

LA DEPRESSIONE NEL LONG COVID: ASPETTI CLINICI E TERAPEUTICI

Gabriele Sani

Fondazione Policlinico Universitario «A. Gemelli» IRCCS
Università Cattolica del Sacro Cuore

Mental health: time to invest in quality

The theme of this year's World Mental Health Day, on Oct 10, is increased investment in mental health. Why invest, and why now? The answer is simple. At the best of times, good mental health is needed for a society to thrive. During a pandemic, good mental health is more important than ever. Without a focus on mental health, any response to COVID-19 will be deficient, reducing individual and societal resilience, and impeding social, economic, and cultural recovery. 2020 has been a difficult year for mental health

terms of quality. For example, great strides have been made in the delivery of telepsychiatry over the past 10 months; individuals who receive these services must be instrumental in their future use and development. This involvement will ensure that telepsychiatry is used in an intelligent, targeted manner that provides appropriate support, rather than being a cost-saving, one-size-fits-all measure that risks exacerbating health inequalities or inadvertently reinforcing social isolation



Mental Health and the Covid-19 Pandemic

Betty Pfefferbaum, M.D., J.D., and Carol S. North, M.D., M.P.E.

Uncertain prognoses, looming severe shortages of resources for testing and treatment and for protecting responders and health care providers from infection, imposition of unfamiliar public health measures that in-

fringe on personal freedoms, large and growing financial losses, and conflicting messages from authorities are among the major stressors that undoubtedly will contribute to widespread emotional distress and increased risk

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COVID-19 and psychiatrists' responsibilities: a WPA position paper

The SARS-CoV-2 virus has changed our world, endangering health, lives, social connections and economies¹, with the likelihood and consequences of future waves of infection still unknown. In this context, the WPA Standing Committee on Ethics and Review has produced a position paper to provide ethical guidance to the profession on the issues raised by the pandemic². This essay summarizes and builds on this position paper, adding more recent information.

During the COVID-19 pandemic, psychiatrists must continue to care for their

proven treatments, potential harms of vaccines, and protective measures. Of course, psychiatrists should safeguard their own health with proper nutrition, sleep, rest and exercise, and promptly seek professional help if they become physically or mentally unwell⁵.

Some health care professionals, working long hours in life-threatening conditions, often without appropriate protective equipment, may develop anxiety, depression, post-traumatic stress disorder (PTSD), insomnia, and excessive irritability and anger^{3,4,6}. Psychiatrists should assist in devel-

supports.

As leaders in their hospitals, health care agencies and communities, psychiatrists may also participate in COVID-19 decision-making committees (including triage), where they should safeguard the rights of persons with mental disorders. They may participate in educational and media activities for patients, health care workers, the public or policy makers about the mental health distress caused by physical distancing, home quarantine, shelter-in-place, isolation, and loss of social support, work and income^{3,7}. Psychiatrists should also advo-

Medical News & Perspectives

Prioritizing Physician Mental Health as COVID-19 Marches On

Jennifer Abbasi

In the spring of 2013, Eileen Barrett, MD, MPH, lost a colleague to suicide. The two worked at the Indian Health Service's Gallup Indian Medical Center in New Mexico, where Barrett was the deputy chief of medicine. Even before the tragic event, she saw workers struggle under administrative burdens and hold themselves personally responsible for problems outside of their control.

With her coworker's death it became painfully clear that clinician wellness had to become a higher priority. "It made me really think that we needed to do more for everybody on the health care team," Barrett, now an associate professor of medicine and an academic hospitalist at the University of New Mexico in Albuquerque, said in a recent interview with JAMA.

As the school's director of graduate medical education wellness initiatives, Barrett has spent a lot of time focusing on physician care since the coronavirus disease 2019 (COVID-19) pandemic began. She wants phy-



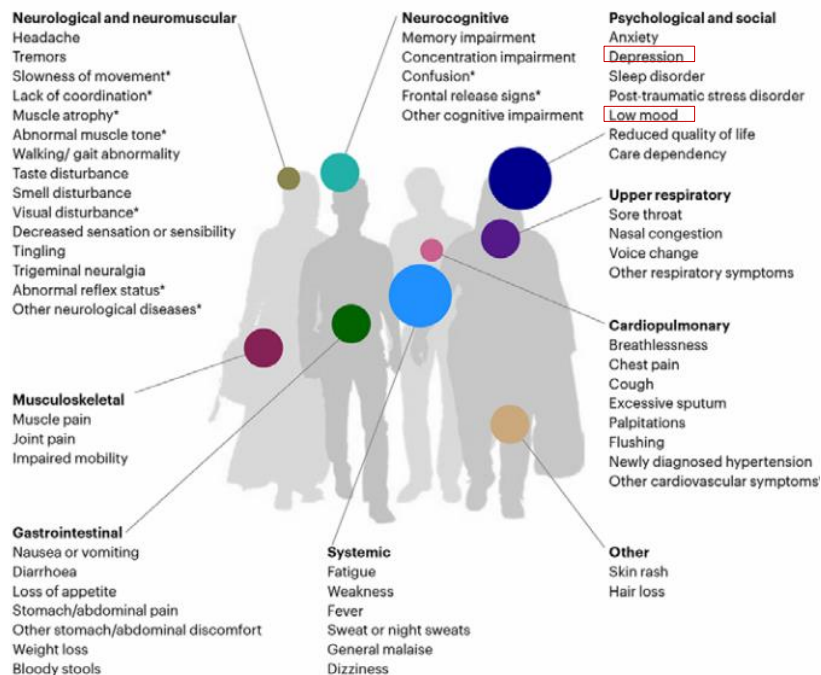
JAMA: What are some of the key stressors that physicians are dealing with during

more than 1200 health care workers in China and their mental health outcomes. They found that there were specific risk factors for

Long-COVID symptoms and signs

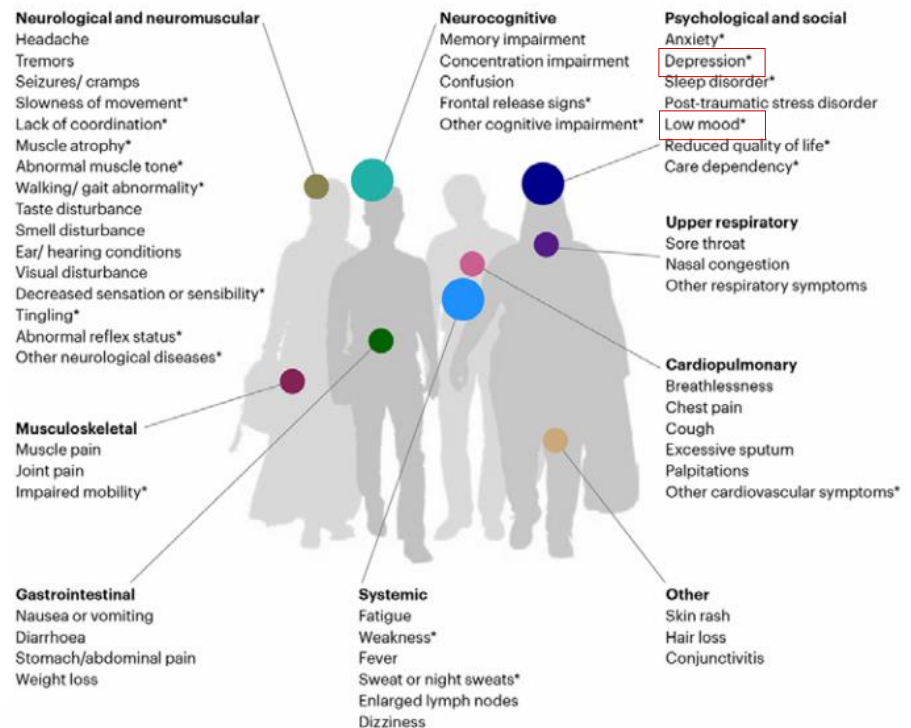
People hospitalised during acute phase of Covid-19

Based on 26 studies with 7147 people*



People non-hospitalised during acute phase of Covid-19

Based on 4 studies with 1168 people*

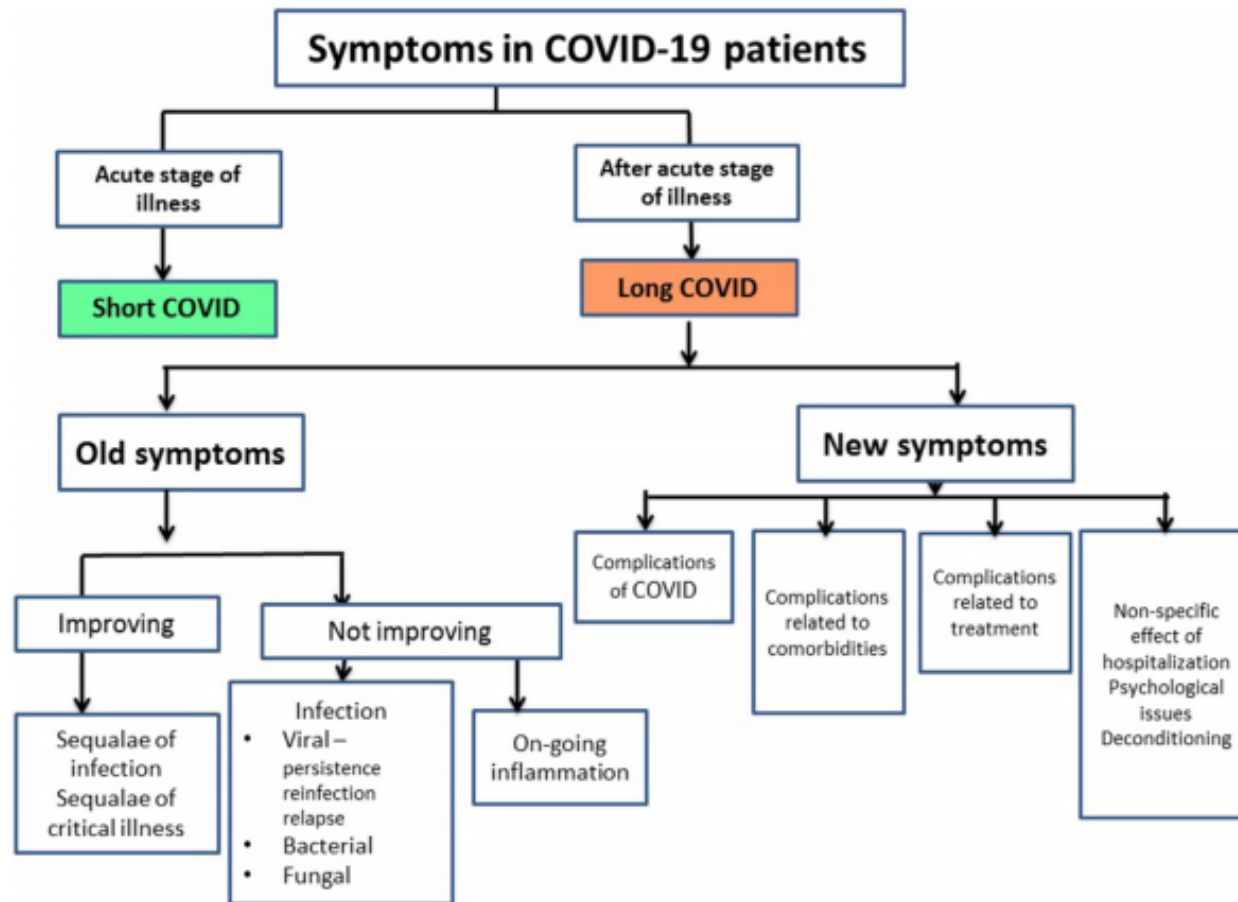


Frequency: Very common Common Less common

Raveendran et al. Long COVID: An overview. Diabetes Metab Syndr. 2021 May-Jun;15(3):869-875.

Michelen et al. Characterising long COVID: a living systematic review. BMJ Glob Health. 2021 Sep;6(9):e005427.

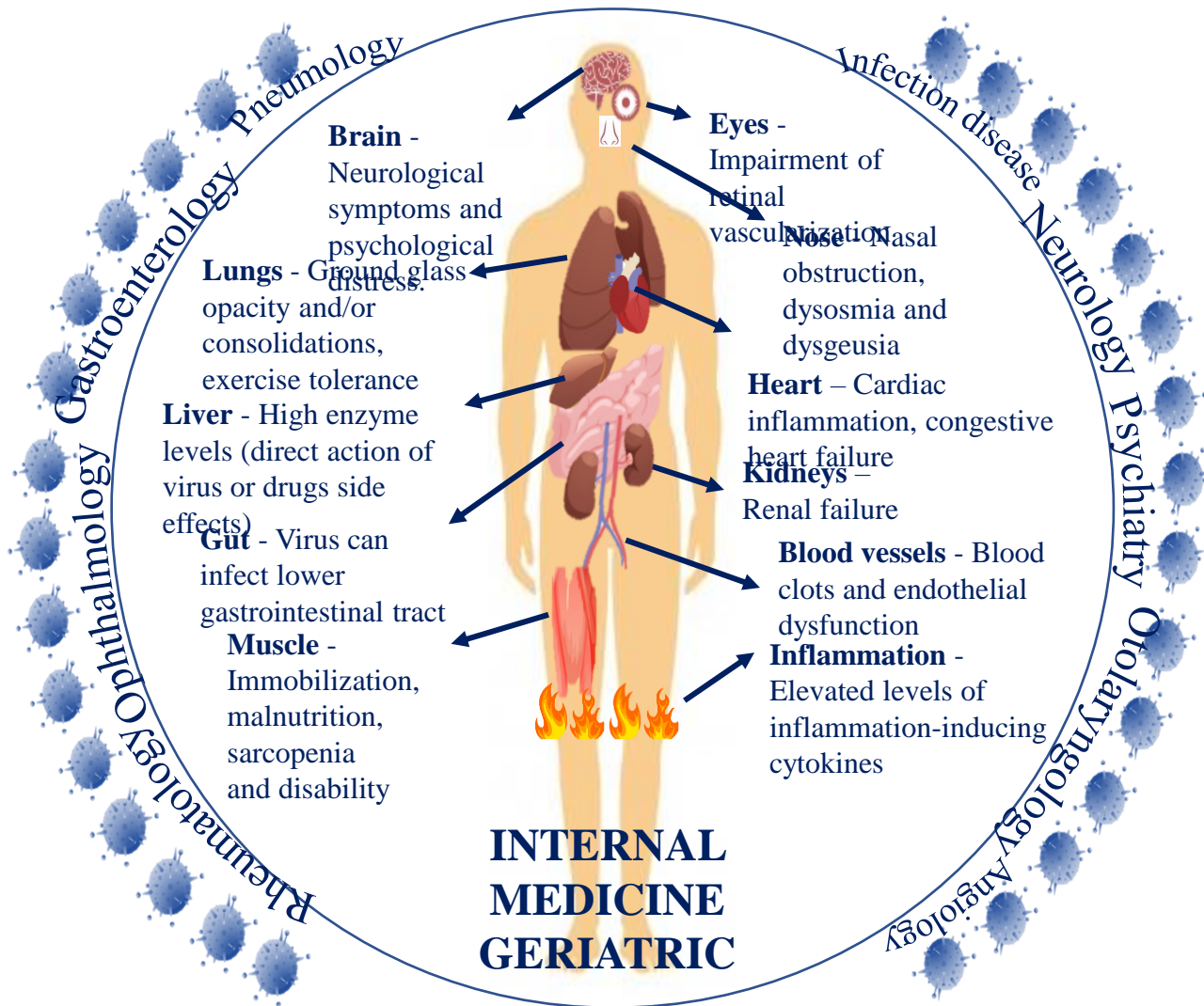
Approach to patients with Long COVID





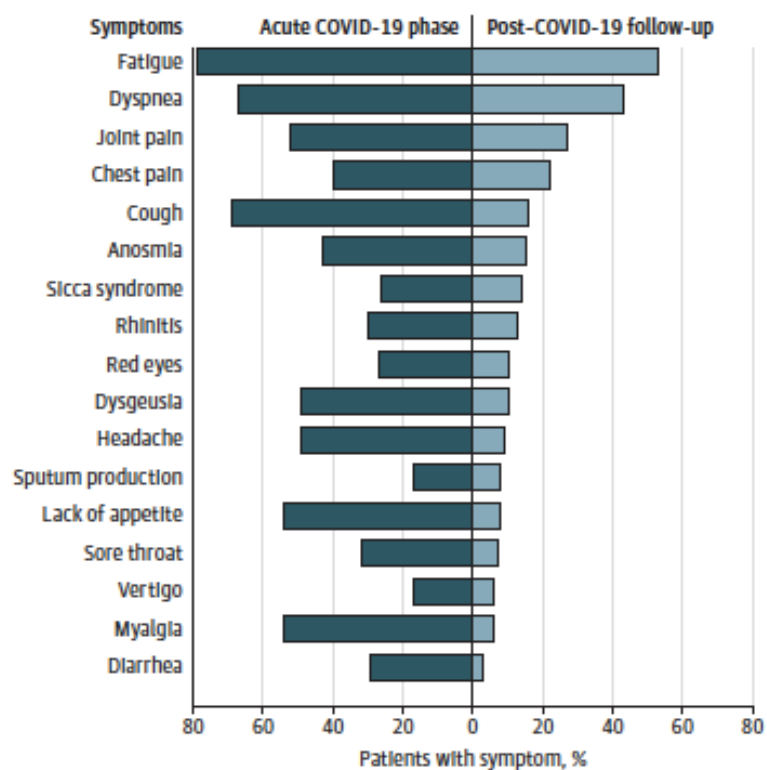
Post-COVID-19 global health strategies: the need for an interdisciplinary approach

Gemelli Against COVID-19 Post-Acute Care Study Group¹



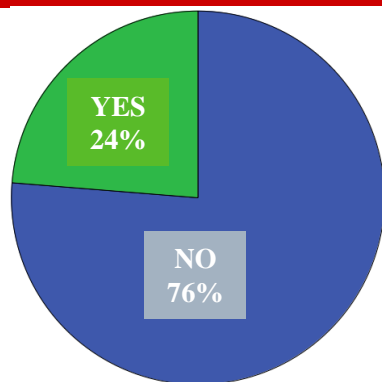
Sintomi medici persistenti in pazienti Post Covid-19

Figure. COVID-19-Related Symptoms

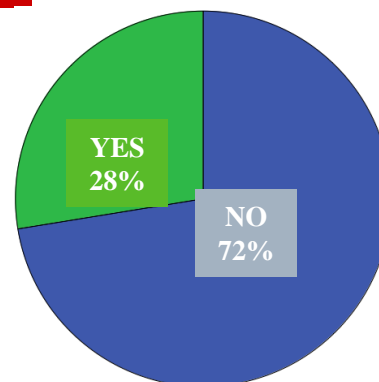


Carfi et al, JAMA 2020

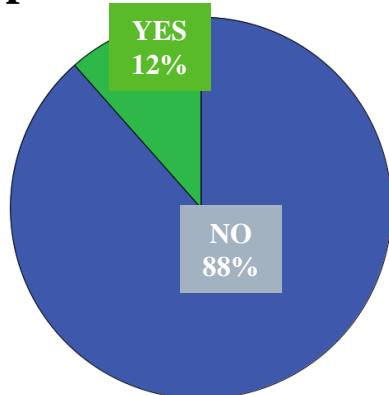
Ha mai sofferto di ansia, depressione, esaurimenti nervosi, dipendenza da sostanze?



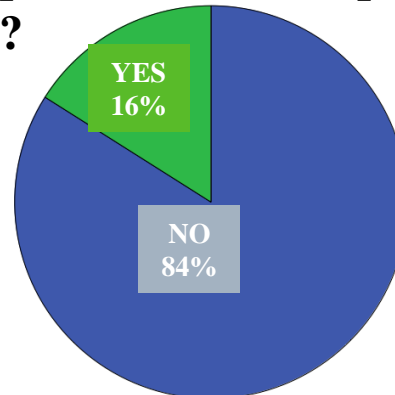
C'è qualcuno in famiglia che ha mai sofferto di ansia, depressione, esaurimenti nervosi, dipendenza da sostanze?



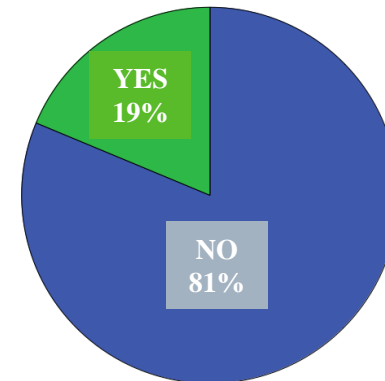
È in cura o è stato in cura da uno psichiatra?



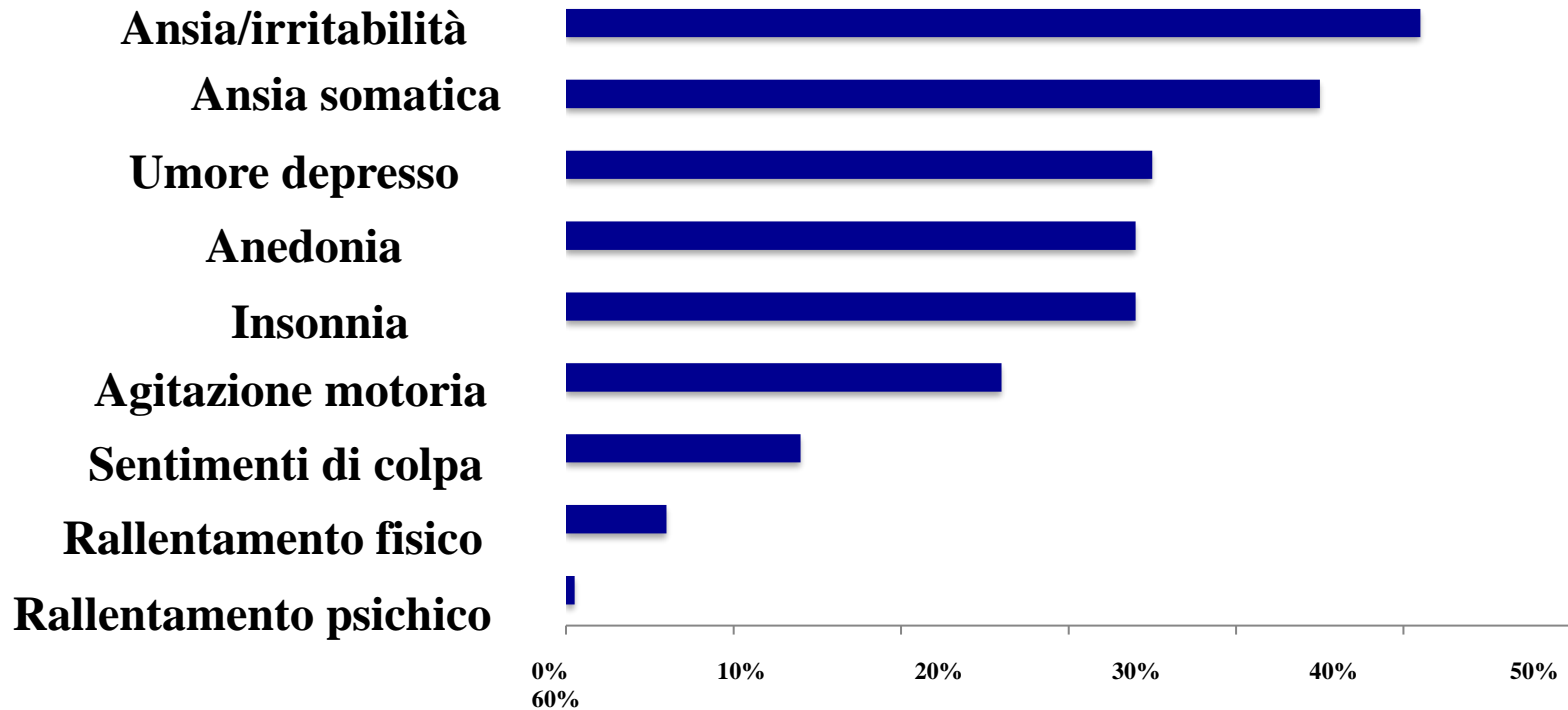
Assume o ha assunto psicofarmacoterapia ?



È o è stato in psicoterapia?



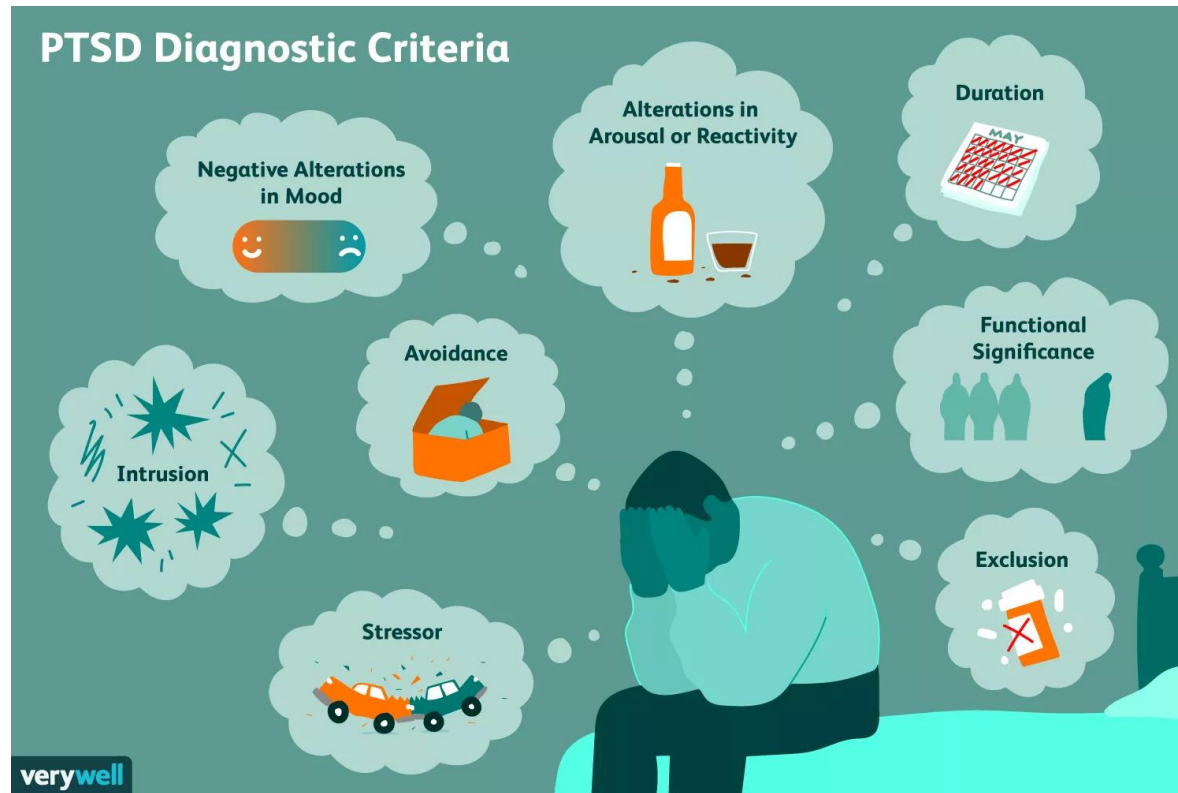
Sintomi psichiatrici in pazienti Post Covid-19



Pazienti che hanno fatto riferimento al Day Hospital Post-Covid-19 del Policlinico Agostino Gemelli (età media: 55 anni)
Depressione valutata tramite Hamilton Depression Rating Scale

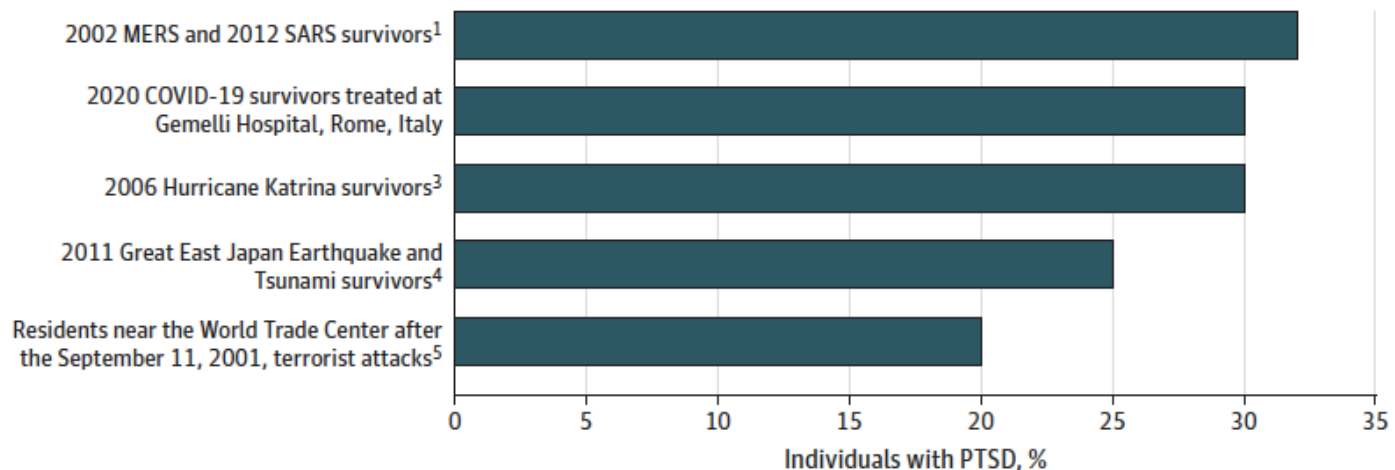
Sani et al, unpublished data

PTSD criteria DSM-5



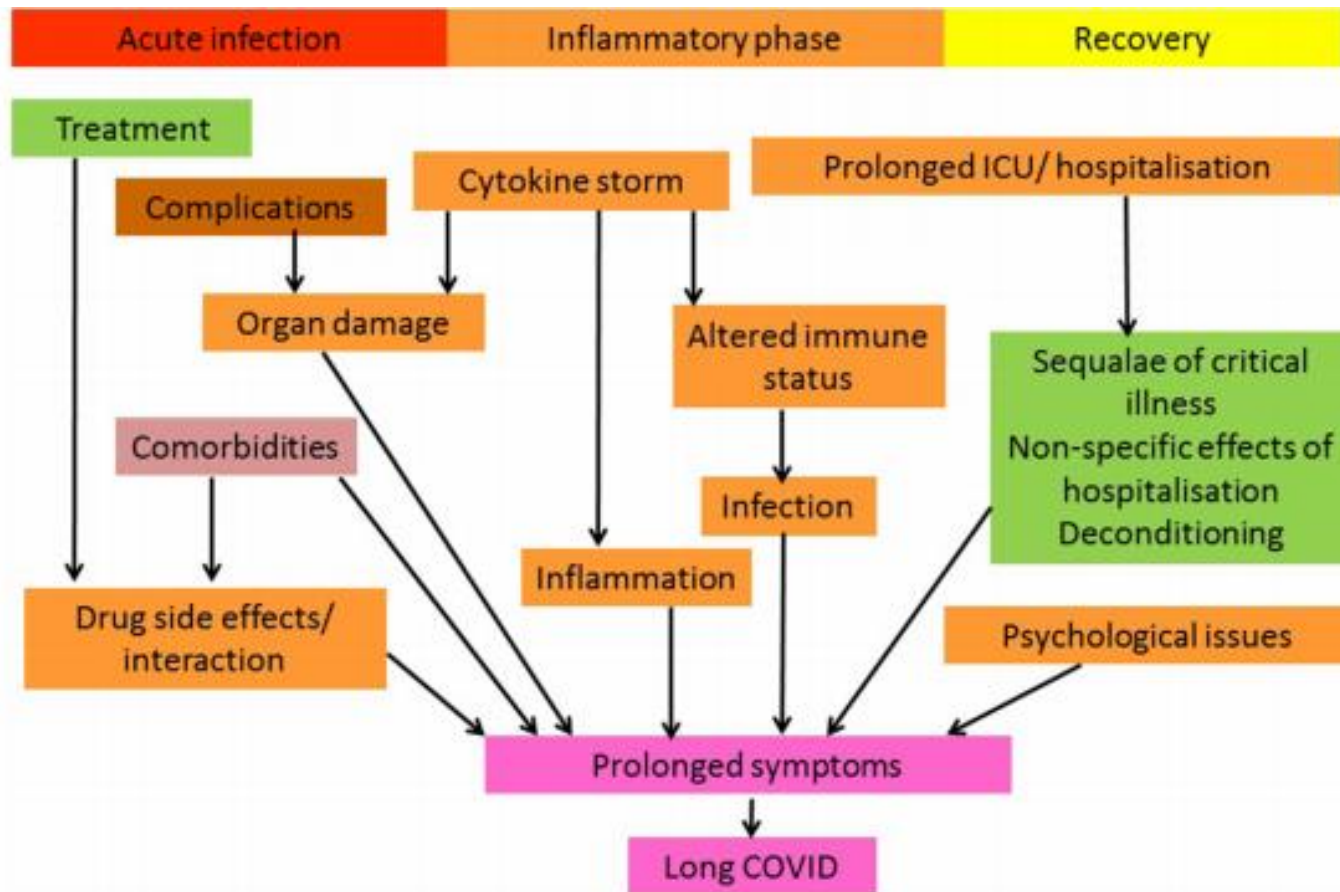
PTSD in pazienti Post Covid-19

Figure. Posttraumatic Stress Disorder (PTSD) After COVID-19 Infection and Other Collective Traumatic Events

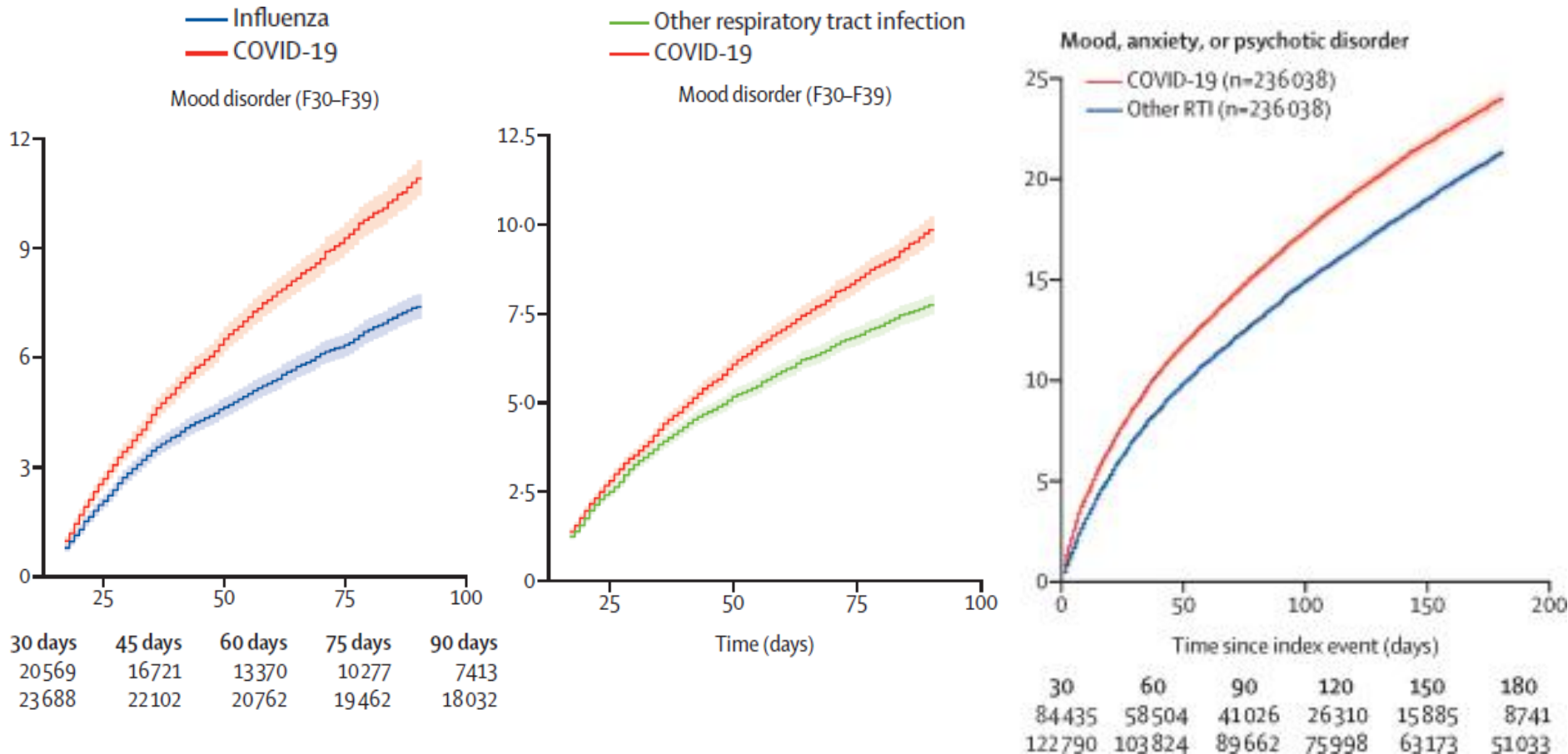


Janiri et al, JAMA Psychiatry
2021

Long COVID: pathophysiological mechanisms



COVID-19 and mood disorders: a bidirectional association



Taquet M, et al. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. *Lancet Psychiatry*. 2021 Feb;8(2):130-140.

Taquet M, et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. 2021 May;8(5):416-427.

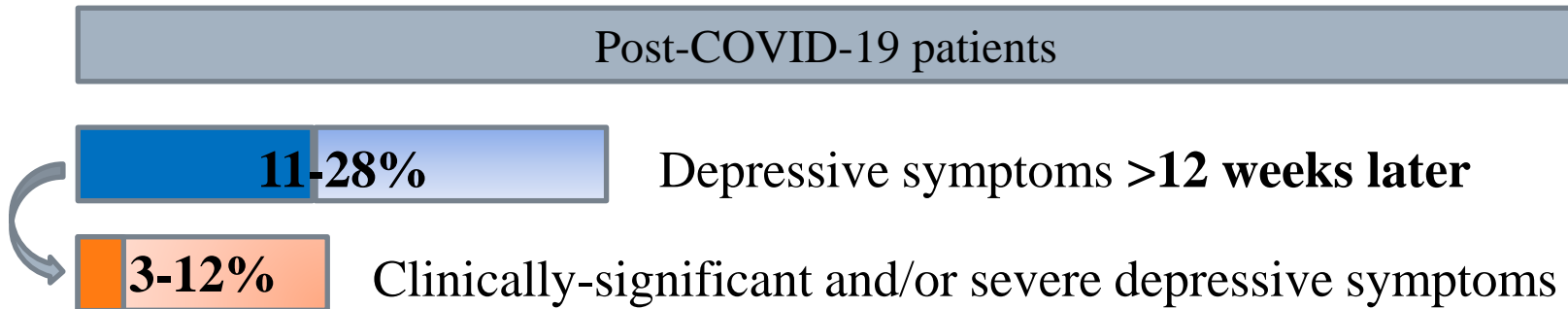
Risk factors for the onset of depressive symptoms after SARS-CoV-2 infection

- ❑ Gender: female
- ❑ Previous psychiatric history: depression and other mental disorders
- ❑ Persistence of psychopathology at one-month follow-up
- ❑ Systemic inflammation: measured by platelet count, levels of neutrophils and lymphocytes (e.g., NLR, PLR, Systemic Immune-inflammatory Index, SII)

Post-COVID-19 depression: onset and frequency

Systematic review: 316 articles screened

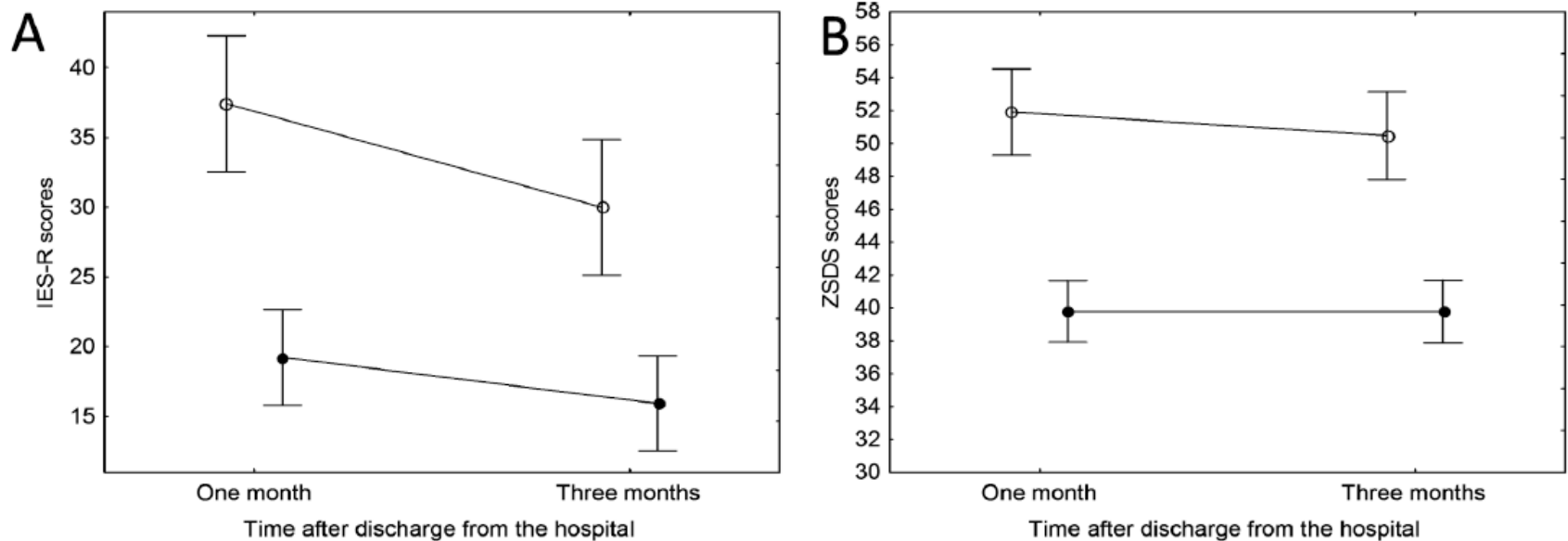
↳ 8 studies included



The severity of acute COVID-19 was not associated with the frequency of depressive symptoms.

Post-acute COVID-19 neuropsychiatric sequelae: *'long lasting'* depression

A prospective cohort study (N=226 COVID-19 pneumonia survivors, 149 males, mean age 58 years) evaluated the psychopathological status at one- and three-months post-discharge.



Characteristic features

- Evidence suggests a **central role of depressive psychopathology**, which seems to be one of the most relevant **predictors** of both **cognitive impairment** (specifically, **executive functions** and **psychomotor coordination**) and **fatigue**, which persist over time in almost a third of COVID-19 survivors.

Specific features of post-COVID-19 depression

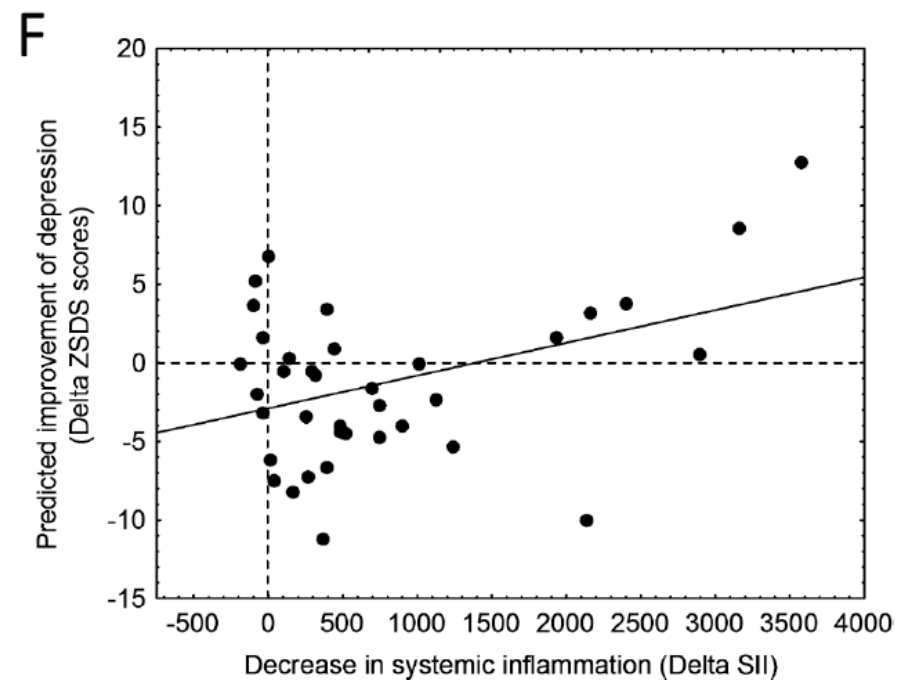
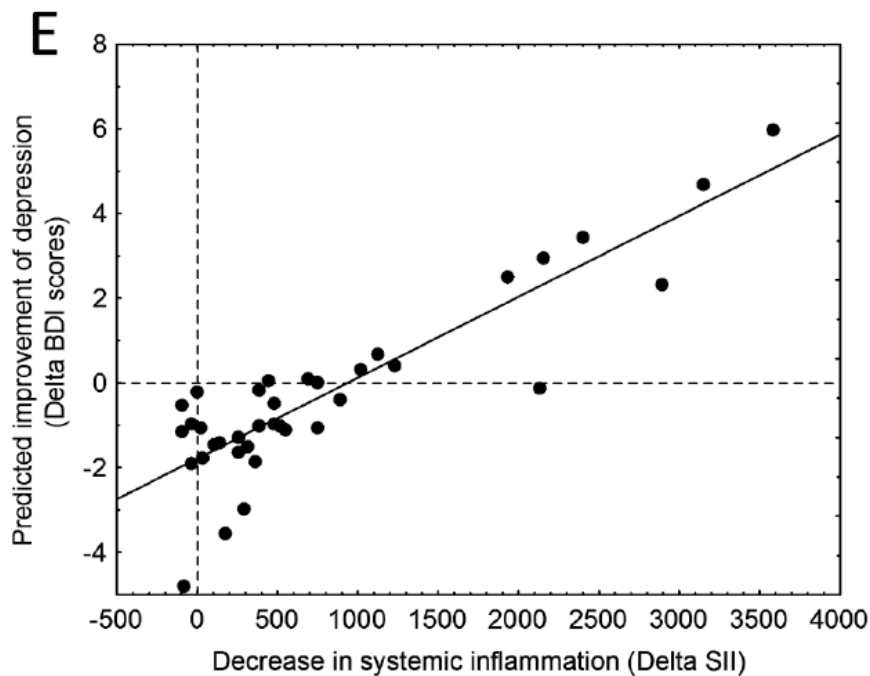
A meta-analysis on COVID-19 consequences indicate that **32%** of individuals experience **fatigue** and **22%** exhibit **cognitive impairment** 12 or more weeks following infection.

Regardless of clinical physical severity, post-COVID **depression** was found to **possibly affect**:

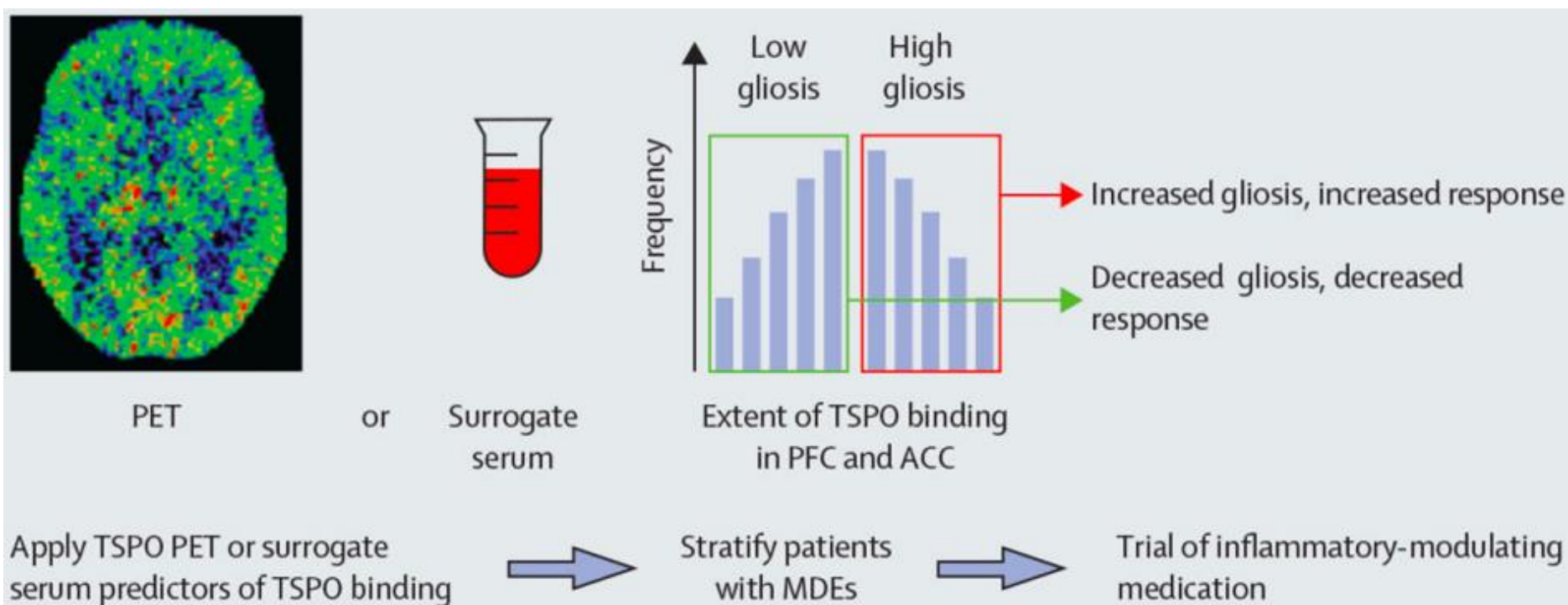
- ❑ fatigue symptoms;
- ❑ cognitive functions (with **poor** performances in at least one cognitive domain and specific impairment of **executive functions** and **psychomotor coordination**);
- ❑ daily functioning.

The role of inflammatory biomarkers in predicting persistence of neuropsychiatric symptoms

COVID-19 could result in **prolonged systemic inflammation** (as for values of Systemic Immune-inflammatory Index, SII) that predisposes patients to **persistent depression** and associated neurocognitive dysfunction.



Anti-inflammatory add-on treatment as new promising strategies in MDD

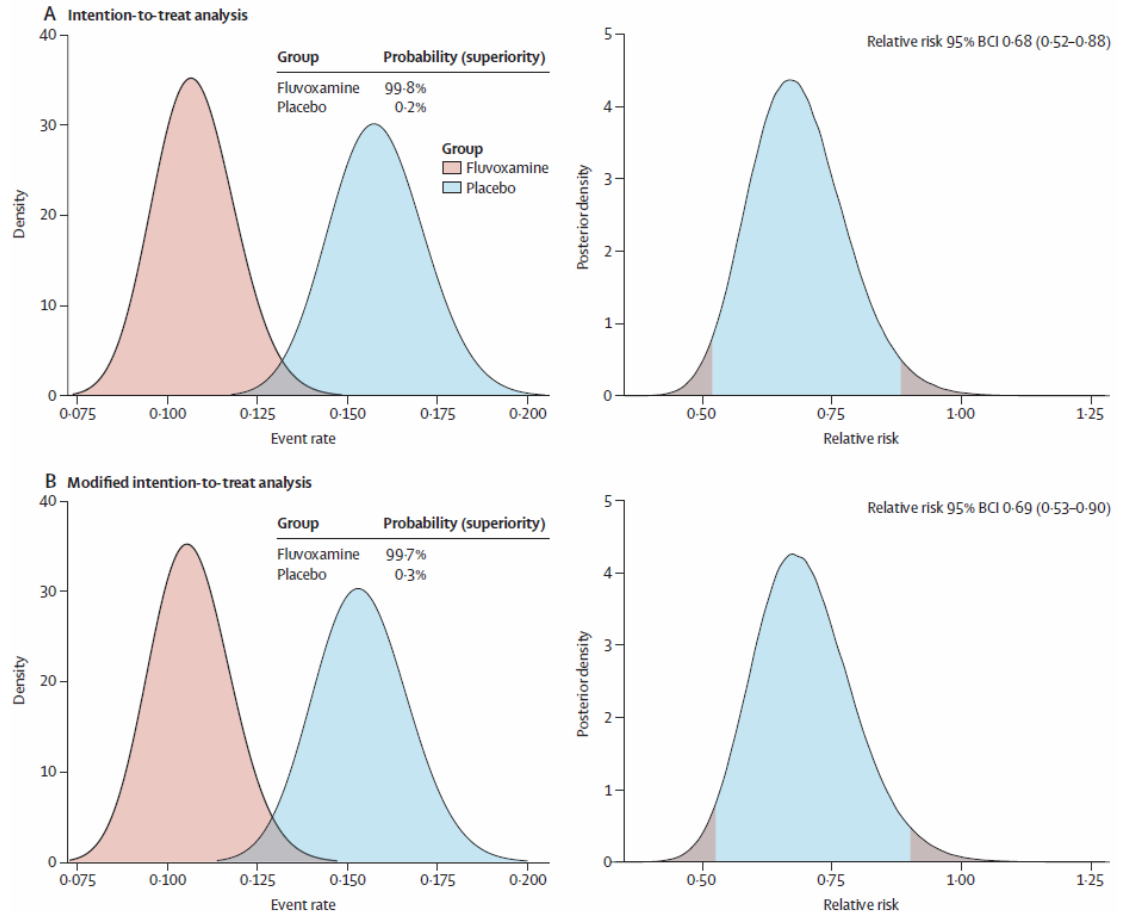


Anti-inflammatory and antiviral properties of antidepressants

Placebo-controlled
randomized trial:
Fluvoxamine group,
N=741 (100 mg
twice daily for 10
days)

vs.

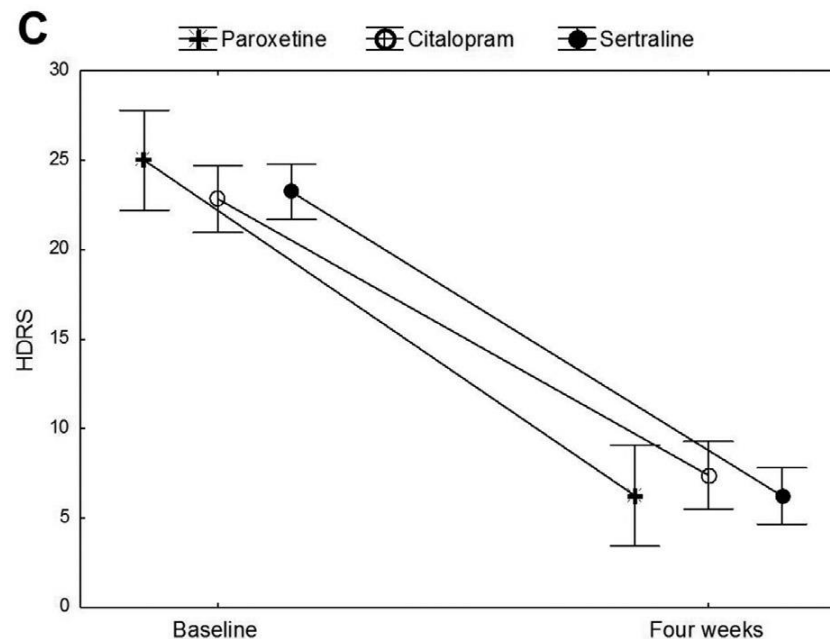
Placebo, N=756



Reis G, et al.; TOGETHER investigators. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. *Lancet Glob Health*. 2022 Jan;10(1):e42-e51.

Post-COVID-19 depression: treatment options

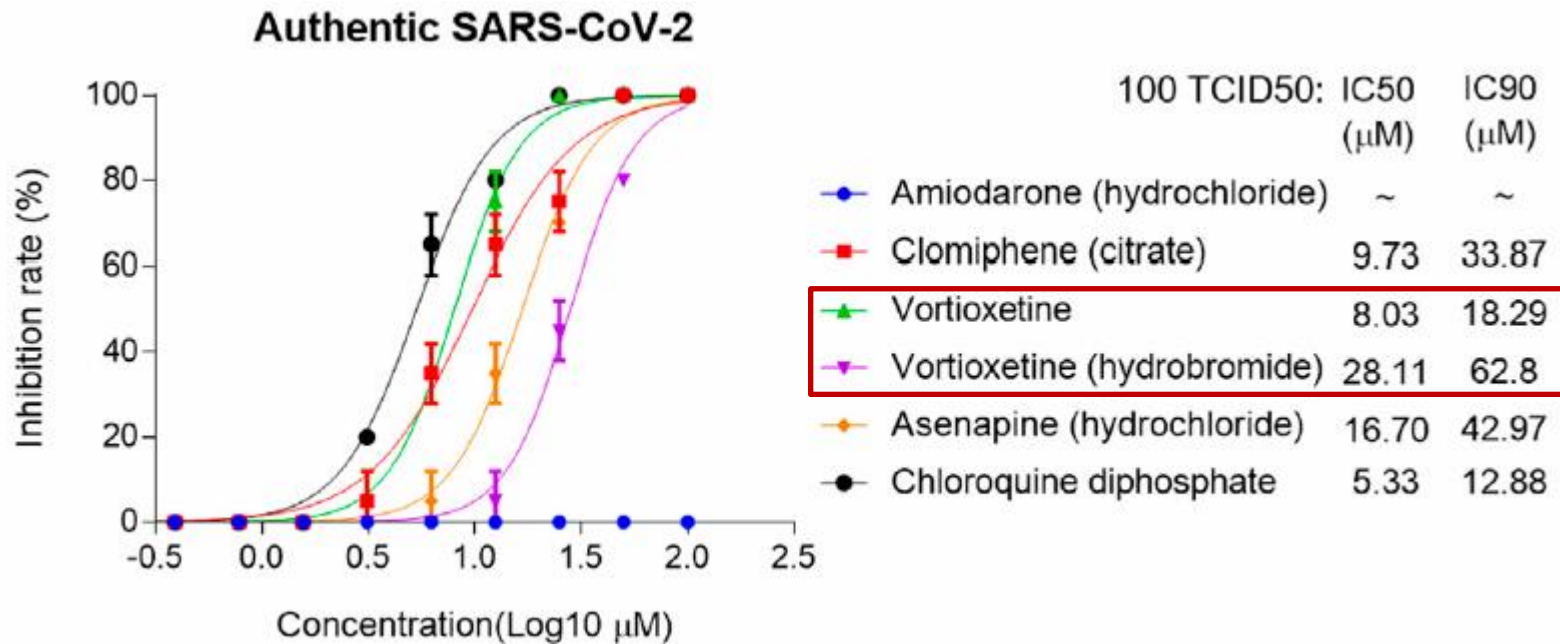
N=60 patients with MDE treated with SSRI in the 6 months after COVID recovery



SSRIs treatment could contribute to the rapid antidepressant response by directly targeting the neuroinflammation triggered by SARS-CoV-2

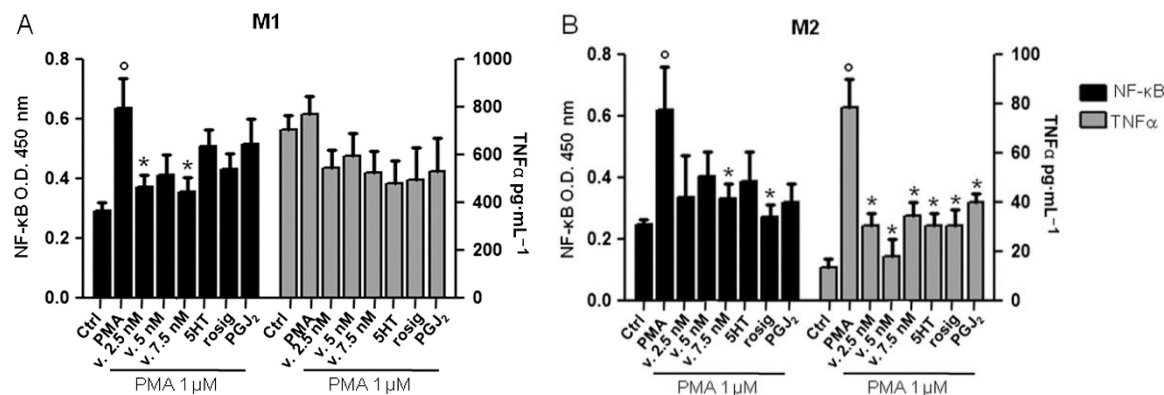
Mazza, M. G., Zanardi, R., Palladini, M., Rovere-Querini, P., & Benedetti, F. (2022). Rapid response to selective serotonin reuptake inhibitors in post-COVID depression. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*, 54, 1–6.

Emerging evidence about the role of antidepressants in SARS-CoV-2 treatment

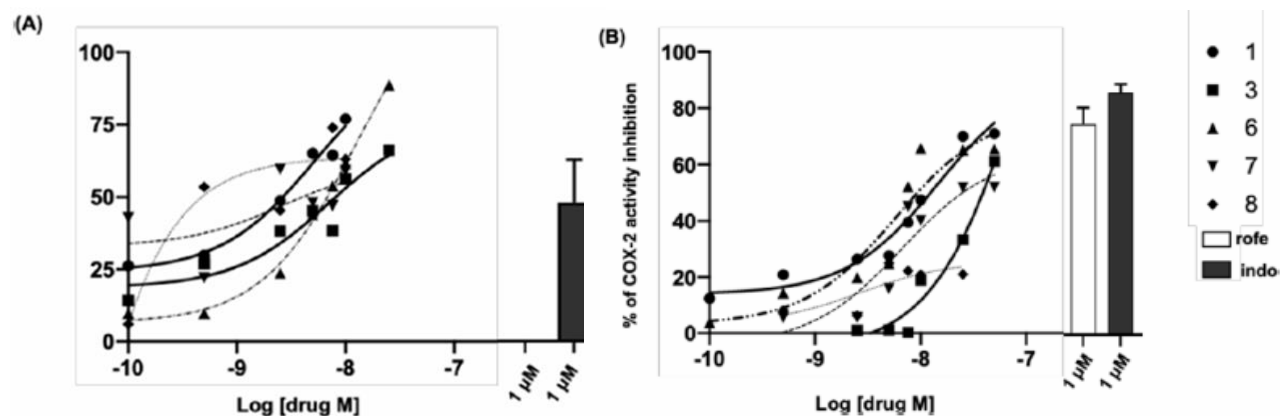


Good **safety/tolerability** profile
➤ *Beneficial effect on **cognitive impairment** in MDD*

Immunomodulatory properties of Vortioxetine



Effect on NF-κB activity and TNFα secretion in PMA-stimulated cells.



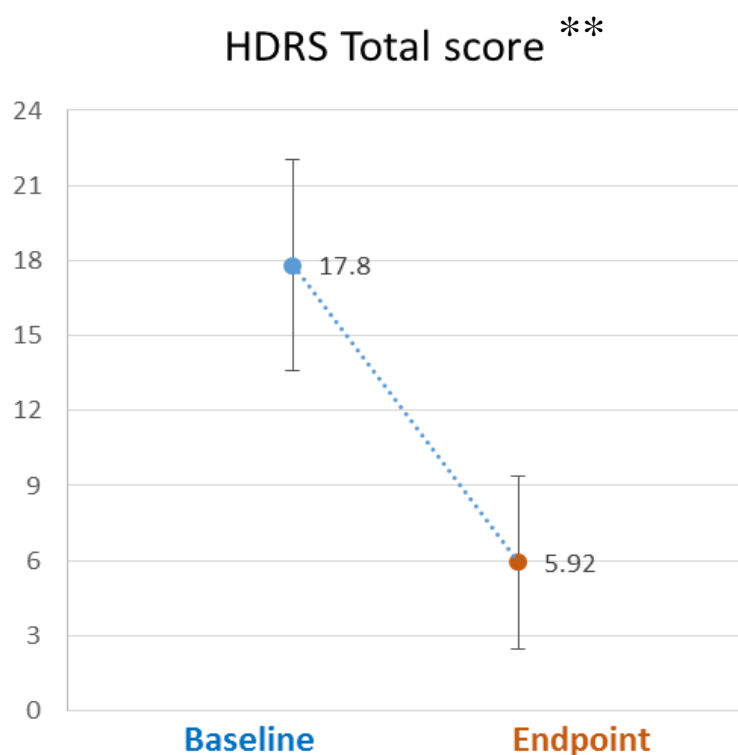
Effects on COX-1 (A) and COX-2 (B) enzyme activity.

Talmon M, et al. Vortioxetine exerts anti-inflammatory and immunomodulatory effects on human monocytes/macrophages. *Br J Pharmacol.* 2018 Jan;175(1):113-124.

Talmon M, et al. Design, synthesis and biological evaluation of vortioxetine derivatives as new COX-1/2 inhibitors in human monocytes. *Bioorg Med Chem.* 2020 Dec 1;28(23):115760.

The effect on depressive symptoms after three-months treatment

**** $p=0.007$**



N=50 patients (49.4% M, 52.1±17.6 years) with **moderate depression** (DSM-5 criteria, Hamilton Depression Rating Scale ≥ 14)
New-onset 44.3% vs Recurrent 55.7%

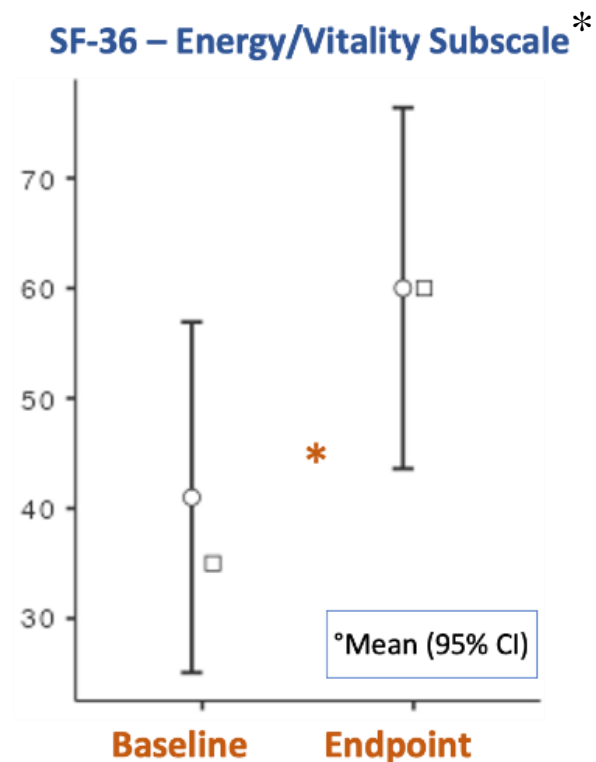
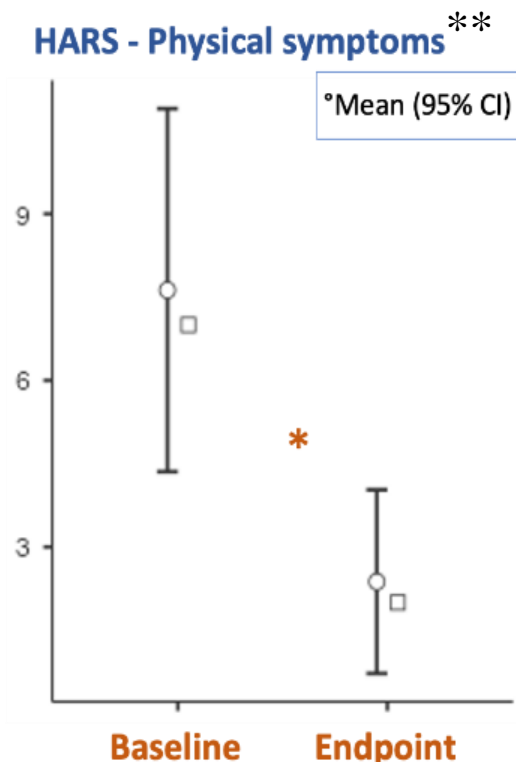
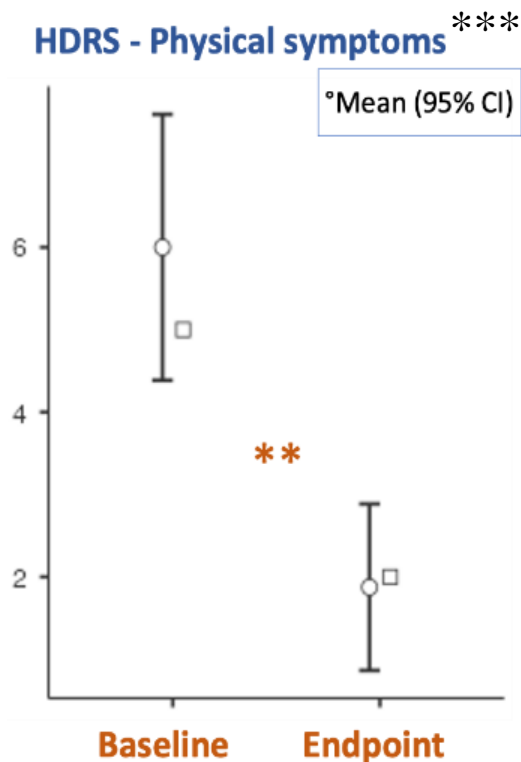
Vortioxetine mean dose: 9.54±3.80 mg/die

Physical features and fatigue, cognitive performances and functioning were retrospectively evaluated through:

- ❑ Physical sub-items of HDRS (6.87±2.23) and HARS (7.34±3.8)
- ❑ SF-36 Energy/Vitality Subscale (36.1±17.9)
- ❑ SF-36 Mental Component Score (33±10.6)
- ❑ PDQ-D5 (10.4±4.74)
- ❑ DSST (41.6±12.4)

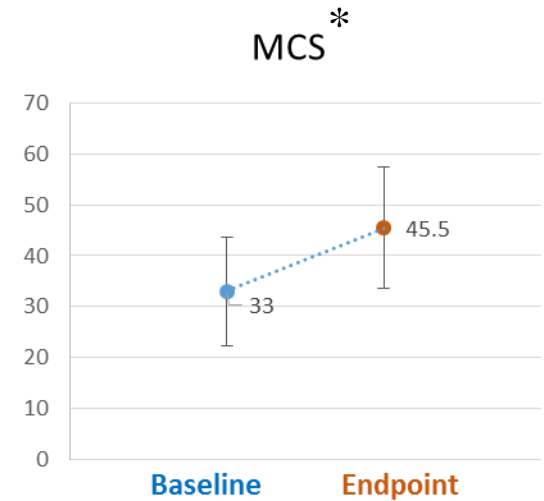
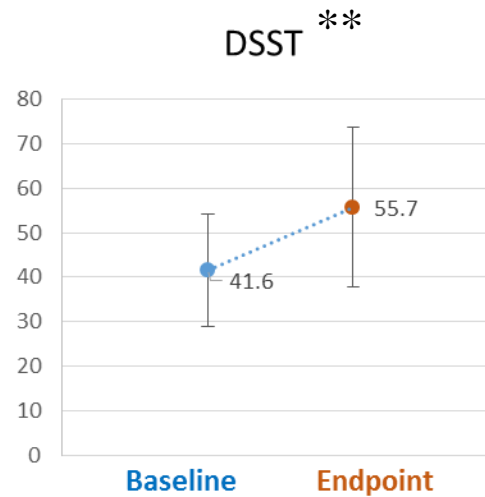
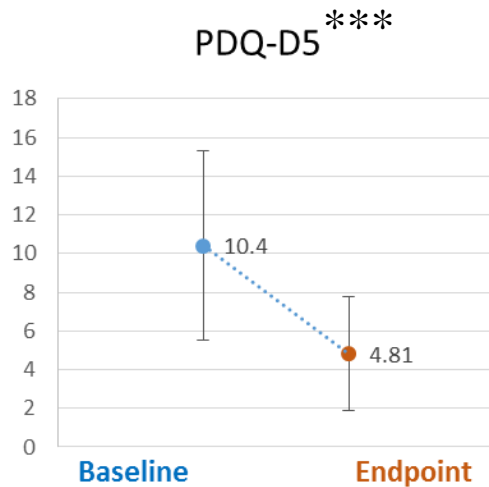
Effects on fatigue and physical correlates

* $p=0.049$, ** $p=0.006$, *** $p<0.001$



Effects on cognition and functioning

* $p=0.019$
** $p=0.004$
*** $p<0.001$



Changes in inflammatory levels

- ❑ C Reactive Protein (CRP) levels and Systemic-Immune-Inflammatory Index (SII) were assessed to evaluate the effect of vortioxetine on inflammatory levels underlying post-COVID-19 MDE

Inflammatory levels	
PCR (mg/L)	
Baseline	14.1 (40.1)
Endpoint	3.88 (3.9)
SII	
Baseline	505 (372)
Endpoint	372 (185)

- ❑ CRP levels and SII showed a decreasing trend after treatment, yet not statistically significant

Clinical and research recommendations

- ❑ **Peripheral inflammation and neuroinflammation** are crucial in the development of **depression**
 - ❑ **Clinical characterization** of all depressive episodes based on a differential association with **immune-metabolic dysregulation** and identification of **markers** easy-to-use in **common clinical practice**, is necessary
 - ❑ Given the prevalence of post-COVID syndrome, **assessing psychopathology of COVID-19 survivors** is mandatory to **promptly diagnose emergent depression**
 - ❑ **Targeted pharmacological treatment**, possibly affecting **inflammatory aspects**, are warranted to reduce the disease burden and related years of life lived with disability and to allow full **remission and functional recovery**
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