



Propuesta de investigación nacional en relación con la epidemiología, y las manifestaciones clínicas de la condición Post-COVID-19.

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¿Por qué necesitamos una investigación nacional relacionada con la condición Post-COVID-19?



Organización
Mundial de la Salud

COVID-19



Hasta el 08 de Mayo del 2022 se reportan 192 países con casos de COVID-19, ascendiendo a 517 millones 089 mil 937 el número de confirmados y 6 millones 276 mil 169 fallecidos.

En la región de las Américas se reportan 155 millones 854 mil 455 casos confirmados y 2 millones 759 mil 761 fallecidos.



IMPACTO DE LA COVID-19

Número pacientes
condición post-
COVID-19



casos hospitalizados
número de fallecidos

número de
casos nuevos



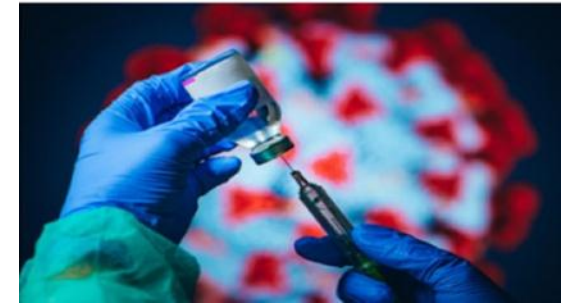
INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

1. Definición de la condición post-COVID-19.
 2. Mecanismos fisiopatológicos no totalmente dilucidados.
 3. Crecimiento acelerado de datos.
 4. Población objetivo y alcance
 5. ¿Qué y como medir la condición Post-COVID-19?
-



Organización
Mundial de la Salud

Condición post-COVID-19



«la condición que ocurre en individuos con antecedentes de infección probable o confirmada por SARS-CoV-2, generalmente tres semanas después del inicio, con síntomas que duran al menos dos meses y no pueden explicarse con un diagnóstico alternativo».

Este nombre no atribuye causalidad ni duración

Existen códigos específicos ICD-10 (U09) e ICD-11 (RA02) para identificarlos

10-20% de los pacientes con COVID-19

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

1.¿ Definición de la condición post-COVID-19?

Terminología y definiciones clínicas diversas

Name/Nombre	Referencia
<i>Chronic COVID Syndrome/Síndrome COVID crónico</i>	Baig AM. Chronic COVID syndrome: Need for an appropriate medical terminology for long-COVID and COVID long-haulers. J Med Virol. 2021. DOI: 10.1002/jmv.26624
<i>Late sequelae of COVID-19/Secuelas tardías de COVID-19</i>	CDC website [consultado 29 Mar 2021] Disponible en: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/late-sequelae.html
<i>Long covid/Covid larga</i>	Mahase E. BMJ. 2020 Jul 14;370:m2815
<i>Long COVID/COVID larga</i>	Perego E, et al. Wellcome Open Research 2020;5:224; Editorial. The Royal Society
<i>LONG COVID/COVID LARGA</i>	Nature Editorial [Let patients help define long-lasting COVID symptoms] 8 October 2020; Long COVID Forum 9-10 December 2020 from ISARIC/GLOPIDR/LONG COVID Support; Lancet Editorial [Facing up to long COVID] 12 December 2020;
<i>Long haul COVID/COVID de larga duración</i>	Nath A. Long-Haul COVID. Neurology. 2020 Sep 29;95(13):559-560.; Scientific American (By Carolyn Barber on December 29, 2020)]
<i>Long-term COVID-19/COVID-19 a largo plazo</i>	A special issue of Journal of Clinical Medicine (ISSN 2077-0383)
<i>Post-acute sequelae/Secuelas post-agudas</i>	NIH-National Institutes of Health (EE. UU.) [consultado 29 Mar 2021] Disponible en: https://videocast.nih.gov/watch=38878
<i>Post COVID syndrome/Síndrome post COVID</i>	NHS-National Health Service (UK) [consultado 29 Mar 2021] Disponible en: https://www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/
<i>Post-acute COVID-19/COVID-19 post aguda</i>	Several papers in: BMJ, Eur J Phys Rehabil Med, Eur J Intern Med
<i>Post-acute sequelae of SARS-CoV-2 infection (PASC)/Secuelas post-agudas de SARS-CoV-2</i>	Subbaraman N. US health agency will invest \$1 billion to investigate 'long COVID' Nature. 2021;591:356. DOI: 10.1038/d41586-021-00586-y

- ✓ long COVID
- ✓ post-acute sequelae of SARS-CoV-2 infection (PASC)
- ✓ post-COVID-19 condition

La mayoría de los datos sobre post-COVID-19 condición se han generado antes del anuncio de la definición.

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

2. Mecanismos fisiopatológicos no dilucidados totalmente .

- ✓ Proceso inflamatorio crónico persistente
- ✓ Fenómeno autoimmune
- ✓ Desbalance hormonal como consecuencia de una alteración en el eje hipotálamico-pituitario-adrenal

Se ha creado un grupo de trabajo de la OMS para esbozar hipótesis plausibles sobre los mecanismos inmunológicos y fisiológicos subyacentes a la condición post-COVID.

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

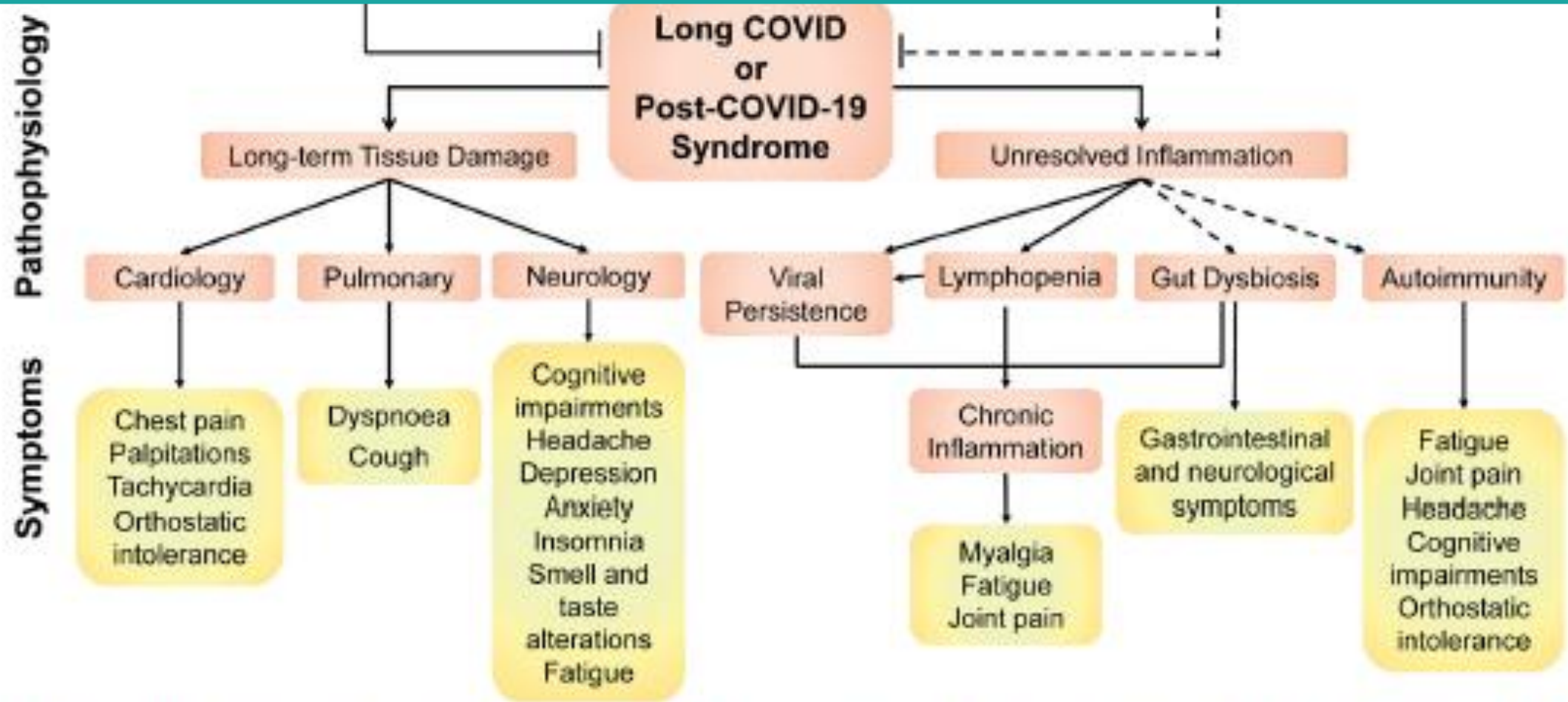
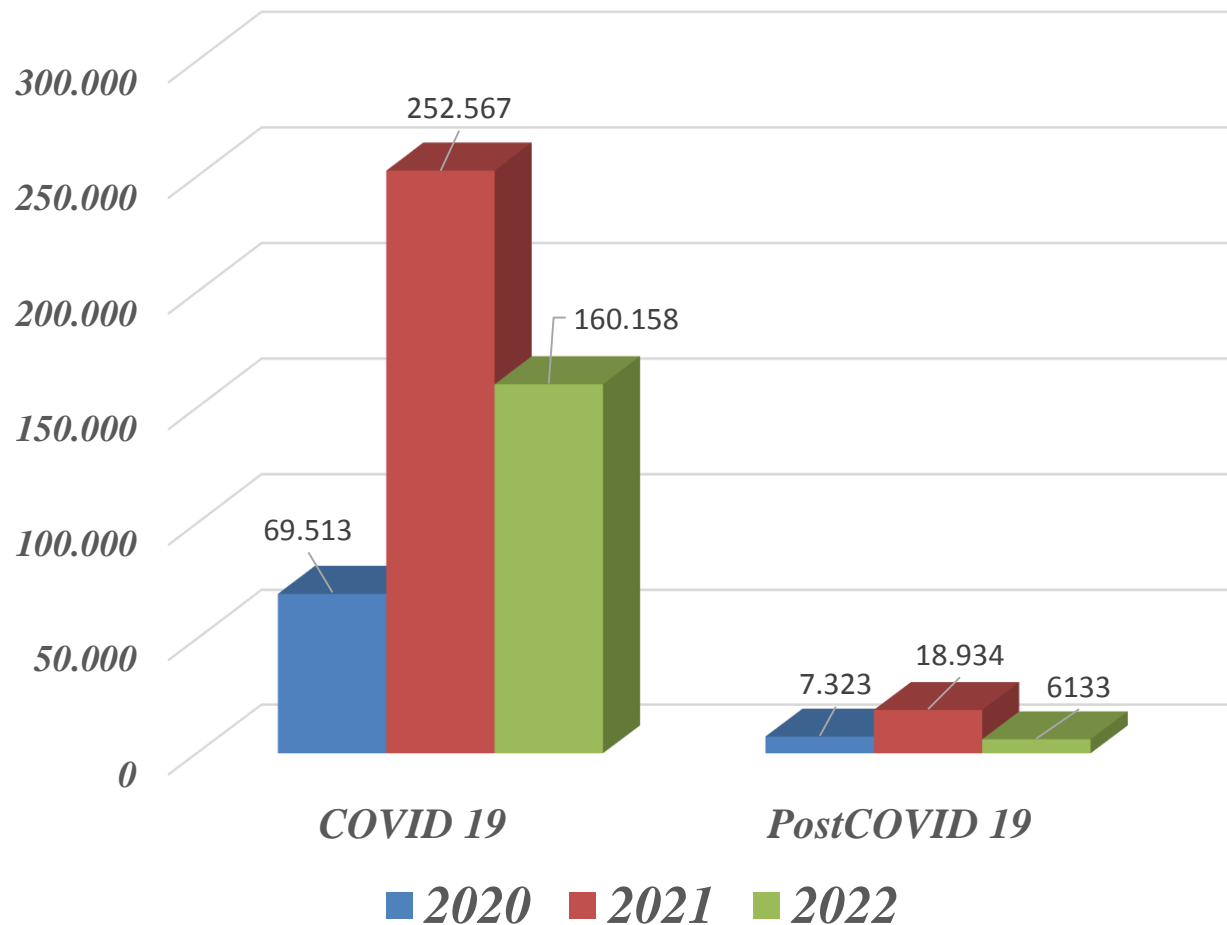


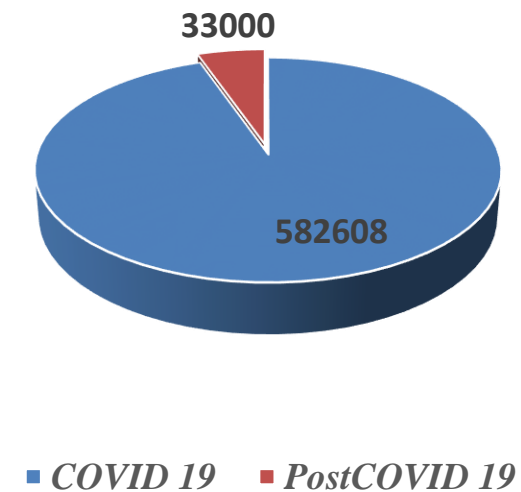
Figure 1. An overview of the symptoms, putative pathophysiology, associated risk factors, and potential treatments involved in long COVID. Note: Dashed lines represent areas where evidence is relatively lacking compared to non-dashed lines. (Color online only).

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

3. Crecimiento acelerado de datos



Cifra global de artículos publicados



INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

3. Crecimiento acelerado de datos



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Table 1
Summary of all included studies in descending order by sample size.

Study	Study design	Location	Sample size	Day zero	Follow-up (d)	Assessment method	Severity
Siqin et al. [30]	Cohort	USA	336,379	Diagnosis date	180	EMR	Mixed IP/OP/ICU
Mai et al. [31]	Cohort	China	3677	Discharge date	144	In person	IP
Carr Remónde-de-la-Herrera et al. [32]	Cohort	Spain	1850	Discharge date	340	Telephone	Mixed IP/ICU
Chen et al. [33]	Cohort	China	1723	Discharge date	186	In person	Mixed IP/ICU
Maung et al. [24]	Cohort	China	1276	Symptom onset	185, 349	In person	Mixed IP/ICU
Remónde-de-la-Herrera et al. [40]	Cohort	Spain	1142	Discharge date	213	Telephone, EMR	Mixed IP/ICU
Kim et al. [42]	Cohort	South Korea	822	Symptom onset or diagnosis date	195	Online	Mixed IP/OP/ICU
Shang et al. [31]	Cohort	China	795	Discharge date	180	Telephone	Mixed IP/ICU
Sensau et al. [52]	Cohort	Norway	676	Diagnosis date	132	Online	OP
Qu et al. [49]	Cohort	China	647	Discharge date	90	In person	IP
Muñoz-Martín et al. [20]	Cohort	Spain	543	Discharge date	365	In person	Mixed OP/IP
Qi et al. [54]	Cohort	China	540	Discharge date	90	IP	IP
Li et al. [35]	Cohort	Norway	458	Symptom onset	112.5	Online, postal mail	OP
Norström et al. [27]	Cohort	Sweden	431	Diagnosis date	220	Online	Mixed IP/OP/ICU
Shaw et al. [28]	Cohort	USA	354	Diagnosis date	158	In person, telephone	Mixed IP/OP/ICU
Zhao et al. [18]	Cohort	France	354	Diagnosis date	268.1	In person	Mixed IP/OP/ICU
Aponte et al. [50]	Cohort	Germany	207	Symptom onset	207	In person	Mixed IP/OP/ICU
Yu et al. [34]	Cohort	China	327	Symptom onset	203.4	In person	Mixed IP/ICU
Sjöblom et al. [33]	Cohort	United Kingdom	327	Discharge date	222	Telephone, in person, postal	Mixed IP/ICU
Sorensen-Hillesø et al. [23]	Cohort	Denmark	304	Symptom onset	365	Telephone	OP
Oh Lundström et al. [22]	Cohort	Italy	303	Diagnosis date	271	Telephone, EMR	Mixed IP/OP/ICU
Subramaniam Parai et al. [68]	Cohort	India	279	Discharge date	90	Telephone	Mixed IP/ICU
Wenborg et al. [32]	Cohort	Norway	247	Diagnosis date	180	In person	OP
Caraffo et al. [25]	Cohort	Italy	200	Discharge date	180	In person	IP
Quintana et al. [21]	Cohort	Belgium	199	Discharge date	94, 180	In person	Mixed IP/ICU
Reverte-Agüero et al. [27]	Cohort	Spain	195	Diagnosis date	180	Telephone	Mixed OP/IP
Jonathan A. Frenkel et al. [41]	Cohort	USA	182	Symptom onset	201	Telephone	Mixed IP/ICU
Pérez-Panero-Ayala et al. [58]	Cohort	Spain	151	Symptom onset	100.5	Telephone, EMR	Mixed OP/IP
Han et al. [43]	Cohort	China	144	Symptom onset	180	In person	Mixed IP/ICU
Shore et al. [29]	Cohort	Austria	135	Symptom onset	93	In person	Mixed IP/OP/ICU
Joshi et al. [52]	Cohort	Spain	134	Discharge date	90	Telephone	Mixed IP/ICU
Kisara-Rubio et al. [50]	Cohort	Spain	134	Discharge date	90	Telephone	Mixed IP/ICU
González-Hernández et al. [54]	Cohort	Mexico	130	Discharge date	90, 180	Telephone	Mixed IP/ICU
Nguyen et al. [47]	Cohort	France	125	Symptom onset	221.7	Telephone	IP
Campese et al. [24]	Cohort	France	120	Discharge date	110.9	Telephone	IP/OP [†]
Martelli et al. [56]	Cohort	Italy	120	Diagnosis date	126	In person	Mixed OP/IP
Truffo et al. [29]	Cohort	Italy	120	Diagnosis date	120	In person	Mixed OP/IP
Leifer Skov et al. [40]	Cohort	Denmark	120	Discharge date	180	In person	Mixed IP/OP/ICU
Jacobson et al. [61]	Cohort	USA	118	Diagnosis date	119.3	In person	Mixed IP/OP/ICU
Cassone et al. [69]	Cohort	Italy	118	Discharge date	180	In person	Mixed IP/ICU
Medina-Rodríguez et al. [59]	Cohort	Spain	114	Discharge date	90	In person	Mixed IP/OP/ICU
Schäfer et al. [50]	Cohort	Sweden	113	Discharge date	152	In person	ICU
Andersson et al. [28]	Cohort	Sweden	113	Discharge date	240	In person	Mixed IP/ICU
Nishi et al. [19]	Cohort	Italy	112	Discharge date	274	In person	OP
Skals et al. [65]	Cohort	Czech Republic	102	Discharge date	90	In person	Mixed OP/IP
T. J. M. Vollen et al. [37]	Cohort	Belgium	101	Discharge date	96	Telephone, in person	Mixed IP/ICU
Tindal et al. [48]	Cohort	Ireland	101	Discharge date	180	Online	Mixed IP/ICU
Baldoni et al. [20]	Cohort	Italy	97	Discharge date	231	Telephone	OP
Seifert et al. [56]	Cohort	Germany	96	Symptom onset	152, 265	In person	Mixed OP/IP
Spittler et al. [22]	Cohort	Italy	91	Discharge date	120	In person	Mixed IP/OP/ICU
Tobias et al. [44]	Cohort	Spain	91	Discharge date	180	In person	ICU
Martelli et al. [57]	Cohort	Italy	88	Discharge date	91	In person	IP
Parry et al. [50]	Cohort	India	81	Discharge date	100.6	EMR	Mixed IP/OP/ICU
Veng et al. [28]	Cohort	Canada	78	Symptom onset	91	In person	Mixed IP/ICU
Chen-Müller et al. [70]	Cohort	Germany	76	Discharge date	120	In person	Mixed IP/ICU
Li et al. [71]	Cohort	China	76	Discharge date	129	In person	Mixed IP/ICU
Nishiura et al. [60]	Cohort	France	72	Discharge date	126	In person	Mixed IP/ICU
Ellen et al. [72]	Cohort	Israel	66	Discharge date	270	Online, telephone	IP
Gracia-Castell et al. [53]	Cohort	Spain	62	Discharge date	90	In person, EMR	ICU
Yip et al. [73]	Cohort	China	60	Symptom onset	90	In person	Mixed IP/ICU
Rutten et al. [77]	Cohort	Italy	59	Discharge date	120	In person, telephone	IP
Wu et al. [30]	Cohort	China	54	Discharge date	133	In person	IP
Syed Mahmood Hossain Tabatabaie et al. [70]	Cohort	Iran	52	Discharge date	61	EMR	Mixed IP/OP/ICU

IP, inpatient; OP, outpatient; ICU, intensive care unit; EMR, electronic medical record.

[†] ICU and OP results pooled and separately.

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Table 2
Summary of studies reporting long COVID-19 symptom prevalence with a comparator group.

Author	Study design (sample size, follow-up (d))	COVID-19 group definition	Comparator group definition	Symptom/subscale assessment method	Newcastle-Ottawa scale	Summary of findings
Maung et al. [24]	Antibody-titration cohort (85 days and 249 days)	Patients with laboratory-confirmed COVID-19 discharged from 20 hospitals (Wuhan, China) (n = 184)	Community adults without COVID-19 from two districts of Wuhan city matched with cases 1:1 by age, sex and educational ^a (n = 184)	Interview, physical examination, questionnaires	7/9	COVID-19 patients had significantly higher prevalence of any of the following symptoms and for each individual symptom: fatigue or muscle weakness, sleep difficulty, hair loss, smell disorder, palpitations, joint pain, decreased appetite, acute diarrhoea, diarrhoea, diarrhoea or vomiting, chest pain, sore throat or difficulty swallowing, skin rash, myalgia, headache. In addition, enough COVID-19 patients had significantly higher mMIC, dry powder score and reported significantly more difficulty with mobility, panic or fear, pain or discomfort, anxiety or depression and mental quality of life.
Siqin et al. [30]	Retrospective cohort (80 d)	Patients with confirmed COVID-19 diagnosis, aged ≥ 16 y and alive at study start	Prospectively matched patients from the same database, with COVID-19 and alive at study start	ICD-10 codes, EMR, surveys with analytic data collected using the "3Box" Analytic Network, controlled for age, sex, race, ethnicity and comorbidity score ^b (n = 105, 97, 87, n = 28, 638)	5/9	COVID-19 had significantly higher burden of hospital- and ICD-10 related diagnosis and ICD-10 codes for mood disorder, anxiety disorder, psychotic disorder, substance use disorder, and insomnia.
Ramirez-Agüero et al. [27]	Prospective cohort (180 d)	Health workers from a tertiary care hospital with suspected and symptomatic COVID-19, confirmed by PCR (n = 182)	Health workers from a tertiary care hospital with suspected COVID-19 with negative PCR, matched for sex and age (n = 122)	Interview	5/9	There was no statistically significant difference in the rate of necessary 5-item diffculty differentiation between those with positive PCR for COVID-19 and those with suspected COVID-19 with negative PCR.
Martelli et al. [56]	Prospective cohort (126 d)	Healthcare workers at university hospital of Brescia (Italy) with previously confirmed diagnosis of moderate COVID-19 (n = 120)	Healthcare workers from the same hospital not previously affected by COVID-19 (n = 30)	Interview, physical examination, questionnaires	5/9	COVID-19 cases did not differ significantly from non-COVID-19 controls in terms of neurological or cognitive deficits but had significantly higher scores for anxiety and depression.
Ellen et al. [72]	Retrospective cohort* (270 d)	Adult patients discharged from the same period as COVID-19 patients due to pneumonia or respiratory infection with negative COVID-19 PCR (n = 42)	Age- and sex-matched patients hospitalized during the same period as COVID-19 patients due to pneumonia or respiratory infection with negative COVID-19 PCR (n = 42)	Questionnaire	6/9	Although there are baseline differences between groups in terms of comorbidity, COVID-19 cases had a significant overall self-reported health change compared to controls.
Sensau et al. [52]	Prospective cohort (132 d)	Adults testing positive for COVID-19 across four laboratories in southeastern Norway, excluding participants later hospitalized (n = 670)	Adults testing negative for COVID-19 across the same sites, including participants later hospitalized (n = 670)	Questionnaire	6/9	COVID-19-positive participants were significantly more likely to report a worsening of health compared to COVID-19-negative participants ^c .

mMTC, Modified Medical Research Council 2012 respiratory test function.

^a Cardiovascular disease, chronic respiratory disease, chronic kidney disease, hypertension, and diabetes.

^b Obesity, hyper tension, diabetes, chronic kidney disease, asthma, chronic liver respiratory disease, nicotine dependence, substance use disorder, ischemic heart disease, and other forms of heart disease, cardiovascular depression, cancer, haematological cancer, chronic liver disease, stroke, dementia, organ transplant, rheumatoid arthritis, lupus, psoriasis, and disorders involving all immune-mediated conditions.

* Study design was derived from abstract methods section and see author description.

^c Multivariate regression model including age, sex, chronic disease, smoking, health professional occupation, income level, fitness, and time from COVID-19 testing to follow-up.

Deben desarrollarse manteniendo el equilibrio entre velocidad y calidad

ESTUDIOS CON Y SIN GRUPO COMPARADOR

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

4. Población objetivo y alcance:

- Cohortes hospitalizadas vs no hospitalizados.
 - Los criterios de ingreso hospitalario varían
 - Individuos asintomáticos (deben incluirse)
 - Niños vs adultos
-

INTERROGANTES O LIMITANTES ACTUALES EN LA INVESTIGACIÓN DE LA CONDICIÓN POST-COVID-19

5. ¿Qué y cómo medir la condición Post-COVID-19?

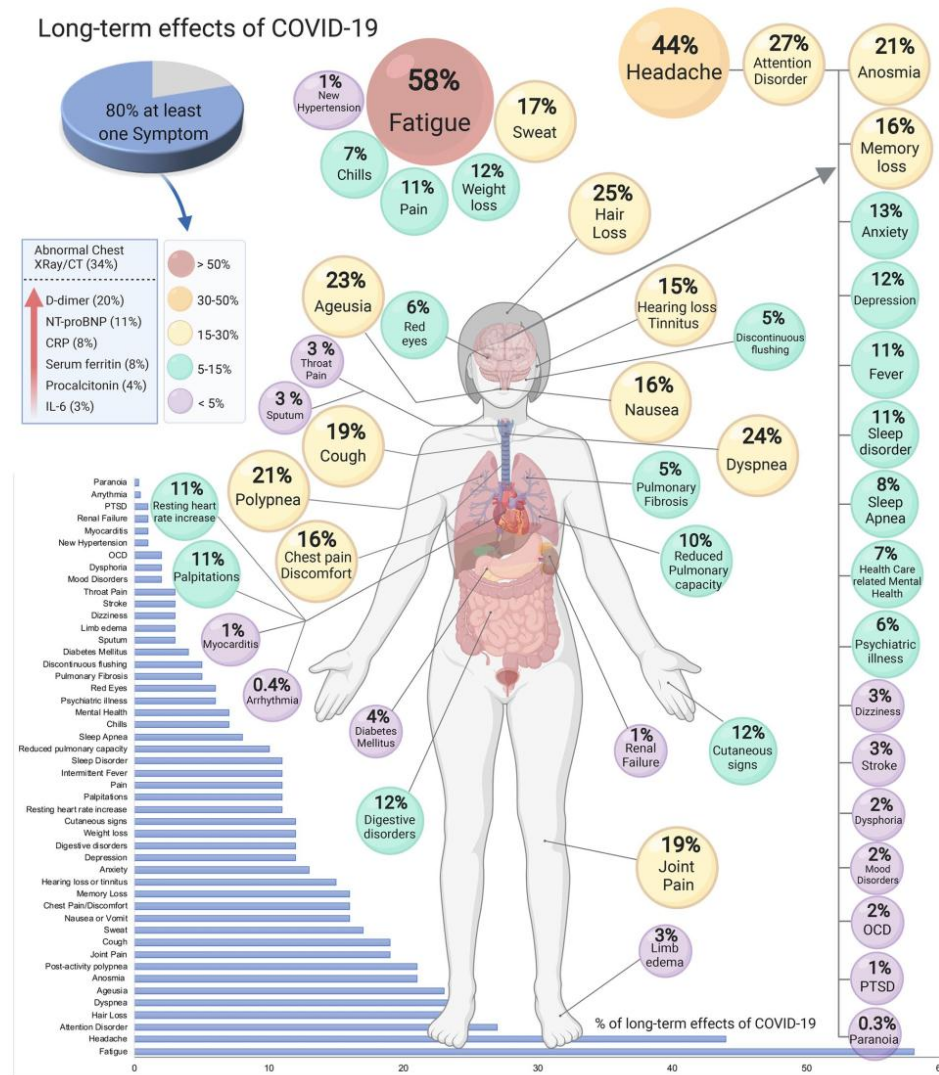
Las herramientas "validadas" existentes (p. ej., instrumentos de calidad de vida) no se han validado en COVID-19

Existe la necesidad de definir qué datos deben evaluarse en los ensayos y en la práctica clínica

IMPACTO DE LAS LIMITANTES EN LA INVESTIGACIÓN POSTCOVID-19



HETEROGENEIDAD EN LA PREVALENCIA DE LOS SÍNTOMAS



Estimado de 55 efectos a largo plazo
Periodo variable 14 to 110 dias post-infección viral

Síntomas más frecuentes

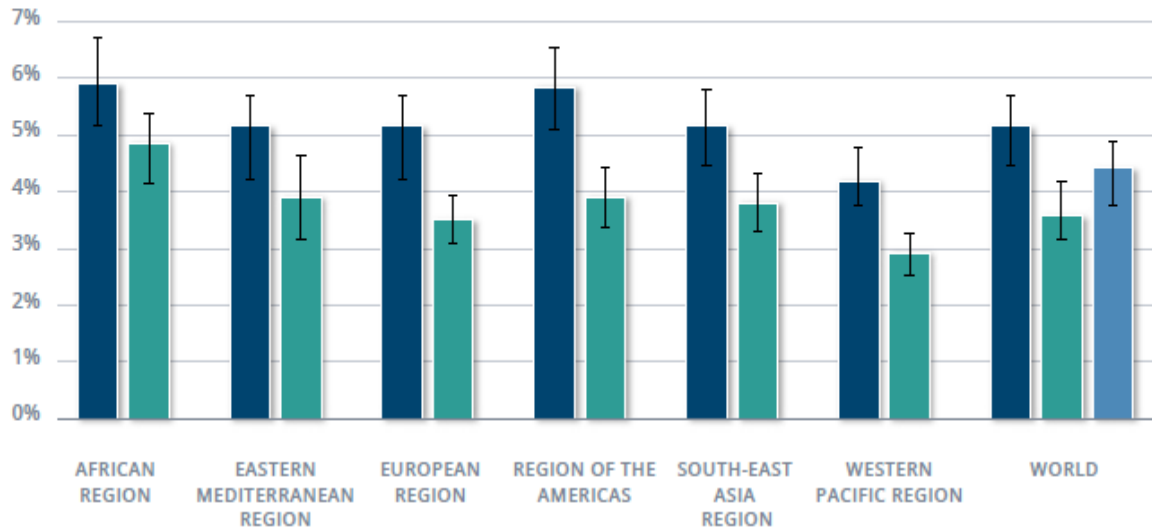
- ✓ Musculo-esquelético
- ✓ Respiratorio
- ✓ Digestivo
- ✓ Neurológico incluyendo la depresión.

Figure 2. Long-term effects of coronavirus disease 2019 (COVID-19). The meta-analysis of the studies included an estimate for one symptom or more reported that 80% of the patients with COVID-19 have long-term symptoms. CRP C-reactive protein, CT computed tomography, IL-6 Interleukin-6, NT-proBNP (NT)-pro hormone BNP, OCD Obsessive Compulsive Disorder, PTSD Post-traumatic stress disorder. This figure was created using Biorender.com.

El 4.4% de la población mundial sufre de depresión (300 millones de personas)

Prevalence of depressive disorders (% of population), by WHO Region

Female Male Both



La pandemia de COVID-19 incrementó en un 25% su prevalencia. Mayor demanda asistencial en servicios de salud

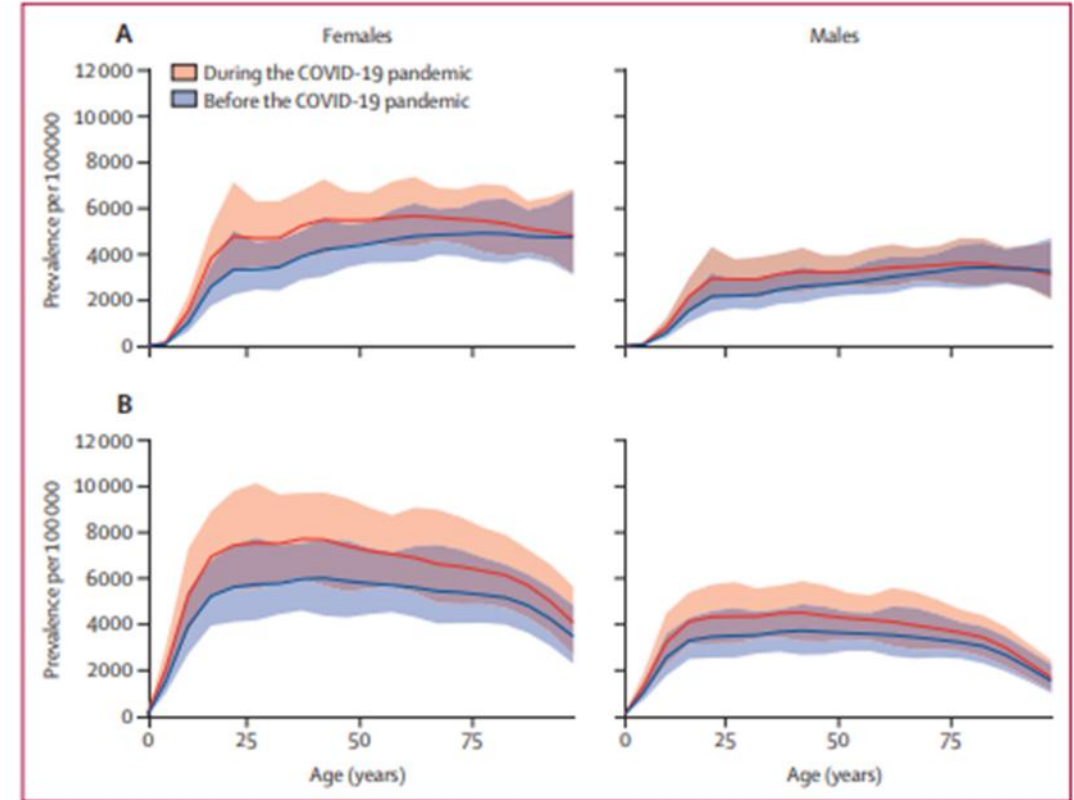


Figure 1: Global prevalence of major depressive disorder (A) and anxiety disorders (B) before and after adjustment for (ie, during) the COVID-19 pandemic, 2020, by age and sex

Global Burden of Disease Study 2015 (<http://ghdx.healthdata.org/gbd-results-tool>)

World Health Organization 2017



Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic



COVID-19 Mental Disorders Collaborators*

www.thelancet.com Vol 398 November 6, 2021

HETEROGENEIDAD EN LA PREVALENCIA DE LOS SÍNTOMAS

Relación con modificadores: comorbilidades, datos demográficos, severidad de la enfermedad aguda, respuesta humoral a RBD Sars-Cov-2.

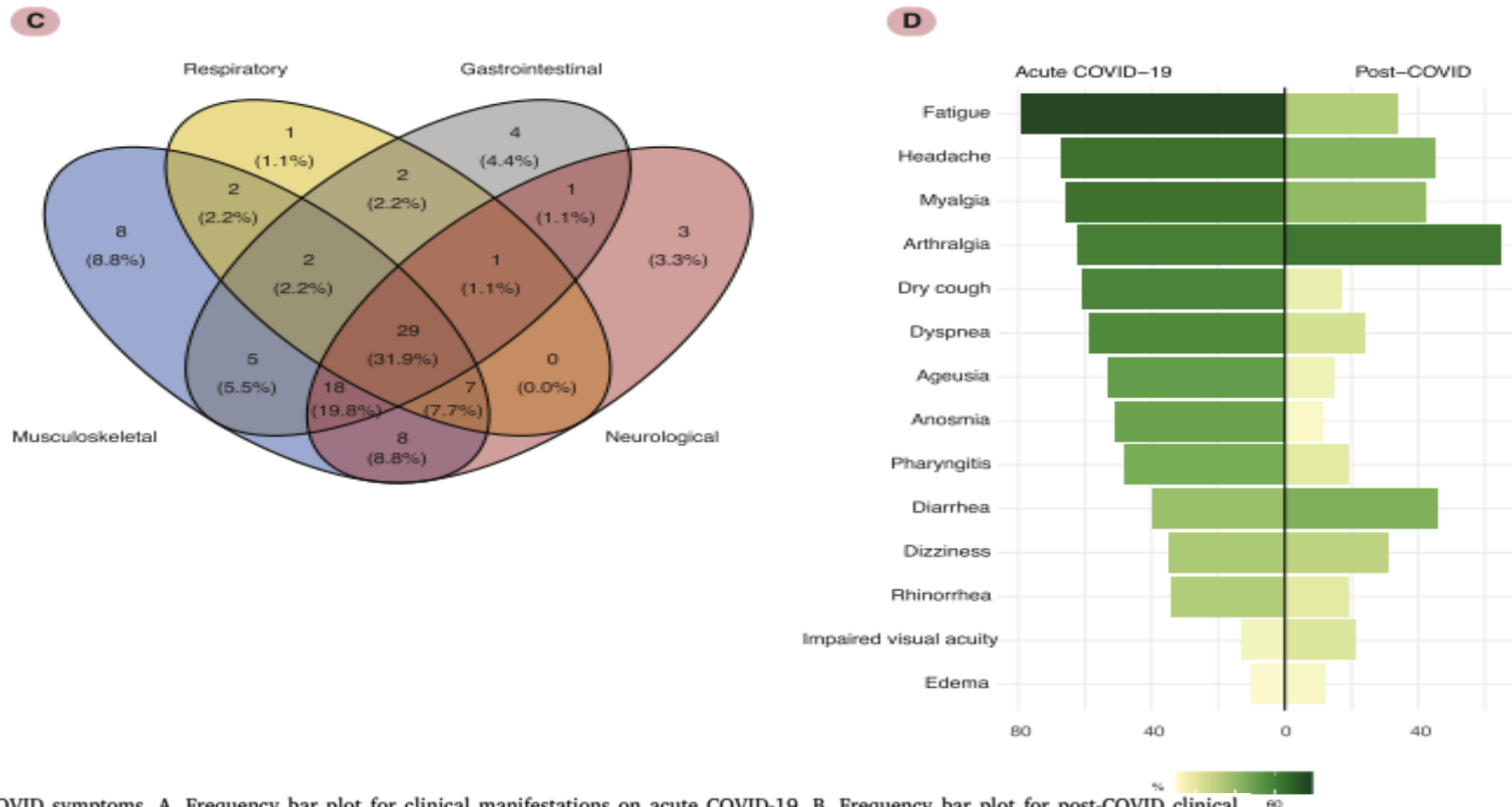
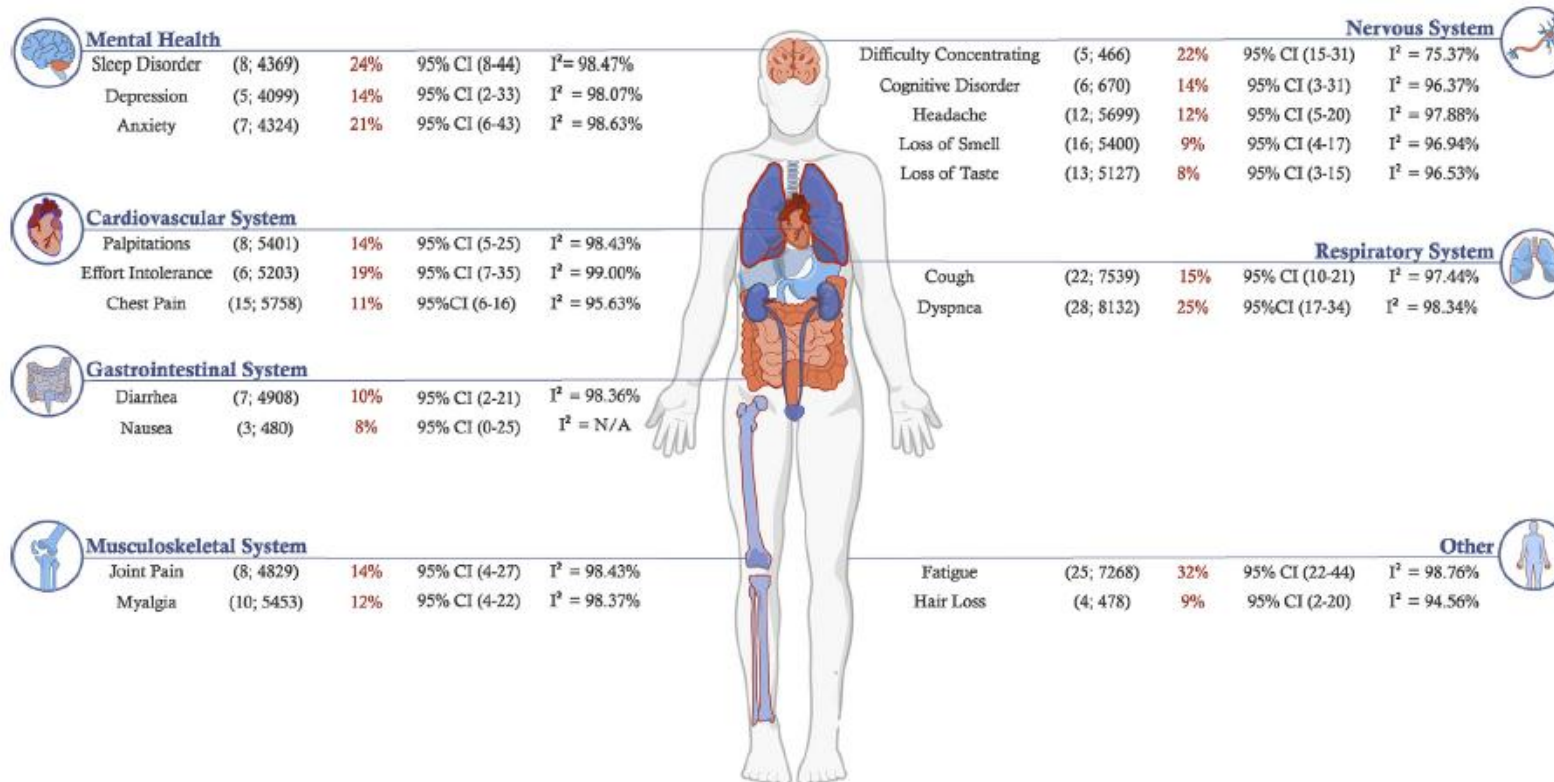


Fig. 2. Acute and post-COVID symptoms. A. Frequency bar plot for clinical manifestations on acute COVID-19. B. Frequency bar plot for post-COVID clinical manifestations. Frequency of depression was estimated by Zung scale. C. Venn diagram with the superposition of the main PCS symptoms. Analysis included 91 patients, because 9 out of 100 patients did not exhibit any of the four main symptoms. D. Mirrored bar plot for symptoms on acute COVID-19 and post-COVID syndrome.

HETEROGENEIDAD EN LA PREVALENCIA DE LOS SÍNTOMAS

Relación con modificadores: periodos de seguimiento

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3- a <6-meses

fatiga 32%,
disnea 25%,
trastornos del sueño 24%,
trastornos de concentración 22%

Fig. 2. Illustration of meta-analysis results with estimated prevalence of symptoms following acute COVID-19 infection across follow-up intervals of (A) 3 to <6 months

HETEROGENEIDAD EN LA PREVALENCIA DE LOS SÍNTOMAS

Relación con modificadores: periodos de seguimiento

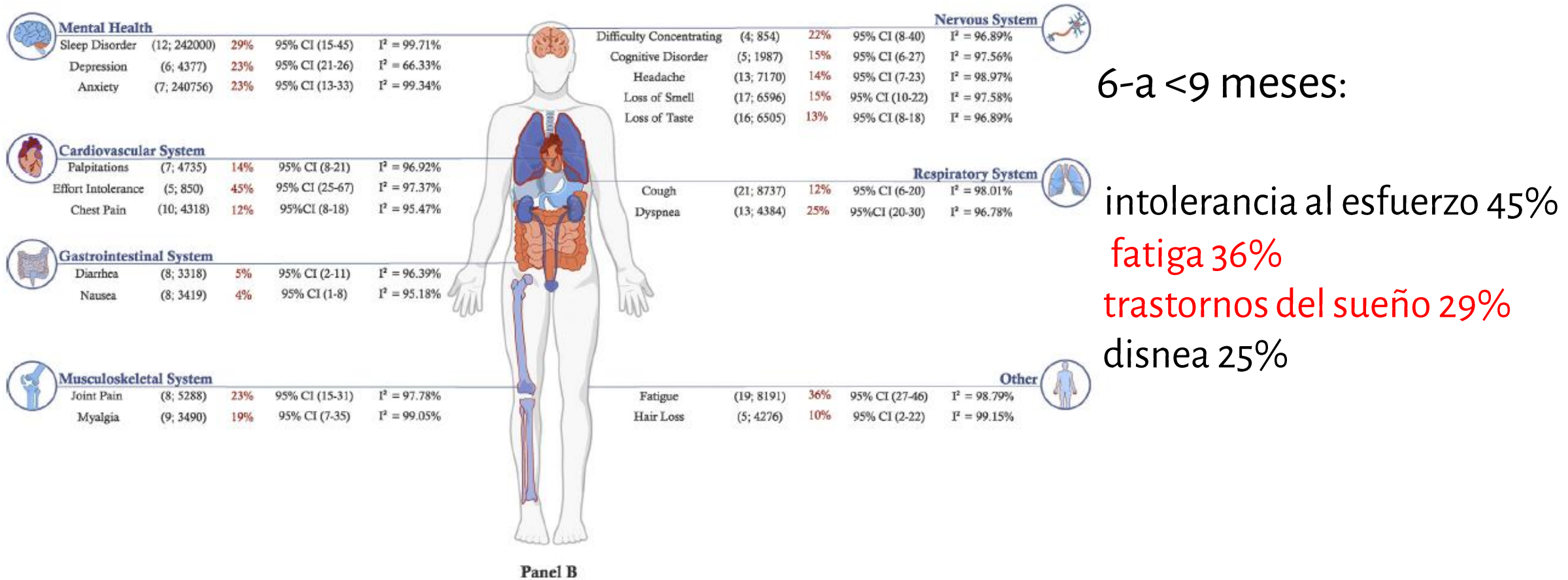


Fig. 2. Illustration of meta-analysis results with estimated prevalence of symptoms following acute COVID-19 infection across follow-up intervals of 6 to <9 months (number of studies, size of population used to calculate point estimate).

Como mitigar estas limitantes

Revisar sistemáticamente los instrumentos de medición utilizados, evaluando validez, capacidad de discriminación y factibilidad.

Proponer nuevos instrumentos de medición, si no existiesen los adecuados para los dominios evaluables priorizados.

El Consorcio Internacional de Infección emergente y respiratoria aguda severa (ISARIC del inglés) ha desarrollado protocolos de seguimiento y encuestas para niños y adultos, con el objetivo de evaluar factores relacionados con las consecuencias en la salud física y psicosocial tras el diagnóstico de COVID-19

Pocas iniciativas internacionales han creado instrumentos para la recolección de datos

¿Objetivos fundamentales de la investigación nacional en relación con la condición Post-COVID-19?

Objetivo General

Describir la prevalencia y las principales manifestaciones clínicas de la condición Post-COVID-19 en la población cubana

Objetivos fundamentales

1. Describir la prevalencia de la condición Post-COVID-19 en la población cubana
 2. Describir las principales manifestaciones clínicas de la condición Post-COVID-19 en la población cubana
 3. Describir la duración de los síntomas y signos de la condición Post-COVID-19 en la población cubana
 4. Evaluar factores de riesgo relacionados con la condición Post-COVID-19 en la población cubana
-

Características generales de la encuesta

1

Aplicada mediante entrevista personal.

2

Descriptiva: Busca obtener las características o actitudes de determinada población.

3

Debe ser objeto de una cuidadosa elaboración.

RESULTADOS ESPERADOS

Estimado de prevalencia de la condición Post-COVID-19 en la población cubana

Principales manifestaciones clínicas y duración de la condición Post-COVID-19 en la población cubana

Obtener resultados en población adulta y pediátrica en el menor tiempo posible, con el objetivo de contribuir a mejorar la calidad de los datos, la armonización y la comparabilidad entre diferentes áreas geográficas.

Participar de las iniciativas internacionales interesadas en la investigación, y en el desarrollo de guías prácticas que contribuyan a la comprensión de los mecanismos fisiopatológicos, diagnóstico y tratamiento de la condición post covid -19
