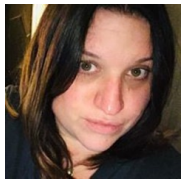
Post-COVID Condition Core Outcome Set study: Neurological & Mental Health Manifestations

Core Outcome Measures in Effectiveness Trials

Tim Nicholson Neuropsychiatry Clinical Senior Lecturer, King's College London, UK
Long COVID clinic, King's College Hospital, London, UK

Fran Simpson



Sarah Gorst

Paula Williamson

Daniel Munblit

Dale Needham

Other key team members

Margaret O'Hara

Athena Akrami

Moscow/Imperial: Nina Seylanova, Callum Parr
Liverpool: Nicola Harman
Magdeberg: Christian Apfelbacher
Dresden: Jochen Schmidt
Sydney: Allison Tong
WHO: Janet Diaz, Nicoline Scheiss, Wouter de Groote, Jacobus Preller, Krutika Kuppalli

Post-COVID Condition Core Outcome Set study

Aim: develop a Core Outcome Set (COS) to optimise collation and comparison for research & clinical practice *globally*

2 stages: 1. 'What' key outcomes should be measured in all studies
2. 'How' to measure these outcomes

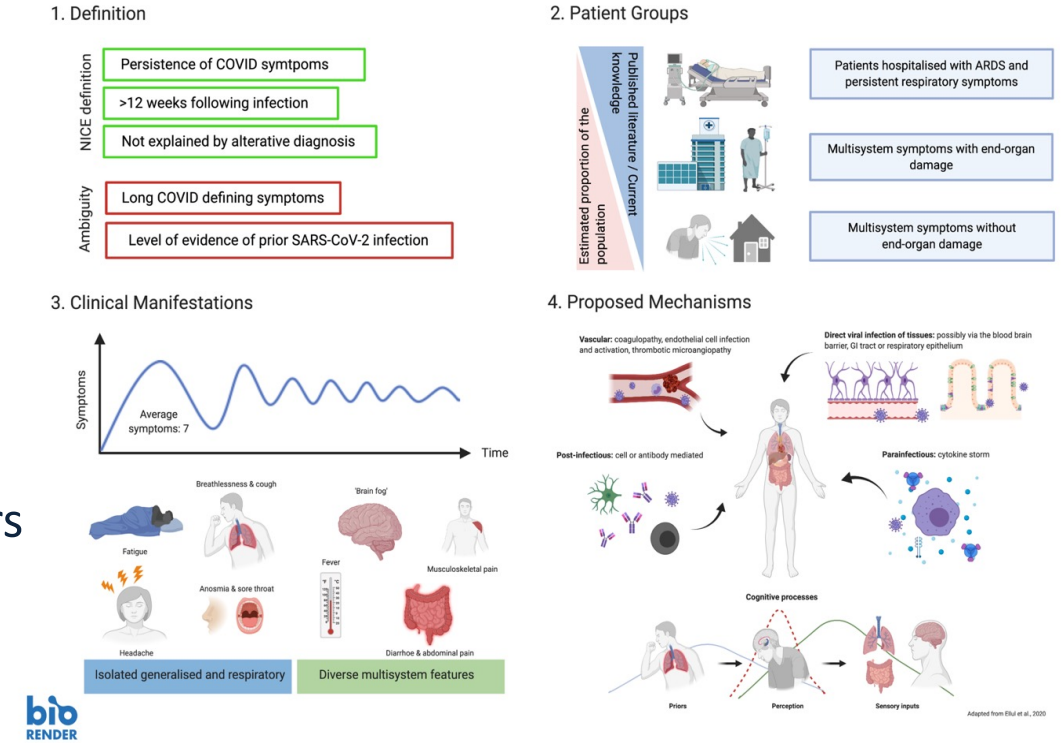
Important points about a COS:

- *Minimum* recommended for all studies; other outcomes often added for specific studies
- Not all outcomes need to be measured at all time points
- Patient and researcher burden is carefully considered in both what & how to measure stages
- Iterative process, especially for new/poorly understood disorder, so are re-evaluated/updated as needed
- Patients' & carers' views key as are those of other stakeholders (e.g. research users and clinical service funders)

Complexities of outcomes in Long COVID

- New disorder(s)
- Many symptoms/domains

  …in many combinations
- Marked fluctuations
- Genetic/other variability
- Relationship to other disorders
- Public health emergency….



D'Cruz & Watson et al *in preparation*

PC-COS study: 'What to measure'

- Methodology working group identified and selected 24 outcomes for rating in 1st round of Delphi study made available in English, Spanish, French, Russia & Chinese languages (on top of 'recovery' which was considered key outcome from/link with acute COVID COS)

- 1,530 participants from 70 countries: 25 European countries (66% of participants), 19 Asian (6%), 12 S.American 12 (5%), 10 African 10 (2%), 3 N.American (19%), 2 Australasian (2%)

- 3 Key stakeholder groups: 1. Professionals (researchers and/or clinicians with PCC expertise)
  2. Professionals with PCC
  3. People with PCC (and family or carers)

	Europe	N.America	S.America	Asia	Africa	Australasia
Professionals	186	190	59	68	26	24
Professionals with PCC	125	23	10	9	1	1
PCC (& family/carer)	701	74	8	17	4	4

Outcome ratings

Survival	Cognitive functioning, symptoms and conditions	Fatigue or exhaustion
Cardiovascular functioning, symptoms, conditions	Mental functioning, symptoms and conditions	Social role functioning and relationship problems
Endocrine and metabolic functioning, symptoms, and conditions	Taste- and/or smell-related functioning symptoms and conditions	Work/occupational changes and study
Hearing-related functioning, symptoms and conditions	Kidney and urinary-related functioning, symptoms and conditions	Stigma
Gastrointestinal functioning, symptoms and conditions	Reproductive and sexual functioning, symptoms and conditions	Satisfaction with life or personal employment
Pain	Respiratory functioning symptoms and conditions	Health care resource utilization
Sleep-related functioning, symptoms, and conditions	Skin, hair, and/or nail-related functioning symptoms and conditions	Family/carer burden
Nervous system functioning, symptoms and conditions	Physical functioning symptoms and conditions	Post-exertion symptoms

2 new outcomes suggested by participants and added in round 2: Eye & Muscle/Joint symptoms & conditions

Outcomes rated from 0-9 with pre-determined consensus thresholds: 80% or more of participants in each group rating the outcome as critical (scoring 7-9)

Those not reaching consensus discussed at independently chaired ‘consensus meeting’:

12 patients: includes 4 Healthcare professionals with PCCUK (7), Ireland (1), Greece (1) Belgium (1), Spain (1), USA (1)

15 Healthcare Professionals/Researchers: includes 1 Healthcare professional with PCC USA (2), India (2), UK (1), Russia (1), Chile (1), Switzerland (1), Belgium (1), Brazil (1), Norway (1), Canada (1), Sweden (1), Nigeria (1), Ghana (1)

Outcomes included in COS

Physiological/clinical	1. Fatigue or Exhaustion 2. Post-exertion symptoms 3. Respiratory functioning, symptoms & conditions 4. Cardiovascular functioning, symptoms & conditions 5. Nervous system functioning, symptoms & conditions 6. Cognitive functioning, symptoms & conditions 7. Mental functioning, symptoms & conditions 8. Pain
Life impact	9. Physical functioning, symptoms & conditions 10. Work/occupational changes and study
Recovery	11. Recovery – added a priori (as link to acute COVID COS)
Survival	12. Survival – added at consensus meeting

Outcomes included in COS

Physiological/clinical

1. Fatigue or Exhaustion ?
2. Post-exertion symptoms ?
3. Respiratory functioning, symptoms & conditions
4. Cardiovascular functioning, symptoms & conditions ?

Neurological & Mental Health

5. Nervous system functioning, symptoms & conditions
6. Cognitive functioning, symptoms & conditions
7. Mental functioning, symptoms & conditions

8. Pain ?

Life impact

9. Physical functioning, symptoms & conditions ?
10. Work/occupational changes and study

Recovery

11. Recovery – added a priori (as link to acute COVID COS)

Survival

12. Survival – added at consensus meeting

Neurological & mental health outcomes

Nervous system: dizziness, fainting, headache, tremors/shaking, seizures/fits, tingling feelings, decreased sensation, stroke, inability to move part of body, lack of coordination/balance, or speech difficulty

Cognitive: memory, communication, concentration, or understanding instructions

Mental functioning: problems with emotions and mood, including anxiety/worrying, avoidance, catastrophizing, panic attacks, depression, suicidal thoughts, or post-traumatic stress disorder

Neurological & mental health contd…

Pain: problems related to uncomfortable feelings in the body that can include sharp or burning pain, dull ache, or stinging or throbbing feeling, pain that comes and goes

Cardiovascular: problems affecting heart (e.g. pounding/racing heart) and blood vessels (e.g., veins or arteries), lightheadedness/fainting (inc on standing)

Fatigue: feeling exhausted, having too little energy, or needing more rest

Post exertion symptoms: Worsening of symptoms following physical or mental exertion that can last for prolonged duration

Physical functioning: physical abilities, inc muscle strength/weakness, arm/leg shaking or unsteadiness, walking, dressing, eating.

Other domains (<u>not in Core Outcome Set</u>): sleep, eye symptoms (esp visual changes/light sensitivity,) taste/smell, hearing (including tinnitus)

Next steps

- Complete ‘How to measure’ phase
- Work with researchers and clinicians to maximise uptake of Core Outcome Set
- Respond/adapt as we learn more about the longer term neurological, cognitive and mental health impacts of COVID-19

Neurological & mental health symptoms in Long COVID

Patient-led survey (3762 patients) Very broad range of complex neuropsychiatric symptoms reported:

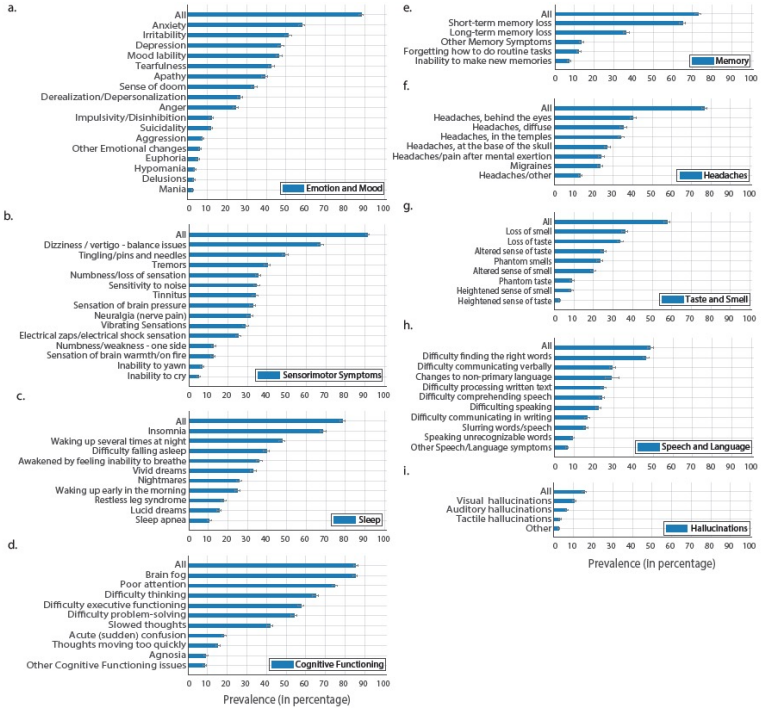


Figure 3: Symptom prevalence estimates for neuropsychiatric symptoms. Similar to Figure 2, for

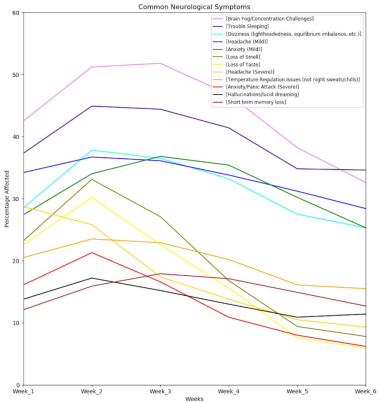


Figure 22. Percentage of respondents affected by "Neurological" symptoms

Davis H et al,
E Clinical Medicine
July 2021

PATIENT-LED RESEARCH COLLABORATIVE

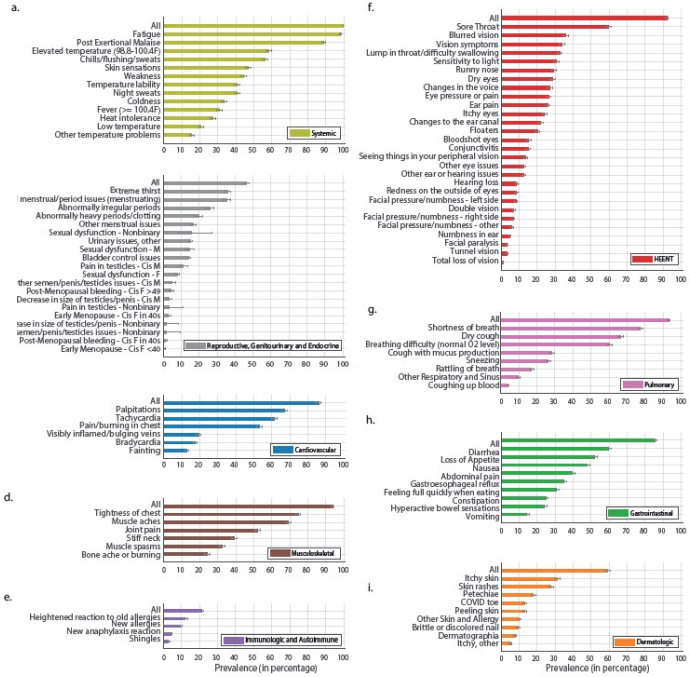
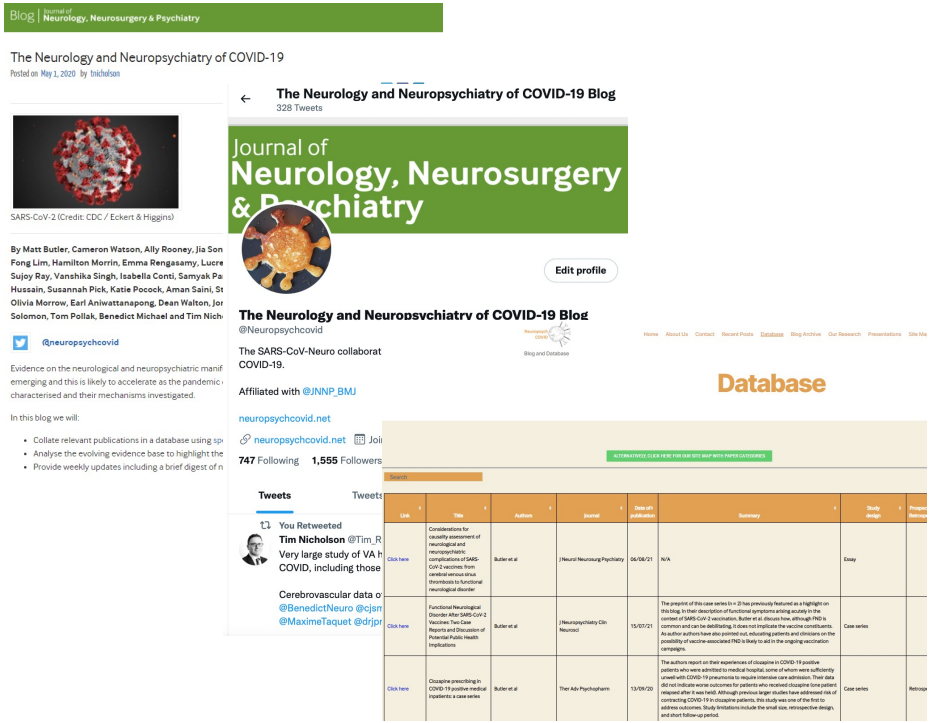
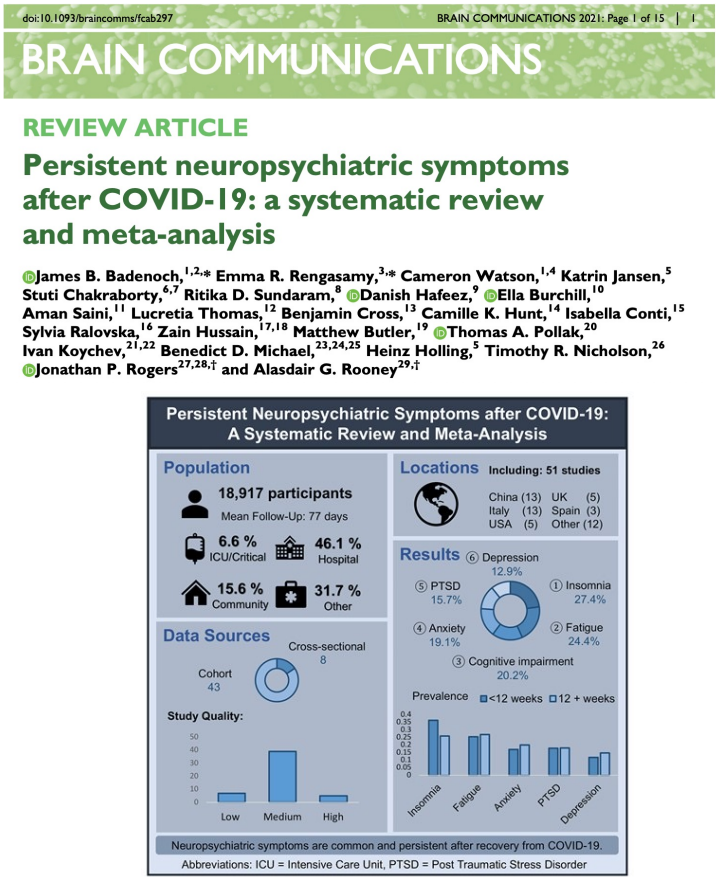


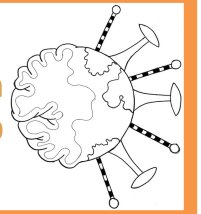
Figure 2: Symptom prevalence estimates (non-neuropsychiatric symptoms). Bars represent the percentage of

Neurology & Neuropsychiatry of COVID-19 blog





Neuropsych COVID



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Neuropsychiatry
Review

Neurology and neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives FREE

Jonathan P Rogers [1,2], Cameron J Watson [3], James Badenoch [4], Benjamin Cross [5], Matthew Butler [6], Jia Song [7], Danish Hafeez [8], Hamilton Morrin [9], Emma Rachel Rengasamy [10], Lucretia Thomas [11], Silviya Ralovska [12], Abigail Smakowski [2], Ritika Dilip Sundaram [13], Camille Kaitlyn Hunt [14], Mao Fong Lim [15], Daruj Aniwattanapong [6,16], Vanshika Singh [17], Zain Hussain [18], Stuti Chakraborty [19], Ella Burchill [20], Katrin Jansen [21], Heinz Holling [21], Dean Walton [22], Thomas A Pollak [6], Mark Ellul [22,23,24], Ivan Koychev [25,26], Tom Solomon [22,23], Benedict Daniel Michael [22,23,24], Timothy R Nicholson [6], Alasdair G Rooney [27]
Correspondence to Dr Jonathan P Rogers, Division of Psychiatry, University College London, London W1T 7NF, UK; jonathan.rogers@ucl.ac.uk

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/neulet

Minireviews

COVID-19 and psychosis risk: Real or delusional concern?

Cameron J. Watson [a,*], Rhys H. Thomas [c,d], Tom Solomon [e,f,g], Benedict Daniel Michael [e,f,g], Timothy R. Nicholson [h], Thomas A. Pollak [b]

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Editorials

Neuropsychiatric complications of covid-19

BMJ 2020 ; 371 doi: https://doi.org/10.1136/bmj.m3871 (Published 13 October 2020)

Matthew Butler, NIHR academic clinical fellow neuropsychiatry [1], Thomas A Pollak, NIHR clinical lecturer in neuropsychiatry [1], Alasdair G Rooney, clinical lecturer in neuropsychiatry [2], Benedict D Michael, senior clinician scientist fellow in neurology [3], Timothy R Nicholson, clinical senior lecturer in neuropsychiatry [1]

ELSEVIER

Psychiatric Clinics of North America

Volume 45, Issue 1, March 2022, Pages 29-43

Emerging Knowledge of the Neurobiology of COVID-19

Matthew Butler MD [a,*], Benjamin Cross MD [b], Danish Hafeez [c], Mao Fong Lim MD [d], Hamilton Morrin MD [e], Emma Rachel Rengasamy MD [f], Tom Pollak PhD [a], Timothy R. Nicholson PhD [a]

CoroNerve Studies Group

COVID-CNS
THE COVID-CLINICAL NEUROSCIENCE STUDY

Journal of Neurology, Neurosurgery & Psychiatry — Latest content | Current issue | Archive | JNNP 100 | Authors

Home / Archive / Volume 91, Issue 8

Editorial

Defining causality in COVID-19 and neurological disorders

Mark Ellul [1,2,3], Aravinthan Varatharaj [4,5], Timothy R Nicholson [6], Thomas Arthur Pollak [6], Naomi Thomas [7,8], Ava Easton [9], Michael S Zandi [10], Hadi Manji [10], Tom Solomon [1,2,3], Alan Carson [11], Martin R Turner [12], Rachel Kneen [1,3,13], Ian Galea [4,5], Sarah Pett [14,15], Rhys Huw Thomas [7,16], Benedict Daniel Michael [1,2,3] CoroNerve Steering Committee

medRxiv — THE PREPRINT SERVER FOR HEALTH SCIENCES | BMJ | Yale

Comment on this paper

Proteome-wide Mendelian randomization identifies causal links between blood proteins and severe COVID-19

Alish B. Palmos, Vincent Millischer, David K. Menon, Timothy R. Nicholson, Leonie Taams, Benedict Michael, COVID Clinical Neuroscience Study Consortium, Christopher Hübel, Gerome Breen

medRxiv — THE PREPRINT SERVER FOR HEALTH SCIENCES | BMJ | Yale

Comment on this paper

Brain Injury in COVID-19 is Associated with Autoinflammation and Autoimmunity

EJ Needham, AL Ren, RJ Digby, JG Outrim, DA Chatfield, AE Manktelow, VFJ Newcombe, R Doffinger, G Barcenas-Morales, C Fonseca, MJ Taussig, RM Bunstead, C Dunai, N Sithole, NJ Ashton, H Zetterberg, M Gissler, A Edén, E Markland, MJ Griffiths, J Cavanagh, G Breen, SR Irani, A Elmer, N Kingston, JR Bradley, LS Taams, BD Michael, ET Bullmore, KGC Smith, PA Lyons, AJC Coles, DK Menon, the Cambridge NeuroCOVID Group, the NIHR COVID-19 BioResource, Cambridge NIHR Clinical Research Facility

doi:10.1093/braincomms/fcab168 BRAIN COMMUNICATIONS 2021: Page 1 of 15 | 1

BRAIN COMMUNICATIONS

The Journal of Neuropsychiatry and Clinical Neurosciences — Current Issue | Archive | About | JNCN in Advance | Author Resources | Author and Reviewer Guidelines

New Consensus Clinical Guidance on Management of COVID-19 Encephalopathy Accepted by *JNCN*

COVID-19 encephalopathy is a disturbance of brain function that may develop in persons with COVID-19. This condition may present clinically as delirium, subsyndromal delirium, or coma and negatively affects clinical outcomes. While research into the biological mechanisms of COVID-19 encephalopathy are ongoing, clinicians are in need of practical guidance on the evaluation and management of patients with this condition.

JNCN has accepted for publication the Clinical Consensus Guidance for Diagnosis and Management of Adult COVID-19 Encephalopathy Patients developed by the Global COVID-19 NeuroResearch Coalition. This document provides much-needed and immediately applicable guidance on the evaluation and management of this condition and is available here for review and download.

Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study

Aravinthan Varatharaj, Naomi Thomas, Mark A Ellul, Nicholas W S Davies, Thomas A Pollak, Elizabeth L Tenorio, Mustafa Sultan, Ava Easton, Gerome Breen, Michael Zandi, Jonathan P Coles, Hadi Manji, Rustam Al-Shahi Salman, David K Menon, Timothy R Nicholson, Laura A Benjamin, Alan Carson, Craig Smith, Martin R Turner, Tom Solomon, Rachel Kneen, Sarah L Pett, Ian Galea*, Rhys H Thomas*, Benedict D Michael*, on behalf of the CoroNerve Study Group†

Summary

Background Concerns regarding potential neurological complications of COVID-19 are being increasingly reported, primarily in small series. Larger studies have been limited by both geography and specialty. Comprehensive characterisation of clinical syndromes is crucial to allow rational selection and evaluation of potential therapies. The aim of this study was to investigate the breadth of complications of COVID-19 across the UK that affected the brain.

Lancet Psychiatry 2020 Published Online June 25, 2020 https://doi.org/10.1016/S2215-0366(20)30287-X

Spectrum, risk factors and outcomes of neurological and psychiatric complications of COVID-19: a UK-wide cross-sectional surveillance study

Amy L. Ross Russell,[1,2,†] Marc Hardwick,[2,3,†] Athavan Jeyanantham,[3] Laura M. White,[4] Saumitro Deb,[5] Girvan Burnside,[6] Harriet M. Joy,[7] Craig J. Smith,[8,9] Thomas A. Pollak,[10] Timothy R. Nicholson,[10] Nicholas W. S. Davies,[11] Hadi Manji,[12,13] Ava Easton,[14,15] Stephen Ray,[15,16] Michael S. Zandi,[13] Jonathan P. Coles,[7] David K. Menon,[17] Aravinthan Varatharaj,[2,3] Beth McCausland,[2,3,18] Mark A. Ellul,[15,16,19] Naomi Thomas,[20,21] Gerome Breen,[22] Stephen Keddie,[23,24] Michael P. Lunn,[12,13] John P. S. Burn,[25] Graziella Quattrocchi,[26] Luke Dixon,[27] Claire M. Rice,[28,29] George Pengas,[2] Rustam Al-Shahi Salman,[30] Alan Carson,[20] Eileen M. Joyce,[13] Martin R. Turner,[31] Laura A. Benjamin,[15,16,32] Tom Solomon,[15,16,19] Rachel Kneen,[15,33] Sarah Pett,[34,35] Rhys H. Thomas,[20,21,36,‡] Benedict D. Michael[15,16,19,‡] and Ian Galea[2,3,‡]; on behalf of the CoroNerve Studies Group[†]

medRxiv — THE PREPRINT SERVER FOR HEALTH SCIENCES | BMJ | Yale

Comment on this paper

Reliability of multi-modal MRI-derived brain phenotypes for multi-site assessment of neuropsychiatric complications of SARS-CoV-2 infection

Eugene Duff, Fernando Zelaya, Fidel Alfaro Almagro, Karla L Miller, Naomi Martin, Thomas E. Nichols, Bernd Taschler, Ludovica Griffanti, Christoph Arthofer, Chaoyue Wang, Richard A.I. Bethlehem, Klaus Eickel, Matthias Günther, David K Menon, Guy Williams, Bethany Facer, Greta K Wood, David J Lythgoe, Flavio Dell'Acqua, Steven CR Williams, Gavin Houston, Simon Keller, Gerome Breen, Benedict D Michael, Peter Jezzard, Stephen M Smith, Edward T. Bullmore

World Encephalitis Day 22nd February

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PC-COS

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Callum Parr (Imperial)
Frances Simpson (Coventry)
Athena Akrami (UCL)
Margaret O'Hara (Birmingham)
Janet Diaz (WHO)
Nicoline Schiess (WHO)
Wouter de Groote (WHO)
Jacobus Preller (WHO)
Krutika Kuppalli (WHO)

…..& many others, including those who participated in surveys!

Neuropsych COVID

@Neuropsychcovid

Matt Butler (KCL)
Cam Watson (QMUL)
Ally Rooney (Edinburgh)
Jamie Badenoch (Birmingham)
Hamilton Morrin (KCL)
Lucy Thomas (
Jia Song (KCL)
Danish Hafeez
Tom Pollak (KCL)
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Dean Walton (Liverpool)
Isabella Conti (Belfast)
Ritika Sundaram (Glasgow)
Ella Burchill (KCL)
Dean Walton (Liverpool)
Jonathan Rogers (UCL/KCL)
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Katie Pocock (KCL)
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Ana Davi
Beth Facer
Eddie Kane
Francesca Moruzzi
Jack Fanshaw
Katrin Jenson
Komal Kapoor
Max Taquet
Sam Pandey

….& many others

…..& maybe you?!

Contact team on twitter
Or timothy.Nicholson@kcl.ac.uk

CoroNerve Studies Group

Ben Michael (Liverpool)
Ian Galea (Southampton)
Sarah Pett
Rachel Kneen
Naomi Thomas
Laura Benjamin
Amy
Rhys Thomas (Newcastle)
Mark Ellul
David Menon
Tom Solomon,
Alan Carson (Edinburgh)
Eileen Joyce (
Mike Dilley
Tony David,
Valerie Voon
Kitti Kottasz,
Peter Markham,
Paul O'Connor,
Keith Bradman
….& many others!

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