestive Complaints
Hemogram	+	+	+	+	+	+	+	+	+	+
c-reactive protein/erythrocyte sedimentation rate/ferritin	+	+	+	+	+	+	+	+	+	+
D-Dimer	+	+	+	+	+	+	+	+	+	+
Na/K	+	+	+	+	+	+	+	+	+	+
Liver profile	+	+	+	+	+	+	+	+	+	+
Renal profile	+	+	+	+	+	+	+	+	+	+
Thyroid function	+	+	+	+	+	+	+	+	+	+
Proteinogram	+	+	+	+	+	+	+	+	+	+
Nutritional profile	+									+
Pancreatic profile				+						+
Natriuretic peptides				+		+				
Muscular enzymes			+	+		+				
Serum cortisol	+									
Rheumatoid factor/antinuclear antibodies/complement		+	+							
Anti-transglutaminase antibodies										+

(b)

OTHER DIAGNOSTIC TESTS	Fatigue	Arthralgia	Myalgia	Chest Pain	Cough	Dyspnea	Anosmia	Dysgeusia	Headache	Digestive Complaints
Vital signs	+	+	+	+	+	+	+	+	+	+
Oxygen saturation	+	+	+	+	+	+	+	+	+	+
Electrocardiogram	+	+	+	+	+	+	+	+	+	+
Chest X-ray/lung ultrasound	+	+	+	+	+	+	+	+	+	+
Spirometry	+			+	+	+				
Chest computed tomography				+		+				
Funduscopy									+	
Joint ultrasound		+								
Abdominal ultrasound										+
Fecal occult blood										+
Digestive endoscopy										+

LONG COVID: E LA DIAGNOSI?

| Post COVID-19 symptom/signs phenotype	Imaging modality
Neurologic/p sychiatry	Brain MRI, spine MRI, functional imaging and advanced MRI techniques, hybrid imaging (PET-MRI, PET-CT)
Cardiovascular	Echocardiography, cardiac MRI, coronary CT angiography, CT pulmonary angiography, doppler vascular ultrasound (carotids, extremities, transcranial), CT or MRI angiography
Pulmonary	Chest CT, chest radiography, lung ultrasound
Hepatic/renal/gastrointestinal, metabolic	Abdominal USG, abdominal CT, abdominal MRI, nuclear medicine Immunologic/rheumatologic Different imaging modalities according to clinical Indication
Paediatric	Different imaging modalities; due to risk of radiation, ultrasound and MR are preferable options

LONG COVID: QUALI TERAPIE?

LONG COVID: QUALI TERAPIE?

Long COVID - studies for Drugs (1)

Drug	Studies
Microbiome immunity formula	1
Mesenchymal stem cells	1
Local corticosteroids vs Antihistamines	1
Lidocaine + ropivacaine	1
Leronlimab (PRO 140)	1
Ivermectin vs Corticosteroid	1
ImmunoSEB + ProbioSEB CSC3	1
Hemp seed oil	1
Essence oils	3
Epoetin alfa	1
Deupirfenidone	1
Conestat alfa	1
Coenzyme Q10	1
Clarithromycin vs Hydroxychloroquine	1
Clarithromycin	1
Bioarginina C	1
BIO 300 Oral Suspension	1
Atorvastatin	1
Apixaban vs Atorvastatin	1
Ampion	1
5-ALA/SFC	1

Long COVID studies - Drugs (2)

Drug	Studies
Vitamin D	1
Ubidecarenone	1
Treamid	1
Theophylline	1
Tadalafil	1
Sacubitril + valsartan	1
S-1226	1
RSLV-132	1
Rosuvastatin	1
Rivaroxaban	1
Resveratrol	1
Probiotics	1
Prednisone	3
Filgrastim vs Prednisone	1
Pirfenidone	2
Pirfenidone vs Nintedanib	1
Palmitoylethanolamide + luteolin	1
Oxaloacetate	1
Omni-Biotic Pro Vi 5	1
Nintedanib	1
Nicotinamide riboside	1
Naltrexone + NAD	1
Mometasone	1

COVID-19 – living NMA Initiative (supported by WHO & Cochrane)

LONG COVID: QUALI TERAPIE?

Date le scarse conoscenze patogenetiche, terapie farmacologiche specifiche sono molto limitate.

Terapie sintomatiche:

- Per tachicardia: betabloccanti o ivabradina
- Per le debolezza muscolare e l'atonia intestinale: piridostigmina
- Per deficit di attenzione e ideazione (brain fog): modafinil

Corretta gestione delle comorbidità

Mobilizzazione precoce

Riabilitazione fisica, polmonare, cardiovascolare e mentale

Supporto psicologico

Tempo stimato per la risoluzione

SINDROME DA POST-COVID-19

POTENZIALI BENEFICI DELL'ATTIVITÀ FISICA

Psicologici
- Depressione e ansia
- Stress post-traumatico

Neurologici
- Deterioramento cognitivo
- Mal di testa
- Alterazioni di gusto e olfatto
- Disturbi del sonno
- Neuropatia periferica
- Vertigini
- Delirium

6-12 settimane

Cardiovascolari
- Oppressione toracica
- Palpitazioni
- Ipotensione ortostatica
- Sincope
- Disautonomia

Respiratori
- Dispnea
- Dolore al petto
- Tosse

8-12 settimane

Muscoloscheletrici
- Fatigue
- Debolezza
- Dolore osteoarticolare
- Dolore muscolare

Altri
- Dolore addominale
- Nausea
- Diarrea
- Anoressia

¿?

Psicologici
- Modulazione del dolore
- ↑Benessere e umore
- ↓Stress

Neurologici
- Stimola la plasticità cerebrale
- ↑Abilità neurocognitive
- ↓Disfunzioni cognitive
- ↓Sovraccarico allostatico
- ↑Qualità del sonno

Cardiovascolari
- ↑Biogenesi mitocondriali
- ↑Vascolarizzazione
- ↑Funzioni cardiovascolari
- Pressione sanguigna
- Normalizzazione della Disautonomia

Respiratori
- ↓Dispnea
- ↑Assorbimento dell'ossigeno
- ↑Funzioni polmonari
- ↑Stress ossidativo

Muscoloscheletrici
- ↑Massa muscolare
- ↑Forza muscolare
- ↑Coordinazione intermuscolare
- ↑Tolleranza agli esercizi

Altri
- ↑Funzioni immunologiche
- ↑Citochine antinfiammatorie
- ↓Citochine proinfiammatorie
- ↓Immunosenescenza

STUDIO REQUPERO

REVIEW ARTICLE

Coenzyme Q10 + alpha lipoic acid for chronic COVID syndrome

Maria Angela Barletta[1] · Gerardo Marino[1] · Barbara Spagnolo[3] · Francesco Paolo Bianchi[2] ·
Paola Chiara Francesca Falappone[1] · Luca Spagnolo[3] · Pietro Gatti[1]

Acido alfa lipoico

ALA, acido tiottico

$C_8H_{14}O_2S_2$

S C O H

Figure 1. CoQ$_{10}$ is an essential component of the electron transport chain within the mitochondria.[2,3]
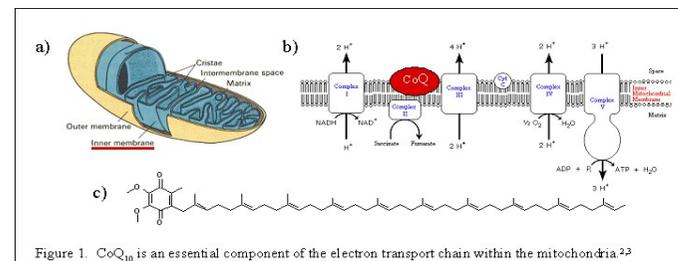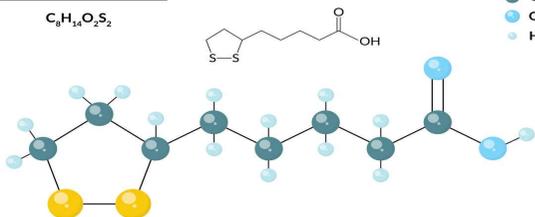
LONG COVID: RUOLO DEL VACCINO

Explained: Long COVID

Q: What is Long COVID?

A: About 10% of individuals with COVID-19 infection will continue to have symptoms lasting more than 12 weeks.

Most common symptoms:

Fatigue, shortness of breath, pain, anxiety and depression, trouble thinking/concentrating ("brain fog")

Vaccines reduce the chance of getting infected with COVID-19 by about **85%**

Vaccines reduce the chance of developing **Long COVID-19** in breakthrough infections by about **50%**
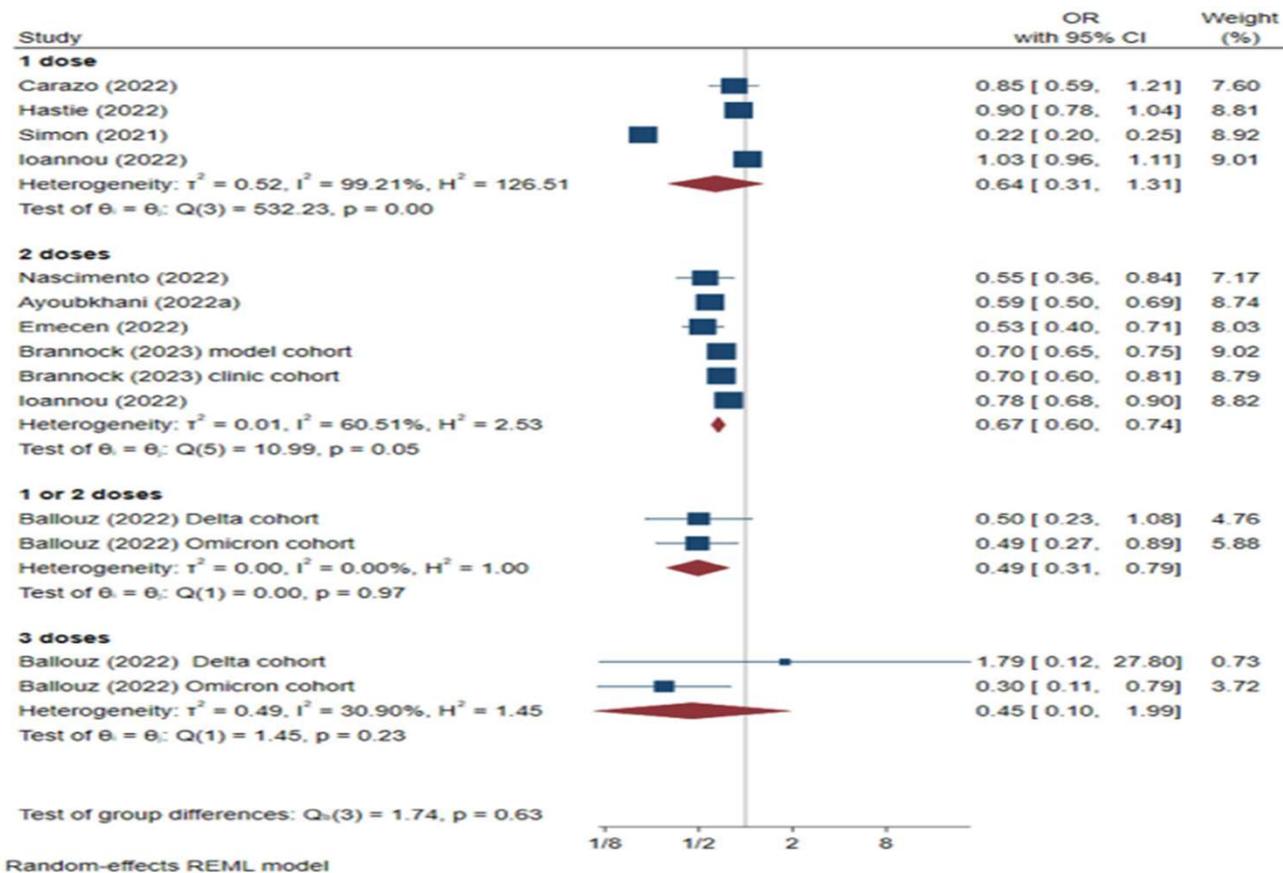
Figure 2. Meta-analysis of the effect of vaccination prior to COVID-19 compared to unvaccinated on the odds of developing PCC, stratified by number of doses.

Jennings S, (2023). A systematic review of the evidence on the associations and safety of COVID-19 vaccination and post COVID-19 condition. Epidemiology and Infection, 151, e145, 1–12

GESTIONE DEL LONG COVID

GESTIONE DEL LONG COVID

Pulmonary/cardiovascular

Symptom assessment through virtual/in-person follow-up at 4–6 weeks and at 12 weeks post-discharge

Dyspnea/persistent oxygen requirement

Consider 6MWT, PFT, chest X-ray, PE work up, echocardiogram and HRCT of the chest as indicated

Hematology

Consider extended thromboprophylaxis for high-risk survivors based on shared decision-making

Neuropsychiatry

Screening for anxiety, depression, PTSD, sleep disturbances and cognitive impairment

COVID-19 clinic

Renal

Early follow-up with nephrologists after discharge for patients with COVID-19 and AKI

Primary care

Consideration of early rehabilitation
Patient education
Consider enrollment in clinical research studies
Active engagment with patient advocacy groups

L'IMPATTO SOCIALE DEL LONG COVID

"I'm diminished and trapped in a 90-year-old body!"
Claire, 48, 3 years of COVID long

"COVID for me is worse than my breast cancer!"
Katelle, 46, 23 months of COVID long

"With my son, I a living life of death, I have no
strength! I see him suffering without being able to do
anything for him!" Nadia, 40, 30 months of COVID
long

"Financially, I'm in a bind" Vincent, 29, 18 months of
COVID long

Impact aggravated by the still uncommon lack of
recognition of the medical profession, employers, social
security

B

Percentage of patients reporting a high disease burden

Legend:
— Personal activities
— Professional activities
— Social activities
— Morale
— Family
— Relationship with caregivers
— Unacceptable Disease State

Time since onset (days)
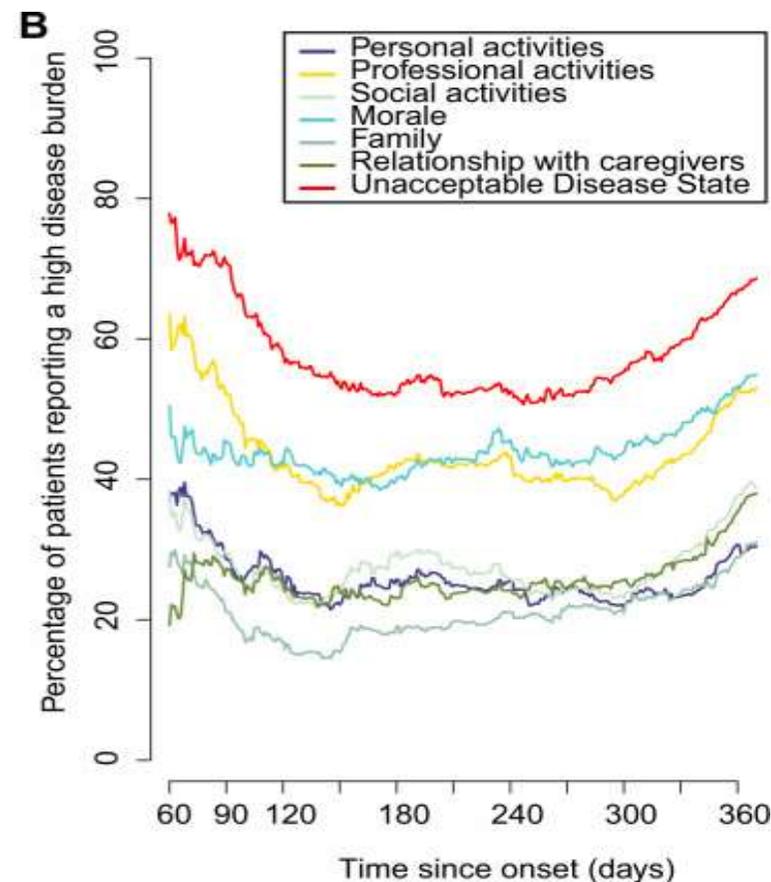
L'IMPATTO SOCIALE DEL LONG COVID

IL PROGETTO "ANALISI E STRATEGIE DI RISPOSTA AGLI EFFETTI A LUNGO TERMINE DELL'INFEZIONE COVID-19 (LONG-COVID)"

è coordinato dall'Istituto Superiore di Sanità (ISS) nell'ambito del programma di attività del Centro Nazionale per la Prevenzione e il Controllo delle Malattie (CCM) del Ministero della Salute per l'anno 2021.

Il progetto, iniziato nel dicembre 2021, è coordinato dal Prof. Graziano Onder e coinvolge per due anni diversi Enti, quali: ARS Toscana, AReSS Puglia, Azienda Sanitaria Universitaria Friuli Centrale, Rete delle Neuroscienze e Neuroriabilitazione (rete degli IRCCS), Rete Aging (rete degli IRCCS), Associazione Rete Cardiologica (rete degli IRCCS), Università Cattolica del Sacro Cuore.

Scopo del progetto è di monitorare le dimensioni e la gestione clinica del problema Long-CoViD, censire i centri clinici che assistono i pazienti con Long-CoViD, definendo una rete nazionale, e strutturare una rete informativa dedicata.

IL PROGETTO "ANALISI E STRATEGIE DI RISPOSTA AGLI EFFETTI A LUNGO TERMINE DELL'INFEZIONE COVID-19 (LONG-COVID)"

- DEFINIRE LE DIMENSIONI DEL FENOMENO LONG-COVID

- DEFINIRE NUMERO, CARATTERISTICHE E DISTRIBUZIONE SUL TERRITORIO NAZIONALE DEI CENTRI LONG-COVID CON L'ISTITUZIONE DEL REGISTRO NAZIONALE DEI CENTRI DI ASSISTENZA LONG-COVID

- DEFINIRE BUONE PRATICHE PER LA GESTIONE E PRESA IN CARICO DELLE PERSONE CON LONG-COVID

- SVILUPPARE UN SISTEMA DI SORVEGLIANZA NAZIONALE DEL LONG-COVID.

- STRUTTURARE UNA RETE CLINICA NAZIONALE DI CENTRI LONG-COVID E ATTIVITÀ DI DIFFUSIONE

Giuliano M, Italian good practice recommendations on management of persons with Long-COVID. Front Public Health. 2023 Apr 20;11:1122141.

SINDROME POST-COVID-19: INTERROGATIVI APERTI

- QUALE LA STORIA NATURALE, QUALI PREVALENZA E INCIDENZA

- QUALI FATTORI INFLUENZANO IL RISCHIO DI SVILUPPARLA

- QUALE SINTOMO PREDICE LA NECESSITÀ DI INTERVENTO SPECIALISTICO

- QUALI ESAMI E CARATTERISTICHE CLINICHE SONO MARCATORI PROGNOSTICI

- L'EFFICACIA DEGLI INTERVENTI PER SESSO, ETÀ, STATO SOCIOECONOMICO

- QUALE EFFICACIA CLINICA DEI MODELLI DI RIABILITAZIONE SUGLI ESITI

- QUALI STRUMENTI SONO CONVALIDATI PER LO SCREENING

SINDROME POST-COVID-19: TAKE HOME MESSAGE

Possiamo considerare il Long Covid un libro bianco ancora da scrivere gli studi sono ancora molto piccoli, alcuni elementi possiamo sottolinearli:
• le persone affette sono più ad alto rischio di mortalità
• hanno maggiori probabilità di utilizzare risorse
• presentano il più delle volte una vasta gamma di sintomi che provocano uno scarso benessere generale per lunghi periodi.

È fondamentale gestire dei follow-up multidisciplinari con l'obiettivo di intercettare precocemente la sintomatologia o il suo peggioramento cercando di valutare la storia clinica del paziente che comprende:
• *lo stato vaccinale dell'individuo*
• *la durata dei sintomi e la gravità nella fase acuta dell'infezione eventuale se c 'e' stata ospedalizzazione*
• *la presenza di malattie concomitanti (diabete mellito, patologie cardiovascolari, obesità, malattie respiratorie etc.)*
• *terapia farmacologica in atto o pregressa*
• *valutazione dei sintomi del long covid*
• *valutazione dell'impatto psicologico del COVID-19 e del Long-COVID*
• *valutazione dell'impatto del COVID-19 e del Long-COVID sugli aspetti nutrizionali negli anziani soprattutto*
• *valutazione della presenza di nuovi sintomi cognitivi o annebbiamento cerebrale ("brain fog")*

TAKE HOME MESSAGE

LONG COVID:

'ONE-SIZE-FITS-ALL' IS NOT THE SOLUTION;

TOGHETHER IS BETTER

15 MARZO 2023:
INTERNATIONAL LONG COVID
AWARENESS DAY

THE DAY OF
LONG HAULER

hashtag **#LongCovidAwarenessDay e #LongCovid**

"I malati di Long Covid non sono malati immaginari
o malati di serie B, devono avere la stessa dignità e
diritti di ogni altro malato"