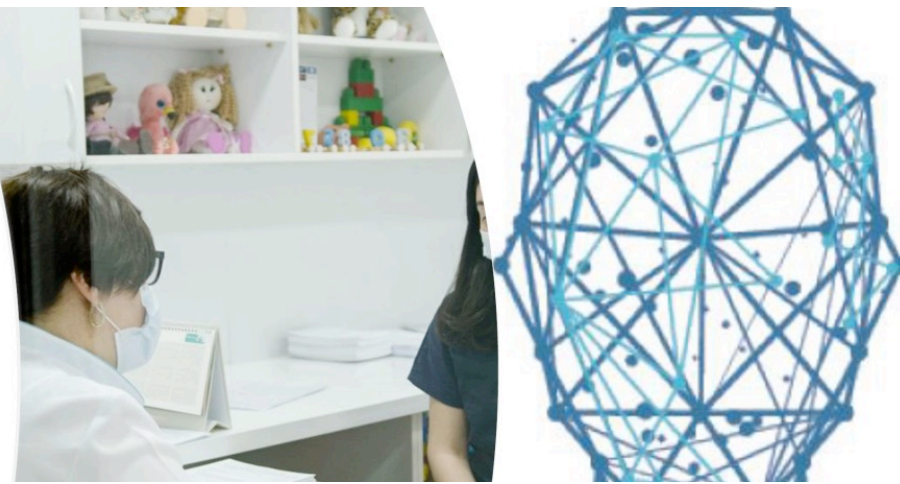Expanding our
Understanding of
Post COVID-19 Condition
Web Series:

**Neurology and
Mental Health**

Tuesday March 1, 2022
1:30-3:30PM CET

Introduction to neurological manifestations in post COVID-19 condition

Professor Alla Guekht, MD, PhD

Moscow Research and Clinical Center for Neuropsychiatry

Russian National Research Medical University

REVIEW

Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions

Ettore Beghi[1] · Giorgia Giussani[1] · Erica Westenberg[2] · Ricardo Allegri[3] · David Garcia-Azorin[4] · Alla Guekht[5] · Jennifer Frontera[6] · Miia Kivipelto[7,8] · Francesca Mangialasche[7] · Elizabeta B. Mukaetova-Ladinska[9] · Kameshwar Prasad[10] · Neerja Chowdhary[11] · Andrea Sylvia Winkler[2,12]

Abstract
Acute and post-acute neurological symptoms, signs and diagnoses have been documented in an increasing number of patients infected by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes Coronavirus Disease 2019 (COVID-19). In this review, we aimed to summarize the current literature addressing neurological events following SARS-CoV-2 infection, discuss limitations in the existing literature and suggest future directions that would strengthen our understanding of the neurological sequelae of COVID-19. The presence of neurological manifestations (symptoms, signs or diagnoses) both at the onset or during SARS-CoV-2 infection is associated with a more severe disease, as demonstrated by a longer hospital stay, higher in-hospital death rate or the continued presence of sequelae at discharge. Although biological mechanisms have been postulated for these findings, evidence-based data are still lacking to clearly define the incidence, range of characteristics and outcomes of these manifestations, particularly in non-hospitalized patients. In addition, data from low- and middle-income countries are scarce, leading to uncertainties in the measure of neurological findings of COVID-19, with reference to geography, ethnicity, socio-cultural settings, and health care arrangements. As a consequence, at present a specific phenotype that would specify a post-COVID (or long-COVID) neurological syndrome has not yet been identified.

Keywords COVID-19 · SARS-CoV-2 · Neurological diseases · Post-COVID

Changes in cognitive functioning after COVID-19: A systematic review and meta-analysis

Lucia Crivelli and Katie Palmer are joint first authors.

Lucia Crivelli [1,*] | Katie Palmer [2] | Ismael Calandri [1] | Alla Guekht [3] | Ettore Berghi [4] | William Carroll [5] | Jennifer Frontera [6] | David García-Azorín [7] | Erica Westenberg [8] | Andrea Sylvia Winkler [9] | Francesca Mangialasche [2] | Ricardo F. Allegri [1,10] | Miia Kivipelto [2]

Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 2022

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[4] Department of Neuroscience, Instituto di Ricerche Farmacologiche

[5] Department of Neurology, Sir Charles Gairdner Hospital and Institute, Perth, Western Australia, Australia

[6] Department of Neurology, NYU Grossman School of Medicine, New York, New York, USA

Figure 2. MoCA meta-analysis forest plot

Neurology and COVID-19: Follow-up and long-term impact Working group

Brain Health Unit (Head – Tarun Dua)

Co-Chairs Ricardo Allegri, Alla Guekht
WHO Technical officer Neerja Chowdhary

David Garcia Azorin, Ettore Beghi, Terry Brugha, William Carroll, Lucia Crivelli, Gabriel de Erausquin, Erika Fink, Abdallah Foad, Jennifer Frontera, Giorgia Giussani, Wouter De Groote, Kimberly Karlshoej; Miia Kivipelto, Francesca Mangialasche, Molly M. McNett, Elizabeta Mukaetova-Ladinska; Erica Westenberg, Andrea Winkler

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Global COVID-19 Clinical Platform
Case Report Form (CRF) for Post COVID conditions (Post COVID-19 CRF")

The WHO has established a Global Clinical Data Platform[1] of COVID-19 and invites all Member States and health facilities to report anonymised patient-level clinical information to the WHO platform using standardized Case Report Form (CRF):
- *Core CRF* captures clinical information of individuals hospitalized for COVID-19
- *Core-P CRF* has information of pregnant women hospitalized for COVID-19
- *MIS-CRF* has information related to multisystemic inflammatory syndrome in children and adolescents temporally related to COVID-19
- *Post COVID-19 CRF*, designed to build upon the Core CRF and assess the medium- and long-term sequelae of COVID-19

The Post COVID-19 CRF includes 3 modules:
Module 1 includes background demographic and clinical information of the acute episode of COVID-19.
Module 2 includes questions to help identifying patients who require further clinical evaluation.
Module 3 includes medical assessment and results of examinations, tests, or diagnosis made during the follow up visit. Based on results, patients should be referred for clinical care, or rehabilitation as per national protocols.

The Post COVID-19 CRF is intended to serve as: (i) A clinical tool that can be used by Member States to document the mid- and long-term sequelae of COVID-19. Uniformity in the follow up of patients could ensure that mid- and long-term clinical and rehabilitation needs are identified, and patients are provided the care they need; **(ii)** WHO is not necessarily recommending the comprehensive testing described in the CRF for all individuals; clinician judgement is required to select the test needed for clinical care. This CRF is a tool for gathering standardized information regarding the post COVID-19 condition through the WHO Clinical Data Platform. Such data collation and its analysis would improve national and global knowledge of the consequences of COVID-19, inform further public health responses and prepare for large investigational studies.

Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19

Daniel Munblit[1,2,3] | Polina Bobkova[1] | Ekaterina Spiridonova[1] |
Anastasia Shikhaleva[1] | Aysylu Gamirova[1] | Oleg Blyuss[1,4] | Nikita Nekliudov[1] |
Polina Bugaeva[1] | Margarita Andreeva[1] | Audrey DunnGalvin[1,5] |
Pasquale Comberiati[6] | Christian Apfelbacher[7] | Jon Genuneit[8] | Sergey Avdeev[9] |
Valentina Kapustina[10] | Alla Guekht[3] | Victor Fomin[11] | Andrey A. Svistunov[11] |
Peter Timashev[12] | Vladislav S. Subbot[13] | Valery V. Royuk[14] | Thomas M. Drake[15] |
Sarah Wulf Hanson[16] | Laura Merson[17] | Gail Carson[17] | Peter Horby[17] |
Louise Sigfrid[17] | Janet T. Scott[18] | Malcolm G. Semple[19,20] | John O. Warner[2] |
Theo Vos[16] | Piero Olliaro[17] | Petr Glybochko[11] | Denis Butnaru[11] | Sechenov
StopCOVID Research Team
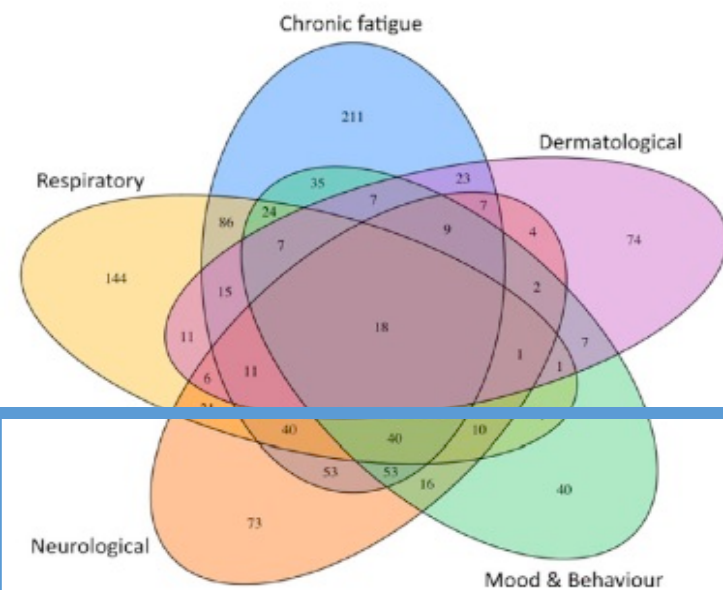
GRAPHICAL ABSTRACT
Word cloud showing persistent symptoms 6–8 months since hospital discharge in people previously hospitalised with COVID-19.

Results: 2,649 of 4755 (56%) discharged patients were successfully evaluated, at median 218 (IQR 200, 236) days post-discharge. COVID-19 diagnosis was clinical in 1291 and molecular in 1358. Most cases were mild, but 902 (34%) required supplemental oxygen and 68 (2.6%) needed ventilatory support. Median age was 56 years (IQR 46, 66) and 1,353 (51.1%) were women. Persistent symptoms were reported by 1247 (47.1%) participants, with fatigue (21.2%), shortness of breath (14.5%) and forgetfulness (9.1%) the most common symptoms and chronic fatigue (25%) and respiratory (17.2%) the most common symptom categories. Female sex was associated with any persistent symptom category OR 1.83 (95% CI 1.55 to 2.17) with association being strongest for dermatological (3.26, 2.36 to 4.57) symptoms. Asthma and chronic pulmonary disease were not associated with persistent symptoms overall, but asthma was associated with neurological (1.95, 1.25 to 2.98) and mood and behavioural changes (2.02, 1.24 to 3.18), and chronic pulmonary disease was associated with chronic fatigue (1.68, 1.21 to 2.32).

KEY MESSAGES

- 6–8 months after hospital discharge, around a half of patients with Covid-19 experienced persistent symptoms
- Chronic fatigue and respiratory problems were the commonest persistent symptoms, with 11.3% having multi-system involvement
- Female sex was associated with higher risk of persistent symptoms

Post-COVID syndrome. A case series and comprehensive review

Juan-Manuel Anaya [a,b,*], Manuel Rojas [a], Martha L. Salinas [b], Yhojan Rodríguez [a,b], Geraldine Roa [a], Marcela Lozano [a], Mónica Rodríguez-Jiménez [a], Norma Montoya [b], Elizabeth Zapata [a], Post-COVID study group [c], Diana M. Monsalve [a], Yeny Acosta-Ampudia [a], Carolina Ramírez-Santana [a]

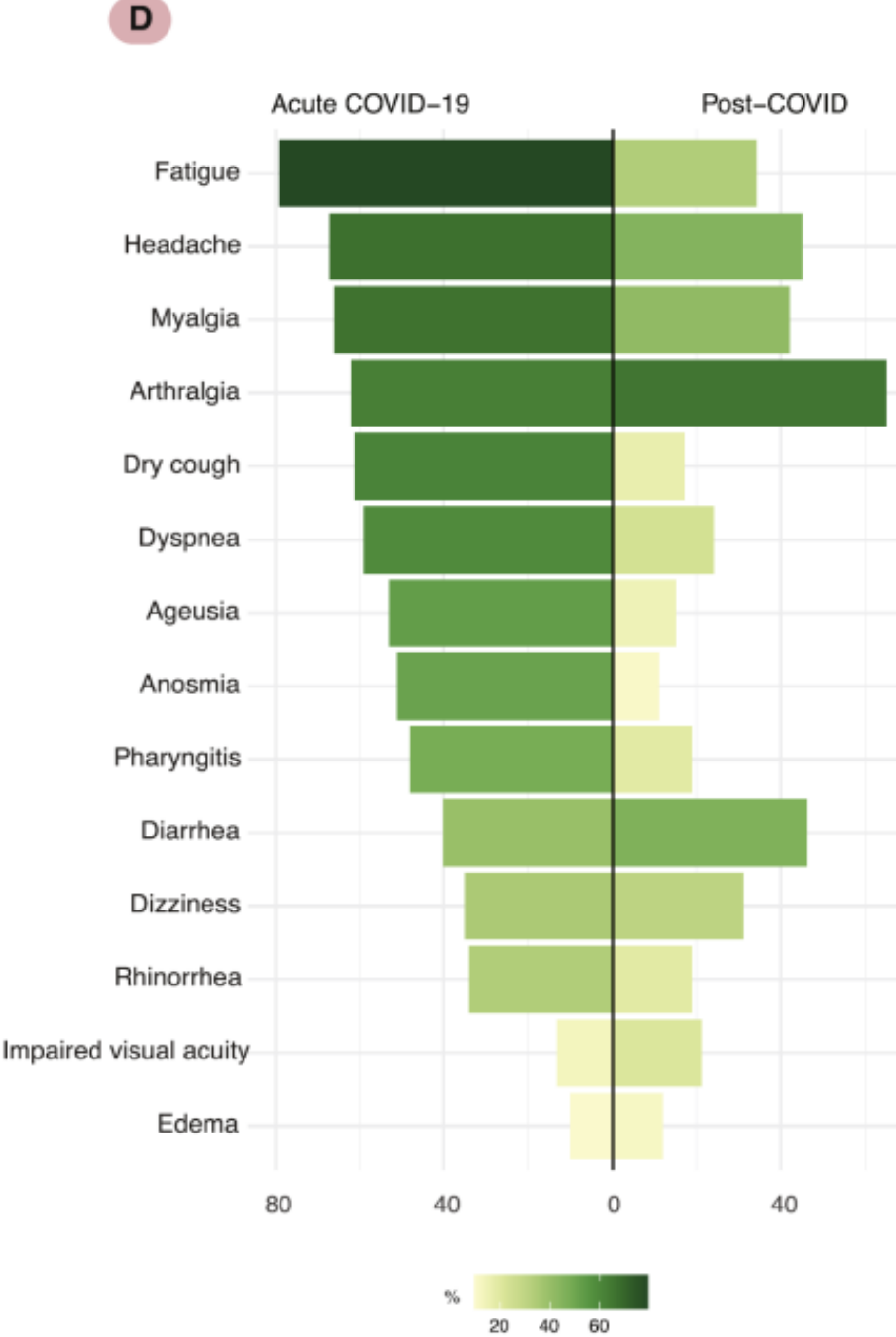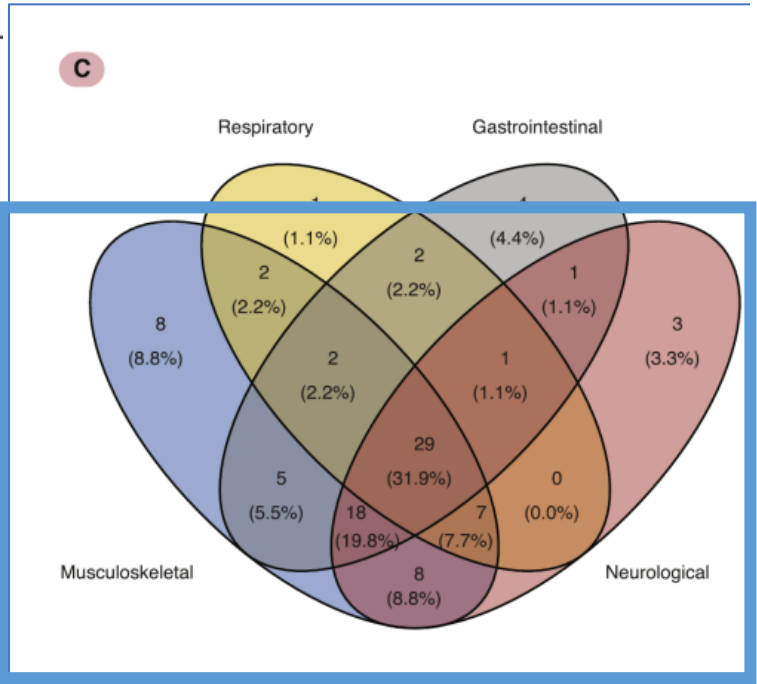[a] Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia
[b] Clínica del Occidente, Bogotá, Colombia
[c] School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

	n: 100
Sex	
Female	53 (53.0%)
Male	47 (47.0%)
Age (Median -IQR)	49 (37.8–55.3)
Body mass index (Median -IQR)	28.1 (25.1–30.4)
Post-COVID time (days, Median -IQR)	219 days (143–258)

- Musculoskeletal, digestive (i.e., diarrhea) and neurological symptoms including depression (by Zung scale) were the most frequent observed in PCS patients.
- A previous hospitalization was not associated with PCS manifestation.
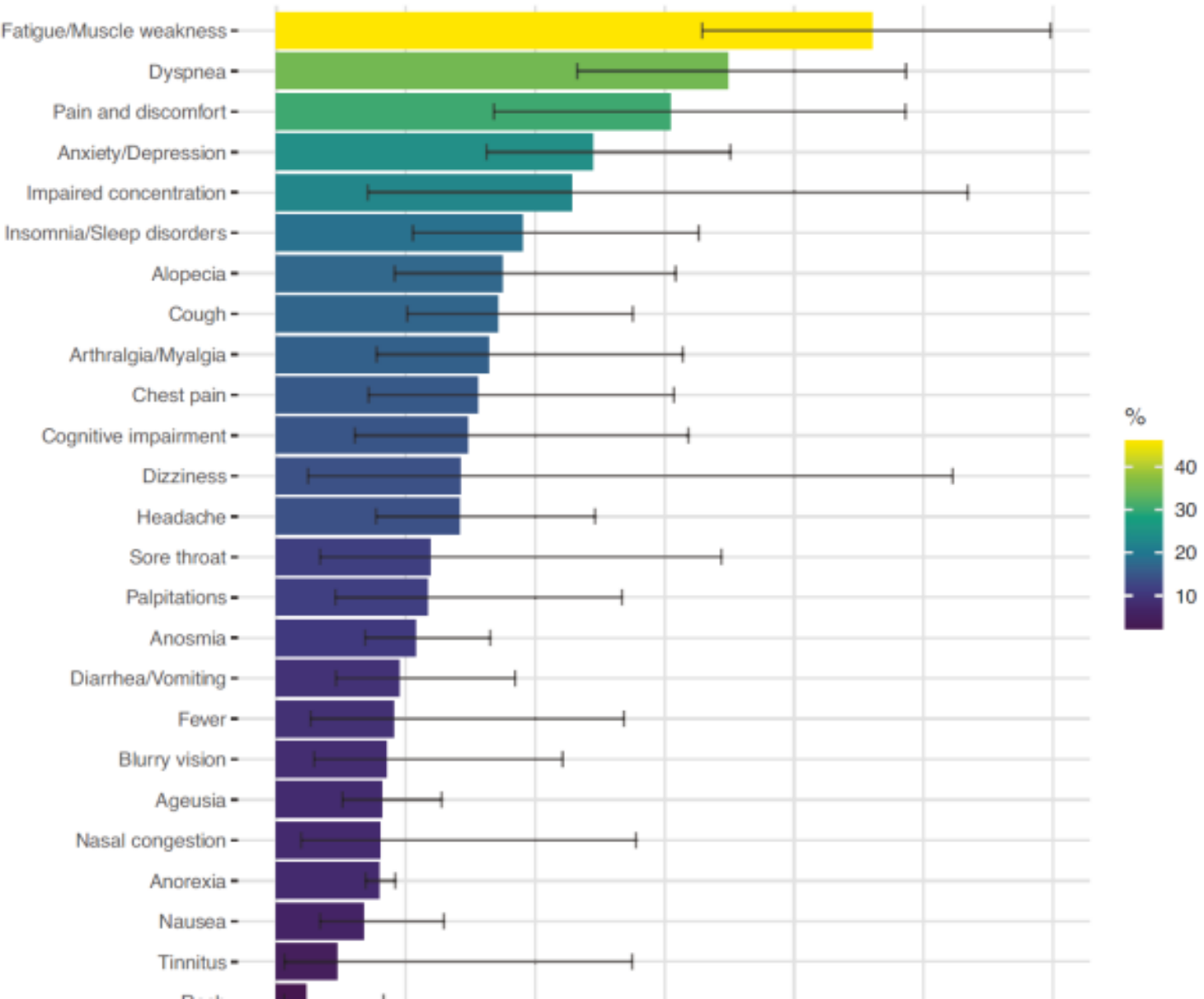- Arthralgia and diarrhea persisted in more than 40% of PCS patients.

Prevalence of Post-COVID manifestations: meta-analysis

Juan-Manuel Anaya [a,b,*], Manuel Rojas [a], Martha L. Salinas [b], Yhojan Rodríguez [a,b], Geraldine Roa [a], Marcela Lozano [a], Mónica Rodríguez-Jiménez [a], Norma Montoya [b], Elizabeth Zapata [a], Post-COVID study group [c], Diana M. Monsalve [a], Yeny Acosta-Ampudia [a], Carolina Ramírez-Santana [a]

[a] Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia
[b] Clínica del Occidente, Bogotá, Colombia
[c] School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia

Frequency bar plot for pooled prevalence of post-COVID manifestations in meta-analysis. Error bar represents the estimated 95% confidence interval. Only those clinical manifestations reported in more than 4 articles were included in this graph.

A Neurological Outpatient Clinic for Patients With Post-COVID-19 Syndrome — A Report on the Clinical Presentations of the First 100 Patients

Fabian Boesl[1]*, Heinrich Audebert[1,2], Matthias Endres[1,2,3,4,5], Harald Prüss[1,3] and Christiana Franke[1]

[1] Department of Neurology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [2] Center for Stroke Research Berlin, Berlin, Germany, [3] German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany, [4] Excellence Cluster NeuroCure, Berlin, Germany, [5] German Centre for Cardiovascular Research (DZHK), Berlin, Germany

TABLE 2 | Evaluation of self-questionnaires and results of MoCA of patients presenting to the neurological post-COVID-19 outpatient clinic.

TABLE 1 | Characteristics of patients presenting to the neurological Post-COVID-19 outpatient clinic.

	Total	Female	Male
Number of patients	100	67	33
Mean age (years)	45.8	45.2	46.9
- Range	20–79	21–68	20–79
Mean time between positive SARS-CoV-2 testing and presentation in outpatient clinic (days)	184.5	186.9	179.7
- Range (days)	85–426	85–426	91–369
Mild COVID-19 course	89	61 (91.0%)	28 (84.8%)
Severe COVID-19 course	11	6 (9.0%)	5 (15.2%)
Symptoms			
Cognitive impairment	72	45 (67.2%)	27 (81.8%)
Fatigue	67	49 (73.1%)	18 (54.5%)
Headache	36	24 (35.8%)	12 (36.4%)
Myalgia	21	15 (22.4%)	6 (18.2%)
Limb pain	9	5 (7.5%)	4 (12.1%)
Other pain	17	12 (17.9%)	5 (15.2%)
Hyposmia	36	27 (40.3%)	9 (27.3%)
Vertigo	20	15 (22.4%)	5 (15.2%)

Moscow Research and Clinical Centre for Neuropsychiatry: Post-COVID Program

Staged approach

- Telemedicine
- Outpatient clinics
- Day hospital
- Inpatient department

Multidisciplinary team

- Neurologist
- Psychiatrist
- Psychotherapist
- Psychologist
- Internal medicine
- Physical medicine and rehabilitation

Non-pharmaceutical interventions

- Psychotherapy
- Psychoeducation
- Biofeedback
- tDCS
- Physical therapy
- Acupuncture
- Hyperbaric oxygen therapy

Moscow Research and Clinical Centre for Neuropsychiatry: Assessment of Post-COVID patients

- **General medical exam***
- Pulmonary
- Cardiac
- Endocrine
- Other

- **Neurological exam***

- **Autonomic testing**
- COMPASS - 31
- HR-variability
- Cardiovascular tests

Mental health assessment
- STAI (anxiety)
- BDI (depression)
- IES-R (PTSD)
- SITBI (suicide ideation and behavior)

Cognitive evaluation
- Executive function (verbal fluency)
- Memory (auditory verbal learning test, digit span)
- Attention (trial making test, symbol digit modality test)
- Visuo-Spatial (Benton test)
- Mental Processing Speed (trial making test, symbol digit modality test)

Follow-up evaluation*

(*modified WHO CRF)

Post-COVID Cohort

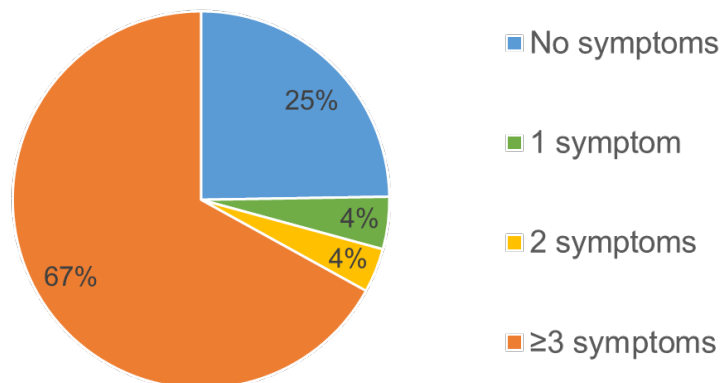**Moscow Research and Clinical Centre for Neuropsychiatry; 2053 patients**
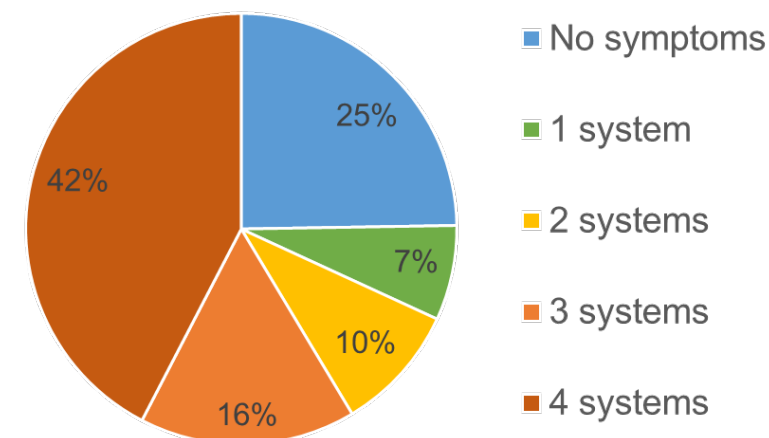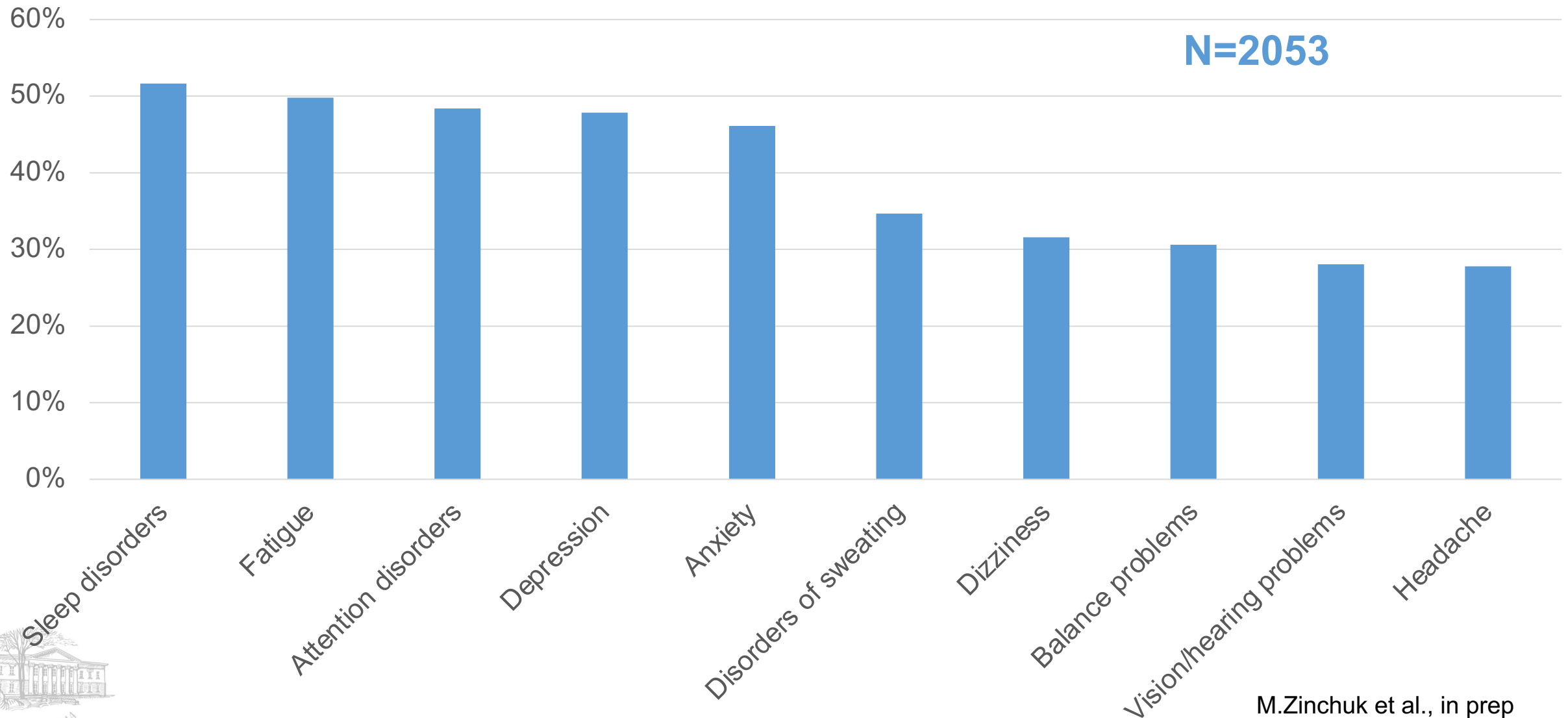
Self-reported severity of COVID-19

- Mild-to-moderate COVID-19 — 90%
- Severe COVID-19 — 9%
- Critical COVID-19 — 1%

COVID-19 onset

- <3 months prior to admission — 12%
- 3-6 months prior to admission — 28%
- >6 months prior too admission — 29%
- Did not recall the COVID-19 time period — 31%

Number of symptoms

- No symptoms — 25%
- 1 symptom — 4%
- 2 symptoms — 4%
- ≥3 symptoms — 67%
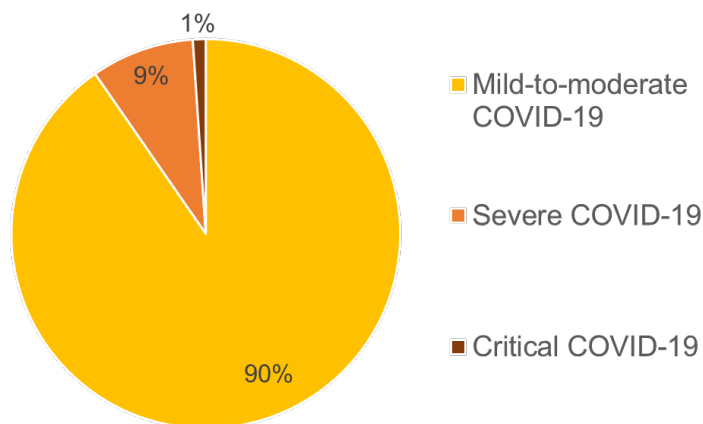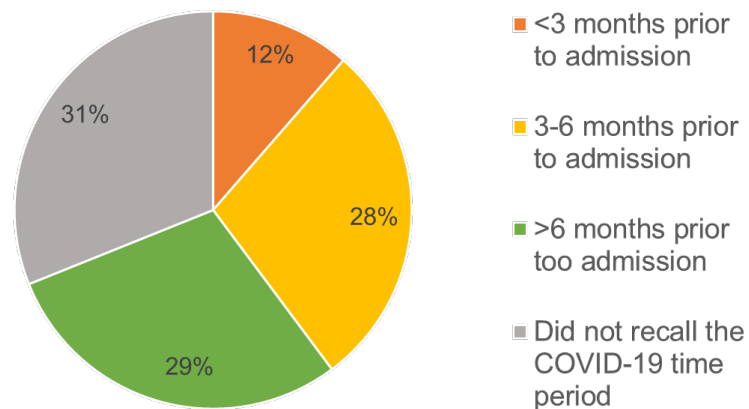
Number of affected systems

- No symptoms — 25%
- 1 system — 7%
- 2 systems — 10%
- 3 systems — 16%
- 4 systems — 42%

Post-COVID-19 Autonomic Symptoms

N=2053

M.Zinchuk et al., in prep
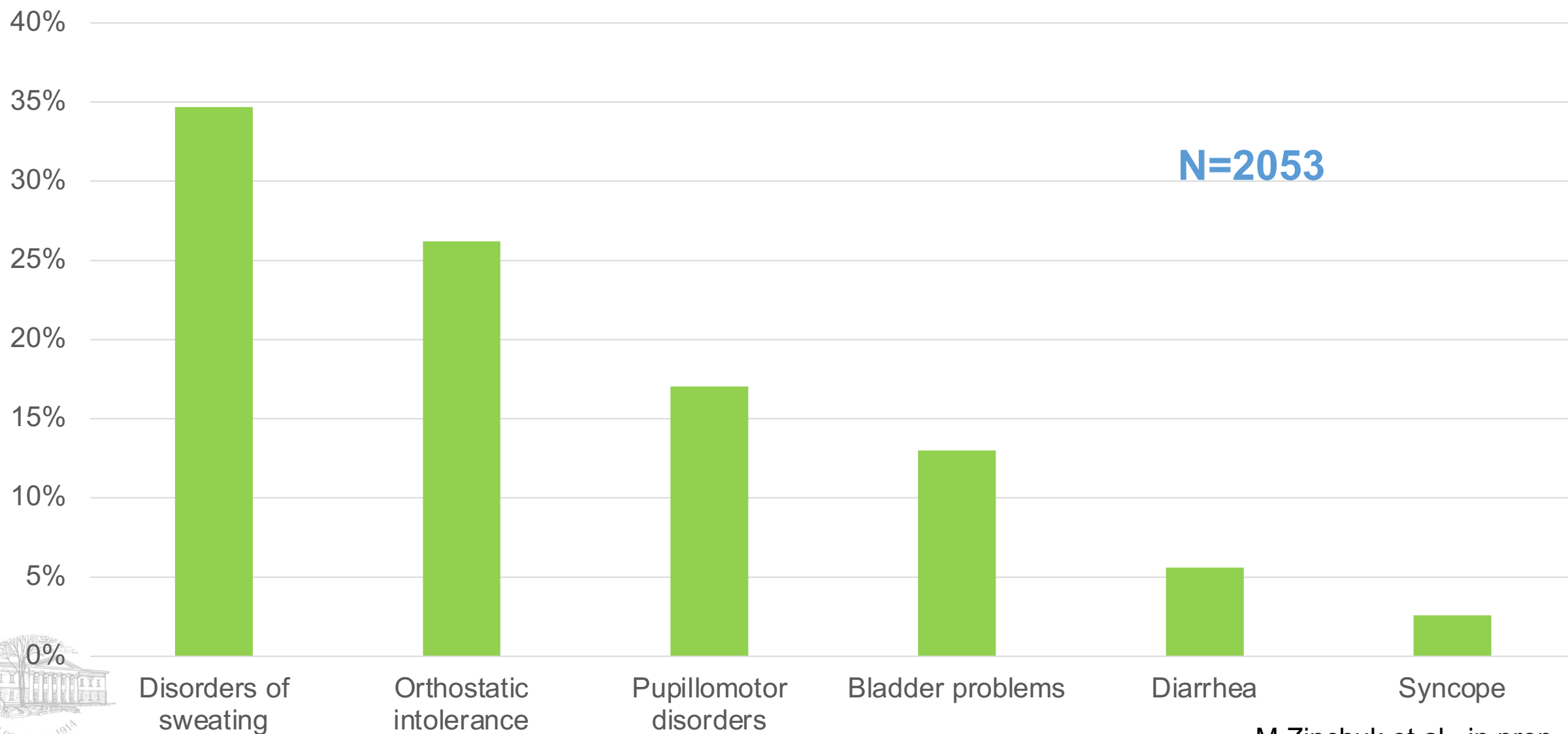
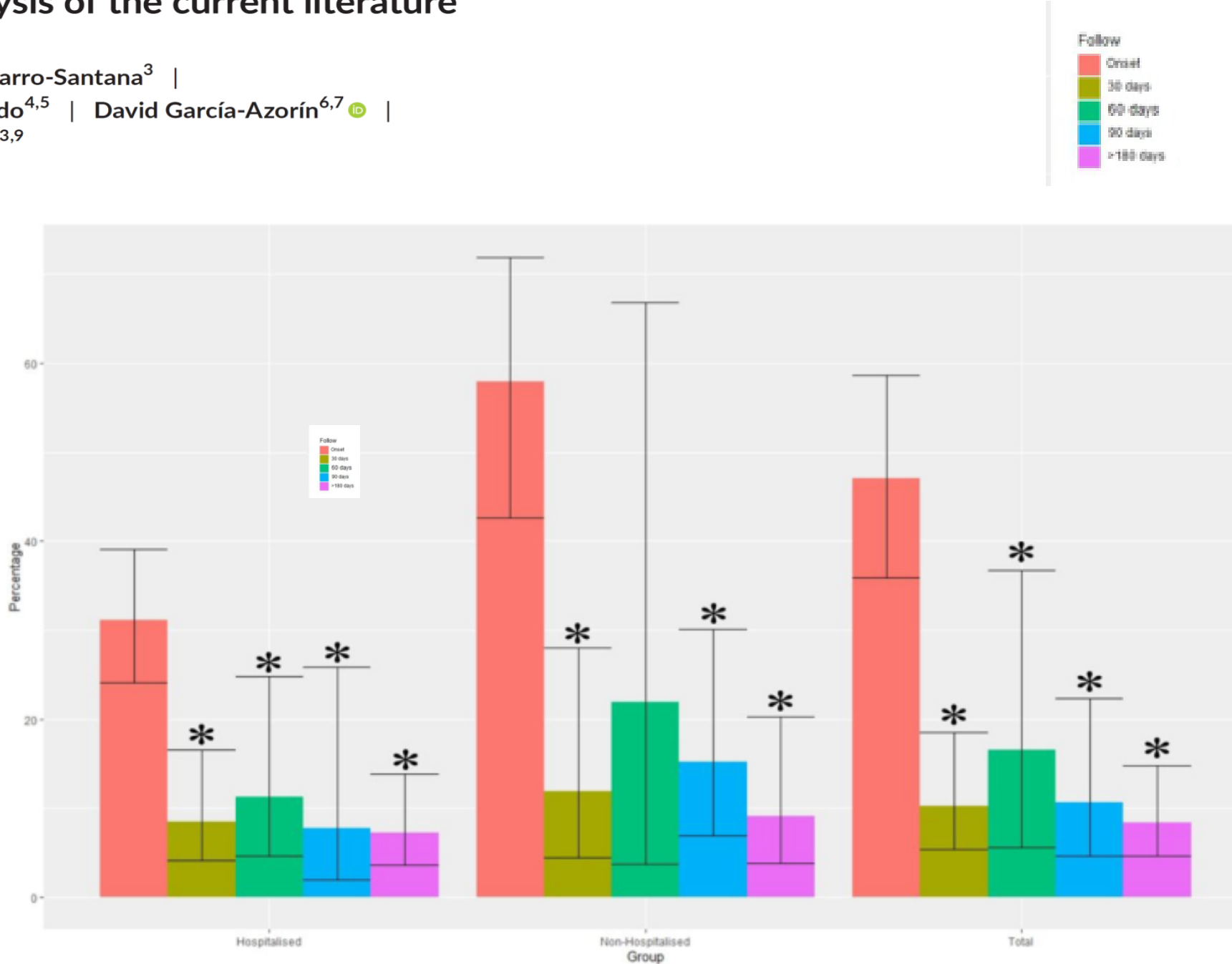# Post-COVID-19 symptoms: time since acute illness

M.Zinchuk et al., in prep
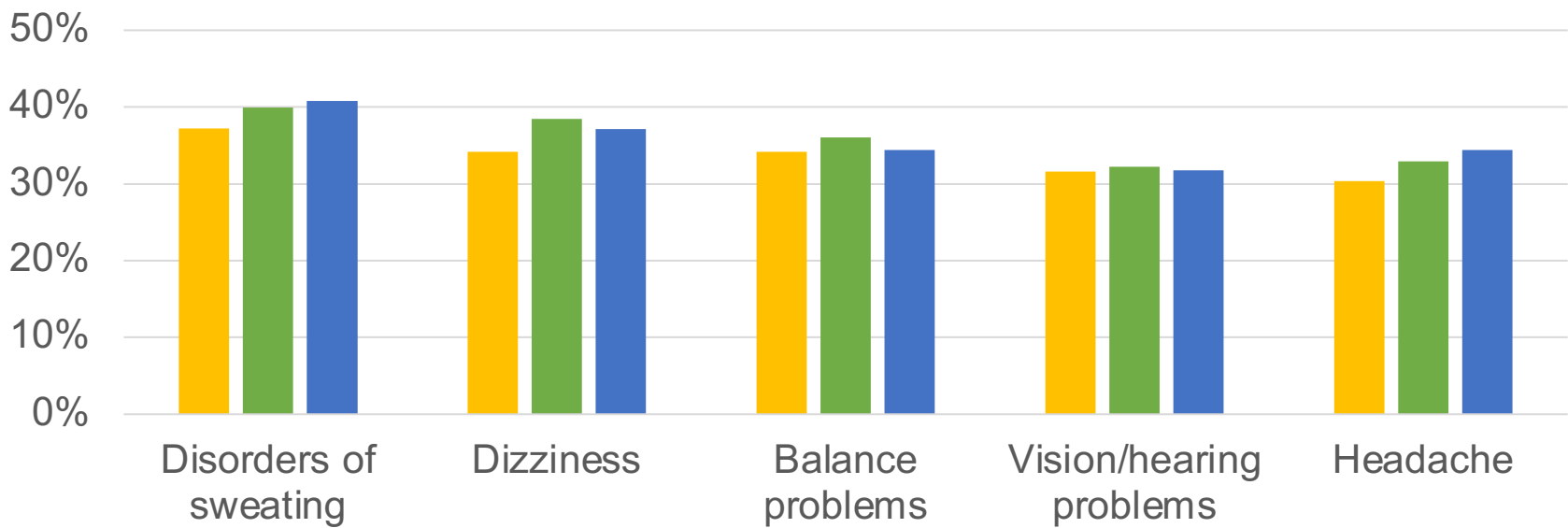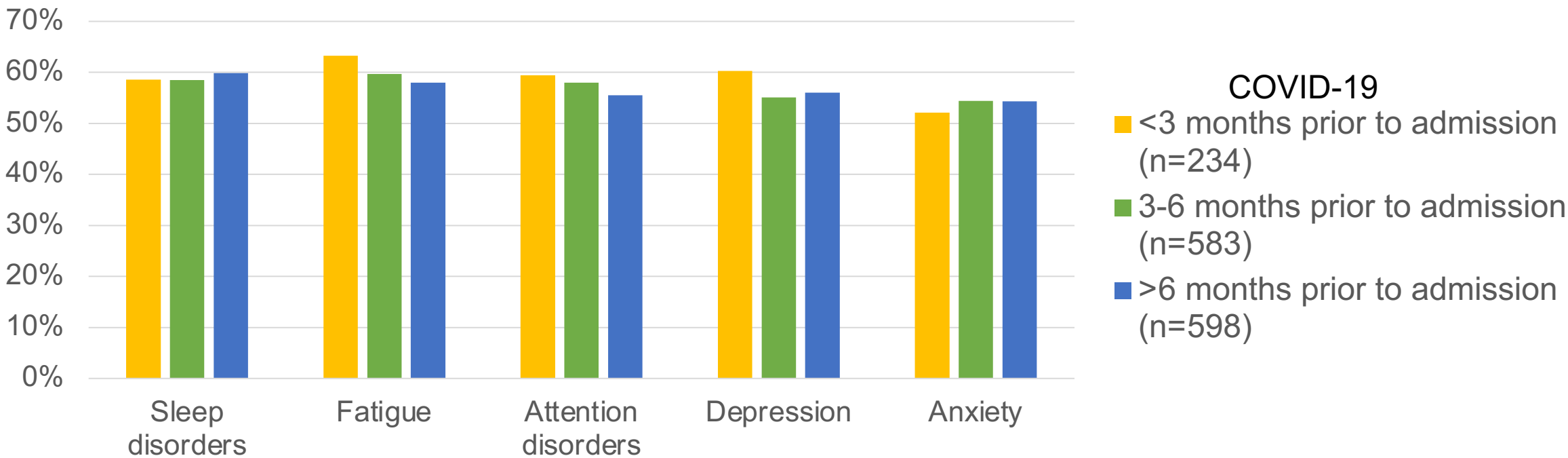
Headache as an acute and post-COVID-19 symptom in COVID-19 survivors: A meta-analysis of the current literature

César Fernández-de-las-Peñas[1,2] | Marcos Navarro-Santana[3] |
Víctor Gómez-Mayordomo[4] | María L. Cuadrado[4,5] | David García-Azorín[6,7] |
Lars Arendt-Nielsen[2,8] | Gustavo Plaza-Manzano[3,9]

- The prevalence of post-COVID headache ranged from 8% to 15% during the first 6 months after the acute infection (vs around 50% during hospitalization.

- The time course of post-COVID **headache seems to be stable during the first 180 days**, but longitudinal studies are needed.

- Identification of risk factors associated with post-COVID headache will ensure immediate action and counselling of this patient population.

FIGURE 2 Time course trend of post-COVID headache from the onset of the symptoms/hospital admission to 30, 60, 90, and ≥180 days after discharge. *Statistically significant effect ($p < 0.001$) showing a time trend during the different follow-up periods. [Colour figure can be

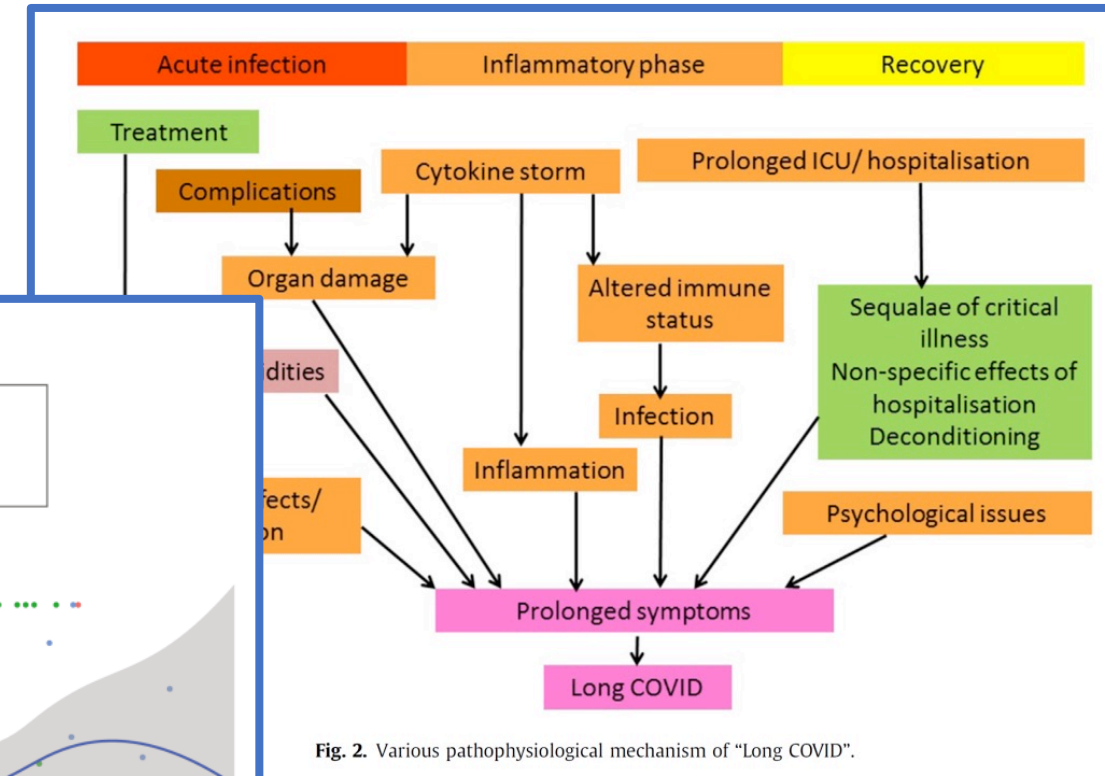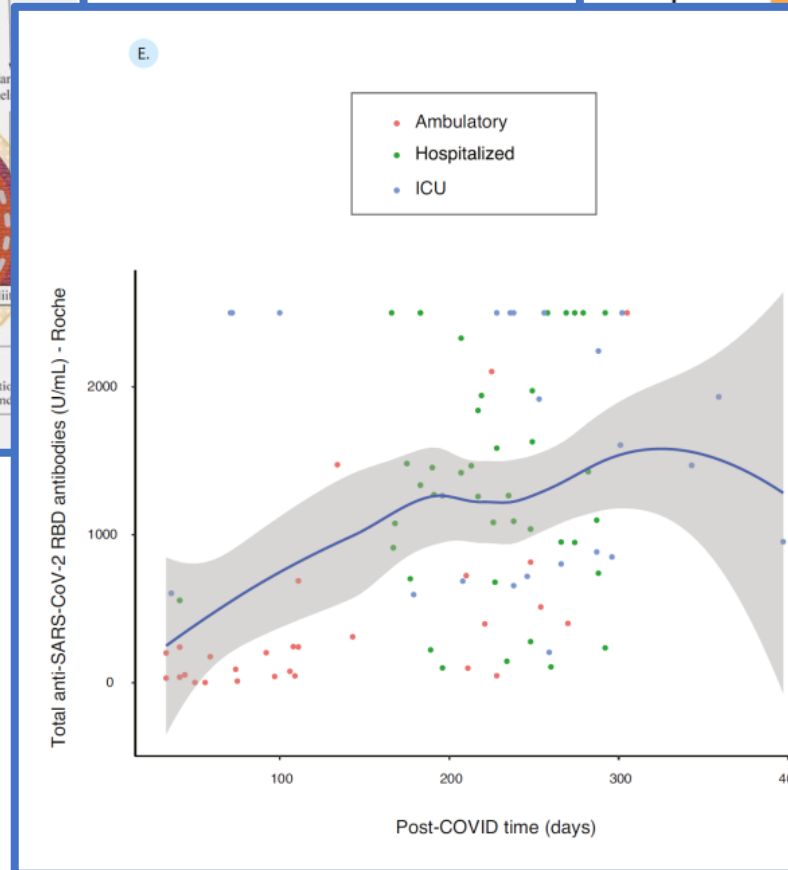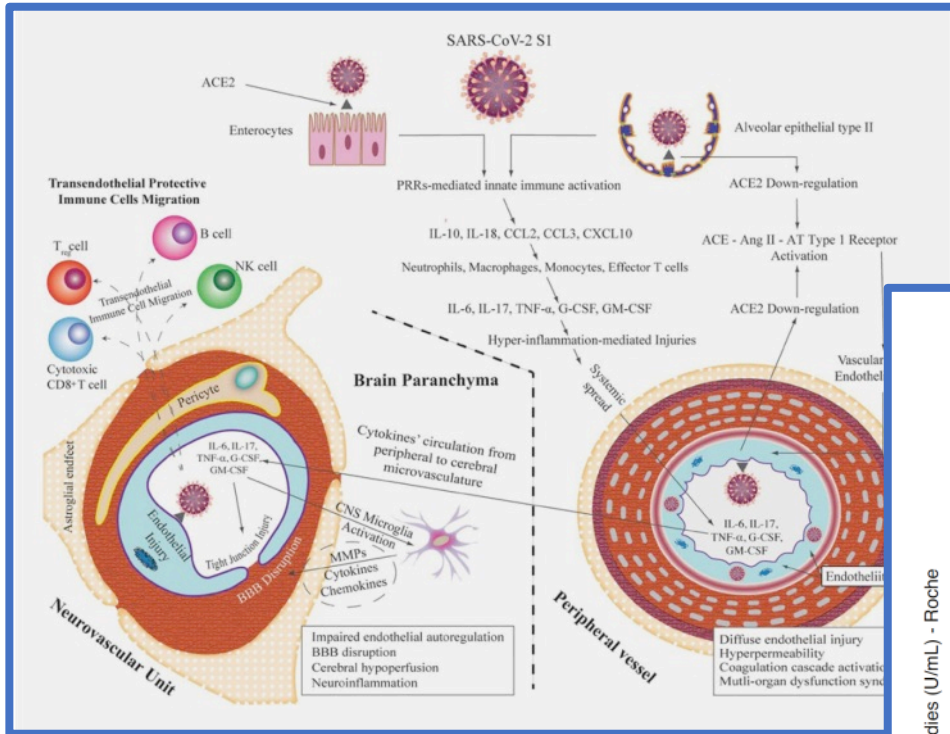# Post-COVID neurological manifestations: mechanisms?

Integrative concepts of the pathophysiology of COVID-19-related central nervous system complications
Najjar S, Najjar A, Chong DJ, et al J Neuroinflammation 2020;17(1):231, doi: 10.1186/s12974-020-01896-0,

Fig. 2. Various pathophysiological mechanism of "Long COVID".

Raveendran & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 869e875

Scatter plot for total anti-SARS-CoV-2 antibodies (by ECLIA, Roche) and post-COVID time.
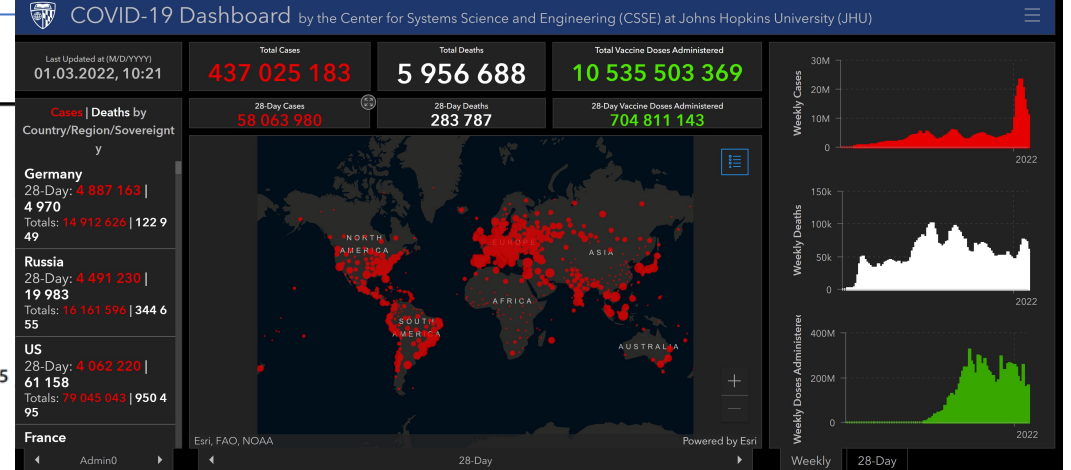
J.-M. Anaya et al. Autoimmunity Reviews 20 (2021) 102947

- Are there specific new-onset neurological symptoms, signs or diagnoses occurring after the acute phase of COVID-19 symptoms that can be interpreted as sequelae of COVID-19?

- Are there neurological symptoms, signs or diagnoses that arise during and persist after the acute phase of COVID-19?

- What are the factors associated with the persistence and/or any new-onset post-acute neurological manifestations?

Journal of Neurology
https://doi.org/10.1007/s00415-021-10848-4

REVIEW

Acute and post-acute neurological manifestations of COVID-19: present findings, critical appraisal, and future directions

Ettore Beghi[1] · Giorgia Giussani[1] · Erica Westenberg[2] · Ricardo Allegri[3] · David Garcia-Azorin[4] · Alla Guekht[...] · Jennifer Frontera[6] · Miia Kivipelto[7,8] · Francesca Mangialasche[7] · Elizabeta B. Mukaetova-Ladinska[9] · Kameshwar Prasad[10] · Neerja Chowdhary[11] · Andrea Sylvia Winkler[2,12]

ANNEX 7

DRAFT INTERSECTORAL GLOBAL ACTION PLAN ON EPILEPSY AND OTHER NEUROLOGICAL DISORDERS 2022–2031

BACKGROUND

1. In November 2020, the Seventy-third World Health Assembly adopted resolution WHA73.10 requesting the Director-General of WHO, inter alia, to develop a 10-year intersectoral global action plan on epilepsy and other neurological disorders, in consultation with Member States, in order to promote and support a comprehensive, coordinated response across multiple sectors.

2. The intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 aims to improve access to care and treatment for people living with neurological disorders, while preventing new cases and promoting brain health and development across the life course. It seeks to support the recovery, well-being and participation of people living with neurological conditions, while reducing associated mortality, morbidity and disability, promoting human rights, and addressing stigma and discrimination through interdisciplinary and intersectoral approaches.

3. The intersectoral global action plan on epilepsy and other neurological disorders 2022–2031 builds on previous global resolutions, decisions, reports and commitments, including resolution WHA68.20 on the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications. A number of preventive, pharmacological and psychosocial approaches are shared by epilepsy and other neurological disorders. This sharing of strategies and approaches (i.e., synergies) can serve as valuable entry points for accelerating and strengthening services and support for epilepsy and other neurological disorders.

- Are there specific new-onset diagnoses occurring after symptoms that can be identified?

- Are there neurological symptoms that arise during and persist after the acute phase of COVID-19?

- What are the factors associated with the persistence and/or any new-onset post-acute neurological manifestations?

Expanding our Understanding of Post COVID-19 Condition Web Series:

Neurology and Mental Health

Tuesday March 1, 2022
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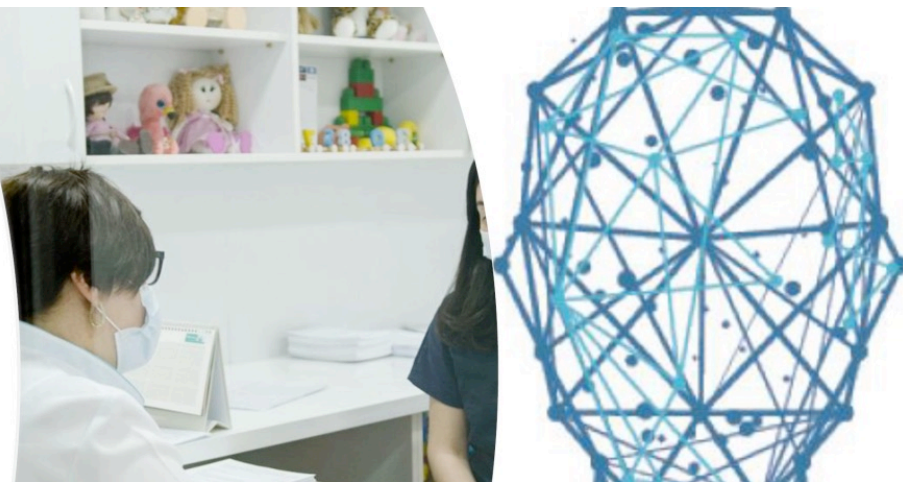
Introduction to neurological manifestations in post COVID-19 condition

Thank you for your attention