

Reward-immune Interactions Uncover Risk Factors for Long COVID

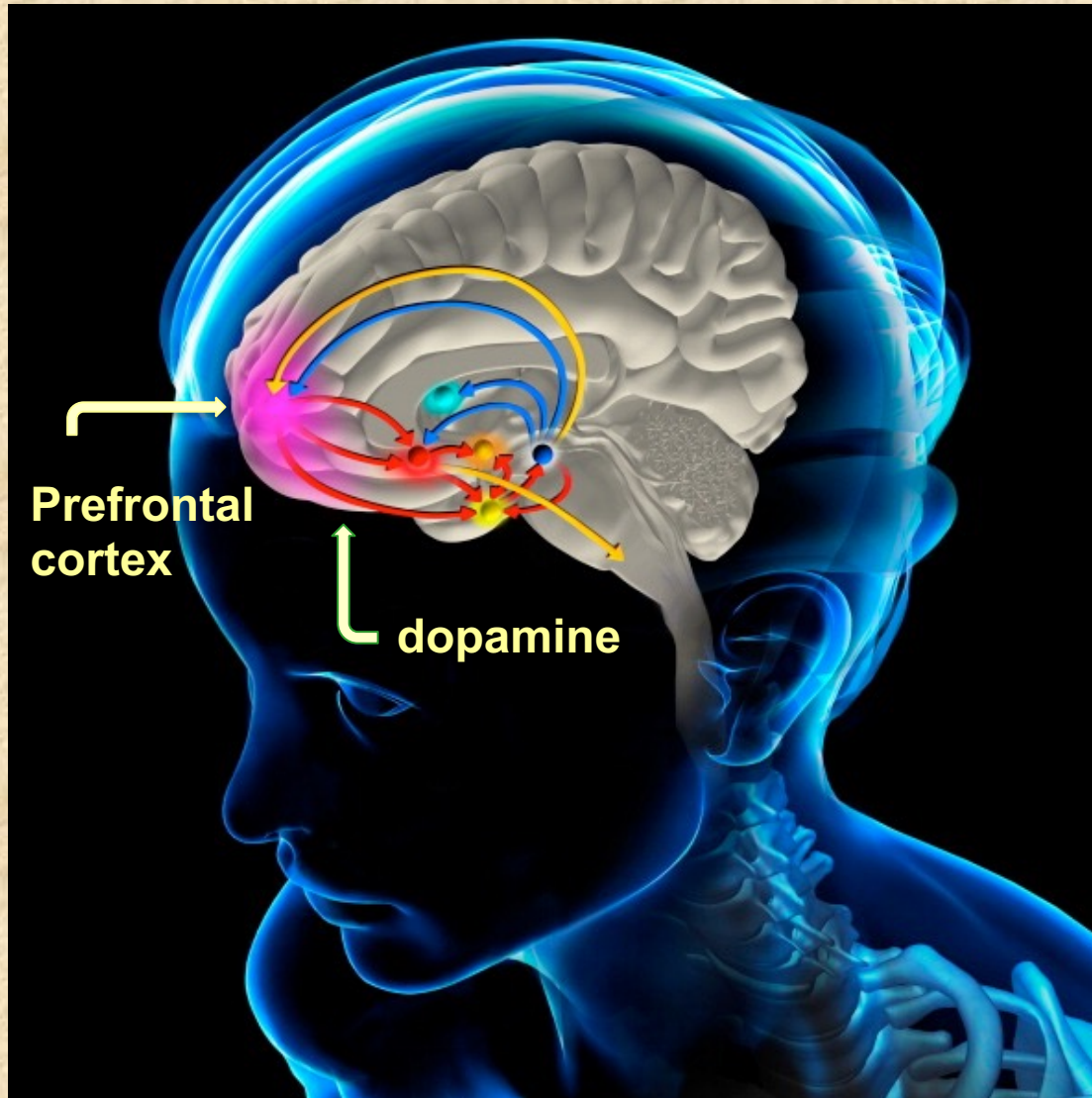
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Kingston, Canada

CAPDA

Dec. 2, 2022

Neurobiology of Reward Processing



Binge eating disorder patients:

- Low positive affect, anhedonia
- Increased striatal dopamine release in response to food cues
- Decreased prefrontal activity modulating response inhibition

Are these changes a cause of consequence of binge eating?

*Binge eating disorder is the most common of all eating disorders.
Binge eating is associated with rising rates of obesity.*

Animal model of sucrose bingeing



- yo-yo diets
- stressor



Sucrose bingeing

- reduces the rewarding effect of sucrose
- increases compulsive and disinhibited responding for sucrose
- disrupts activity of dopamine neurons



Immunocompromised State

Sucrose bingeing produces:

- brain necrosis
- elevated cytokines
- increased white blood cell counts
- neuroinflammatory markers

Excessive sucrose intake produces immunocompromised state, rendering animals susceptible to infection....



and depression

Inflammation Alters Reward Processing



Psychiatric disorders characterized by reward dysfunction are associated with alterations in neuroimmune responses.

- addiction, depression, Alzheimer's

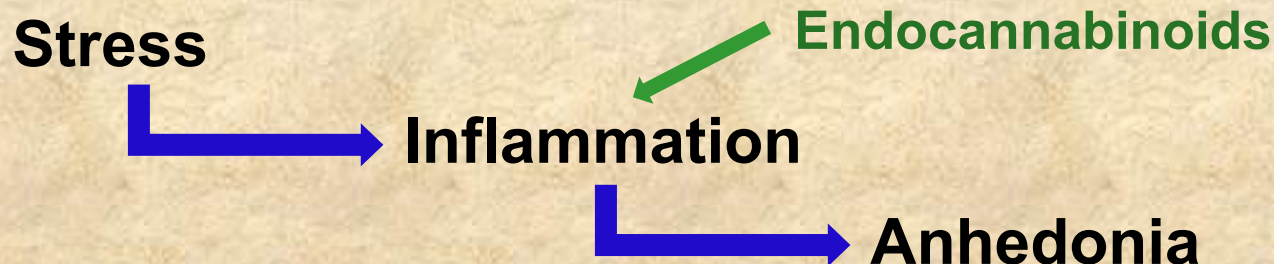
Review

Neuroscience and Biobehavioral Reviews 2016

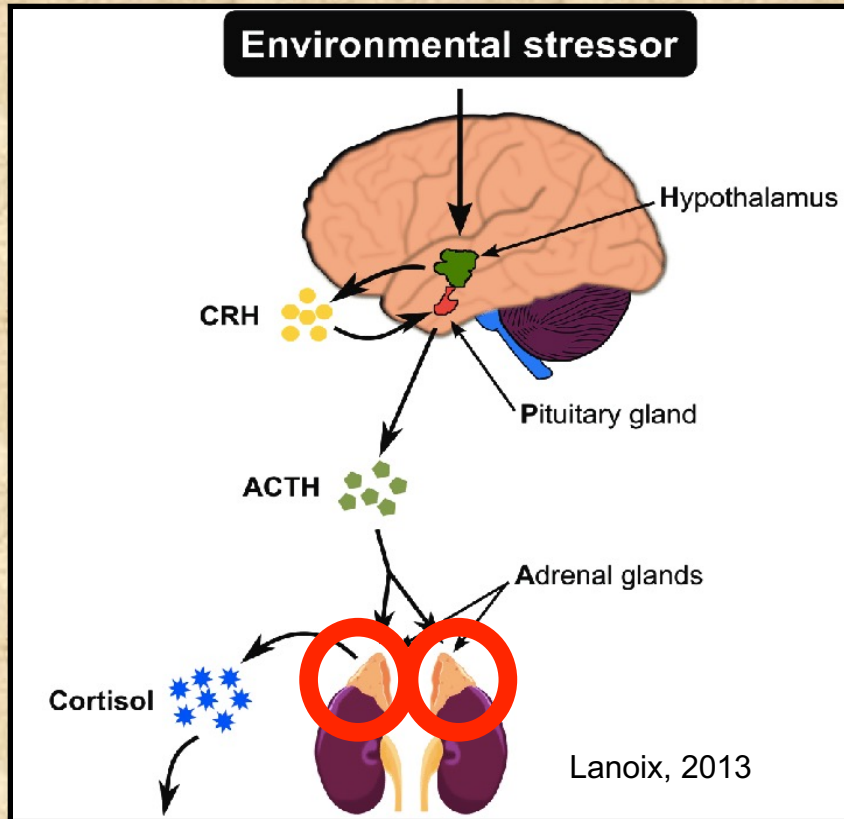
Mapping inflammation onto mood: Inflammatory mediators of anhedonia

Walter Swardfager^{a, b, c}, Joshua D. Rosenblat^{d, e}, Meriem Benlamri^f, Roger S. McIntyre^{a, d, e}

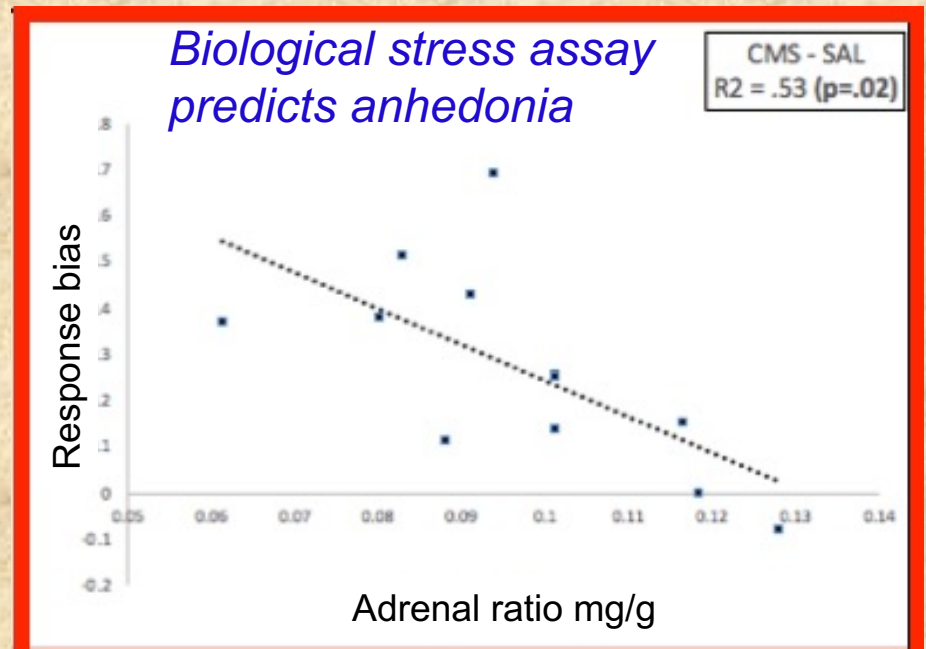
Stress Impacts Reward Processing

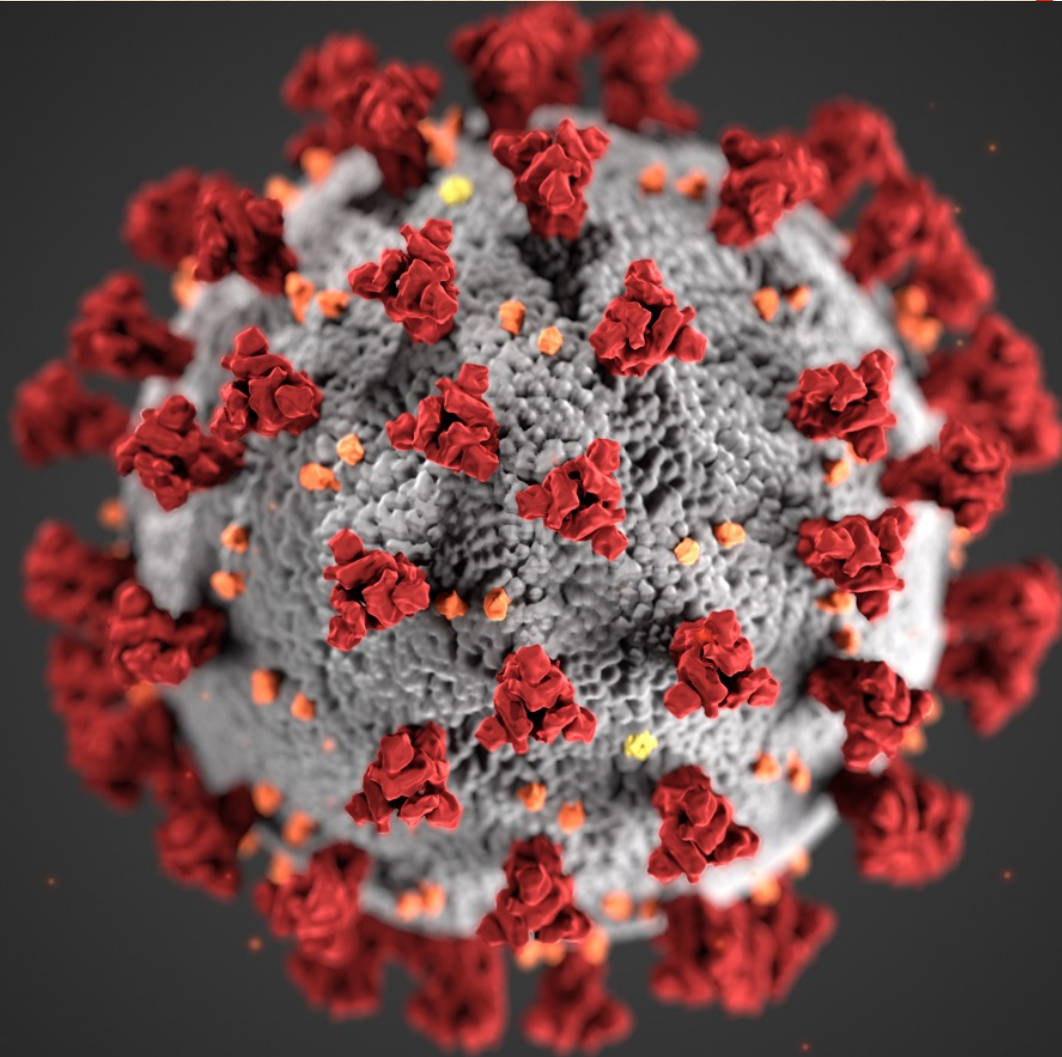


Stress, Inflammation, and Anhedonia



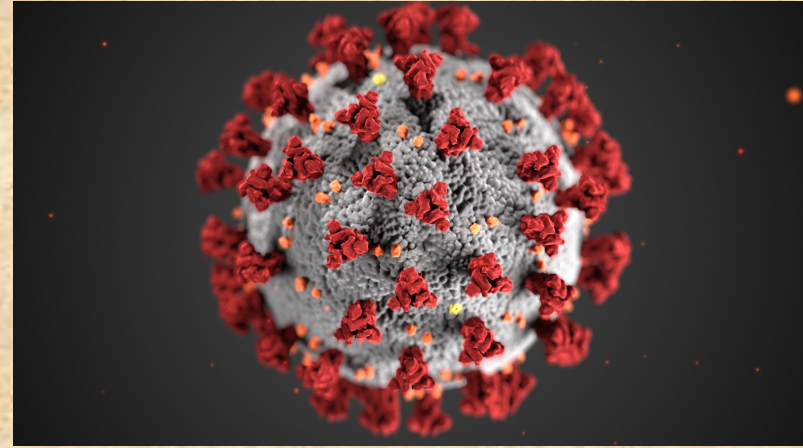
- Chronic stress elevates ACTH release, leading to adrenal gland hypertrophy
- Stress-related disorders, including major depression, are associated with increased adrenal volume





testing participants in stress paradigm 21-29 hours after flu vaccination, a period of peak inflammatory responses.”

Stress and Inflammation: A Naturalistic Experiment



COMMENTARY

Stress and Health, 2020

WILEY

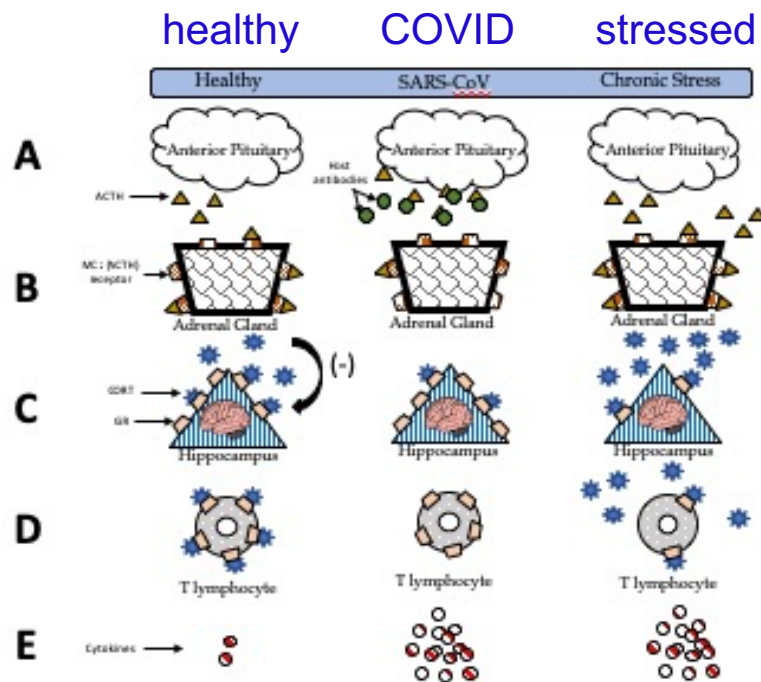
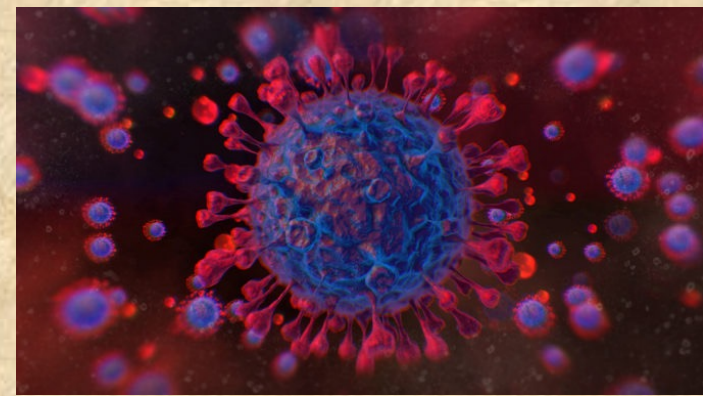
Does inflammation link stress to poor COVID-19 outcome?

Steven J. Lamontagne^{1,2}  | Diego A. Pizzagalli² | Mary C. Olmstead^{1,3}

SARS-CoV2 is primarily a respiratory virus, but...

- prognosis is worsened by pre-existing conditions characterized by inflammation
 - hypertension, obesity, diabetes
 - aging associated with increased inflammatory responses
 - males are more susceptible to poor COVID outcomes

Cytokine Storm: State of Intense Hyperinflammation



- chronic stress and SARS-CoV2 induce inflammation
- interaction amplifies inflammation producing cytokine storm
- psychiatric conditions characterized by hypercortisolism will be associated with poor prognosis following COVID infection

Prediction:

Chronic stress impacts adrenal function, rendering individuals more susceptible to negative COVID outcomes

Does COVID-19 Impact Brain Reward Function?

Post-COVID symptoms include:

- lack of interest in daily activities
- 'brain fog'

Anhedonia and cognitive control
predict poor outcome in depression

Self Report Measures

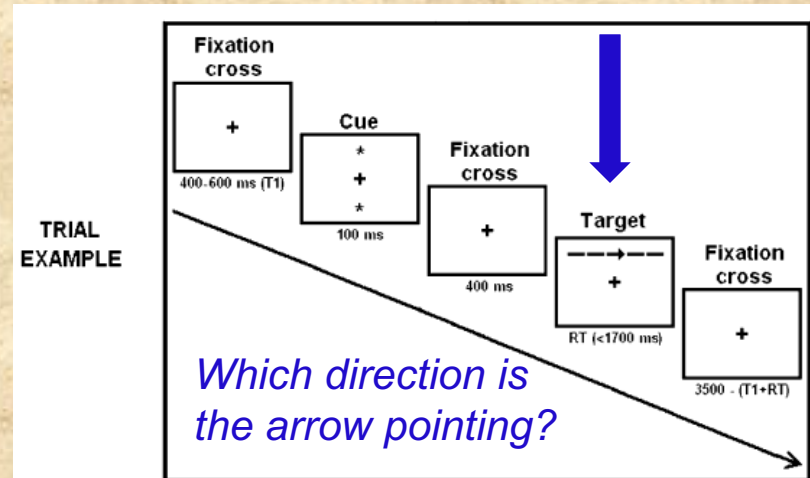
- depression
- anxiety
- anhedonia
- stress
- cognitive control

Queen's University

EMOTION AND COGNITIVE PERFORMANCE DURING COVID-19

Have you recently recovered from COVID-19?
We want to see how your emotions and
cognitive performance have been impacted!

Attentional Network Task



Post-acute sequelae of COVID-19: Evidence of mood & cognitive impairment



Steven J. Lamontagne^{a,b,*}, Makaila F. Winters^a, Diego A. Pizzagalli^{b,c}, Mary C. Olmstead^{a,d}

^aDepartment of Psychology, Queen's University, Kingston, Ontario, K7L 3N6, Canada

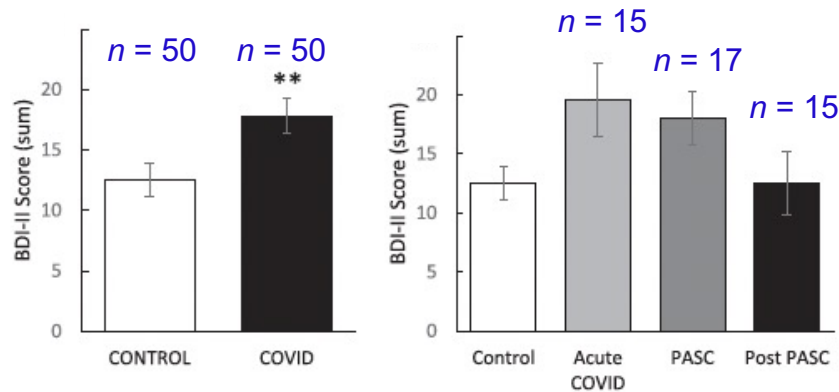
^bCenter for Depression, Anxiety and Stress Research, McLean Hospital/Harvard Medical School, Belmont, MA, USA

^cMcLean Imaging Center, McLean Hospital, Belmont, MA, USA

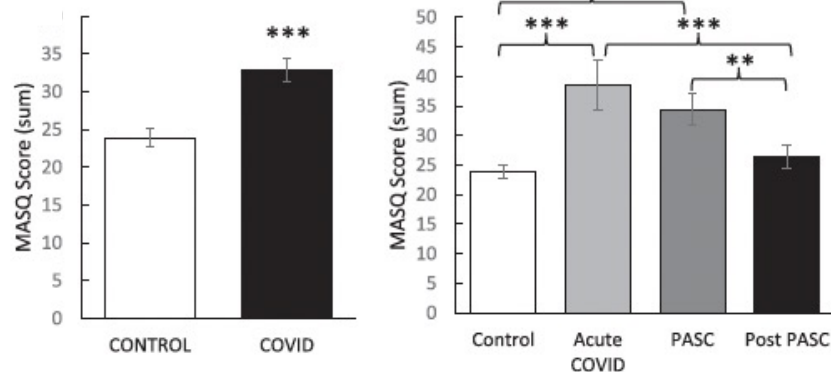
^dCentre for Neuroscience Studies, Queen's University, Kingston, Ontario, K7L 3N6, Canada

Brain, Behavior, & Immunity (2021)

Depression



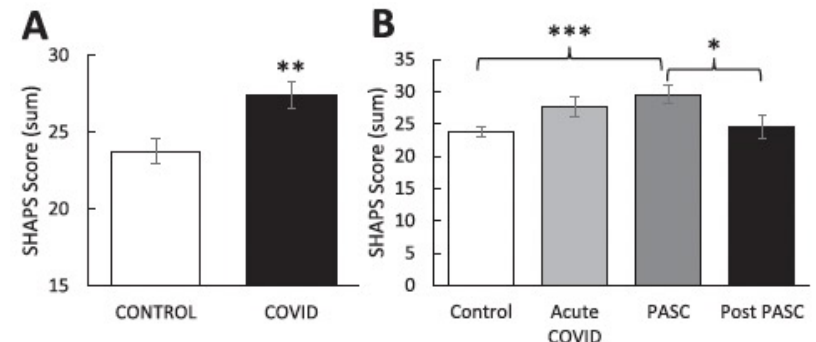
Anxiety



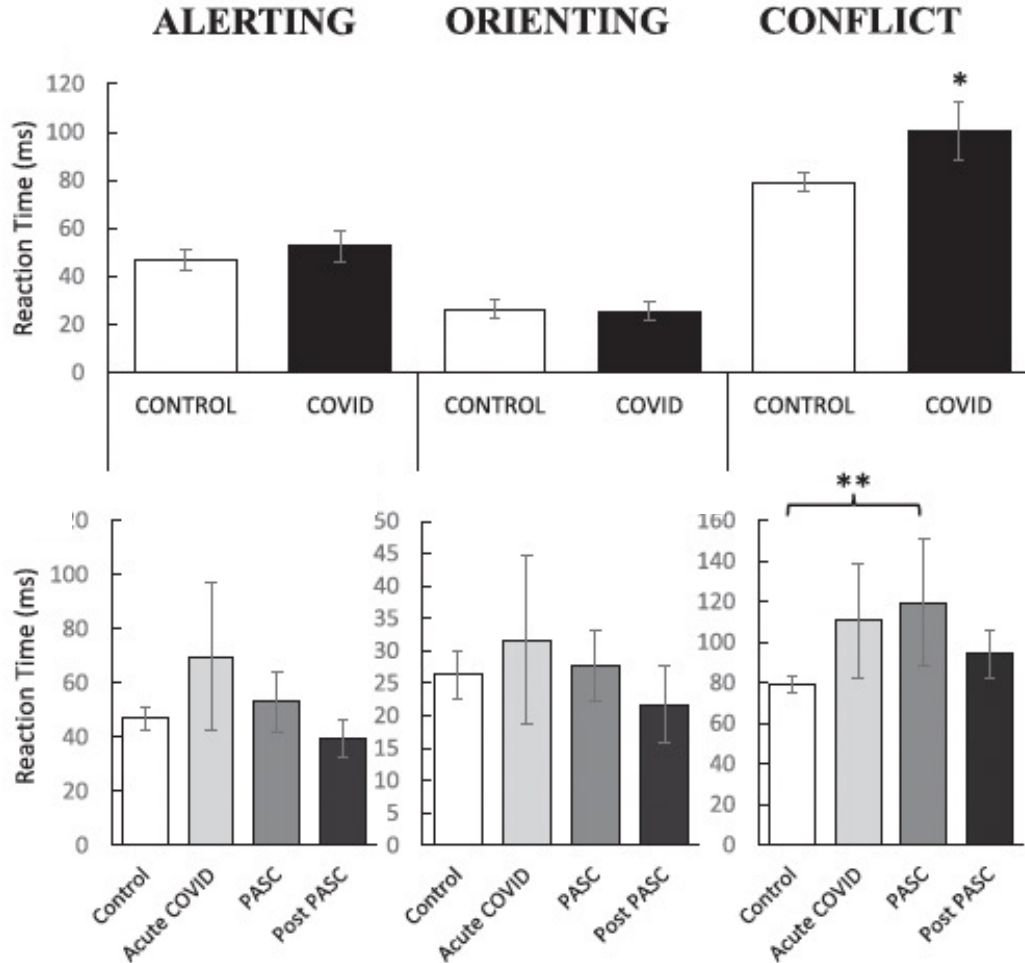
Long COVID

- 1-4 months post-infection
- increases depressive scores
- increases anxiety
- increases anhedonia
- “whopping effect”

Anhedonia



Long-COVID Selectively Impairs Cognitive Control



Increased conflict score consistent with:

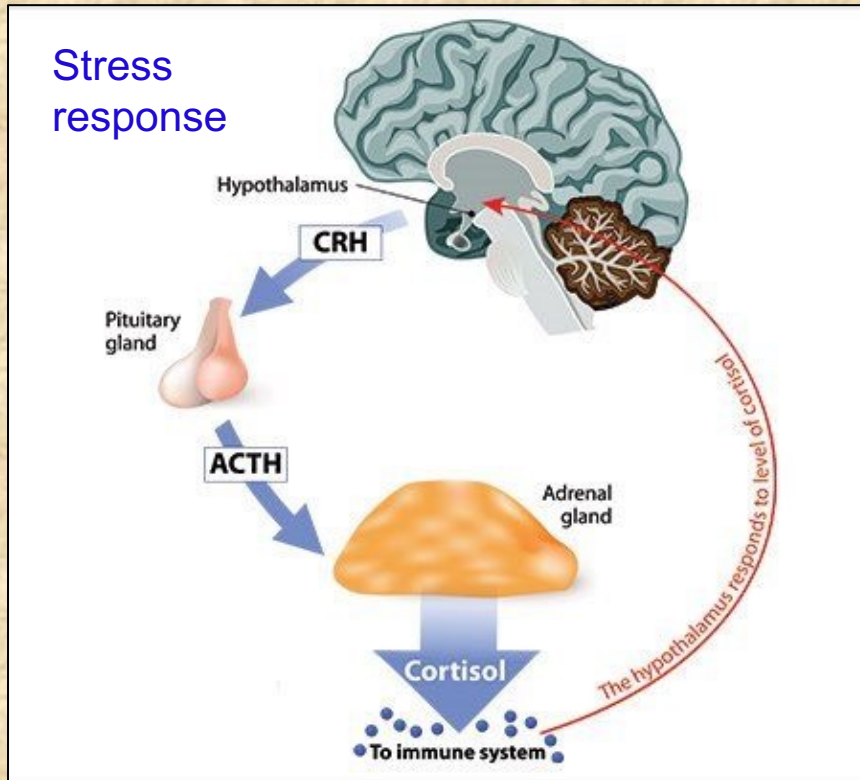
- reduced activity in dorsal anterior cingulate cortex
- health conditions with increased inflammation
- performance of depressed patients

News in focus *Nature* March 18 2021

**NIH WILL INVEST
\$1 BILLION TO
STUDY 'LONG COVID'**

US health agency will fund researchers to track people's recovery.

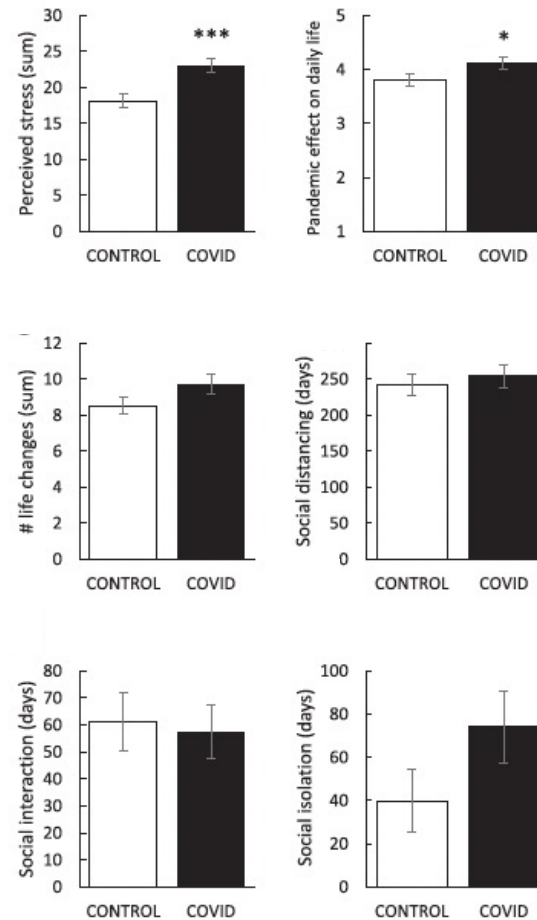
Stress-COVID Interactions



SARS-coV-2

- virus that causes COVID-19
- mimics amino acid ACTH sequence
- antibodies destroy ACTH
- decreases cortisol production

Self-reported Stress

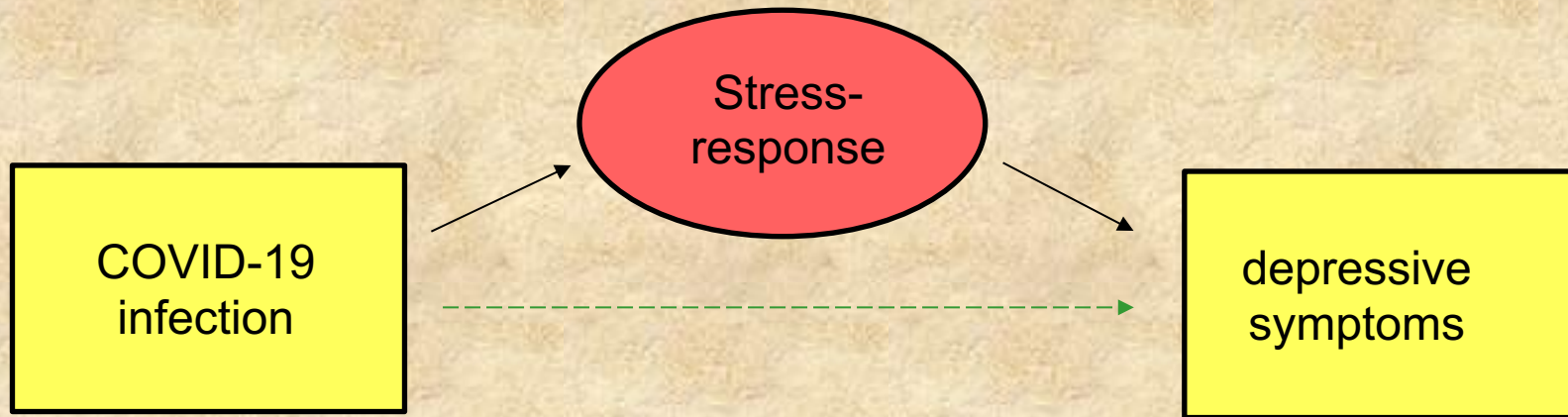


Stress Perceived stress scale (PSS)

- independent of pandemic-related stress experiences (Pandemic Stress Index)
- *perceived stress does not moderate COVID effects on depression, anhedonia, or anxiety*

Biological Basis of Stress-COVID Interactions

Assessing long-term adrenal functioning & depressive symptoms in COVID-19 survivors



- Self-report measures: *depression, anxiety, anhedonia*
- Behavioural measure: *Implicit Association Task*
- Perceived stress: *Pandemic Stress Index*
- Cortisol responses to acute stressor

Challenges:

Most participants have been vaccinated multiple times, and the majority have been infected with COVID, also multiple times!

Next Steps: Large-Scale Meta-Analyses

The Journal of Infectious Diseases

MAJOR ARTICLE



Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review

Chen Chen,^{1,a} Spencer R. Hauptert,^{1,a} Lauren Zimmermann,^{1,2,Ⓢ} Xu Shi,¹ Lars G. Fritsche,^{1,3,4} and Bhramar Mukherjee^{1,2,3,4,5,Ⓢ}

¹Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; ²Center for Precision Health Data Science, University of Michigan, Ann Arbor, Michigan, USA; ³Rogel Cancer Center, University of Michigan Medicine, Ann Arbor, Michigan, USA; ⁴Center for Statistical Genetics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; and ⁵Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

Review

Psychological Symptoms in COVID-19 Patients: Insights into Pathophysiology and Risk Factors of Long COVID-19

Angel Yun-Kuan Thye¹, Jodi Woan-Fei Law^{1,Ⓢ}, Loh Teng-Hern Tan^{1,2,Ⓢ}, Priya Pusparajah¹, Hooi-Leng Ser^{1,Ⓢ}, Sivakumar Thurairajasingam^{2,*}, Vengadesh Letchumanan^{1,*} and Learn-Han Lee^{1,*}

Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: Gender makes a difference

Valentina Bucciarelli^{a,*}, Milena Nasi^b, Francesco Bianco^a, Jelena Seferovic^c, Vladimir Ivkovic^d, Sabina Gallina^e, Anna Vittoria Mattioli^b

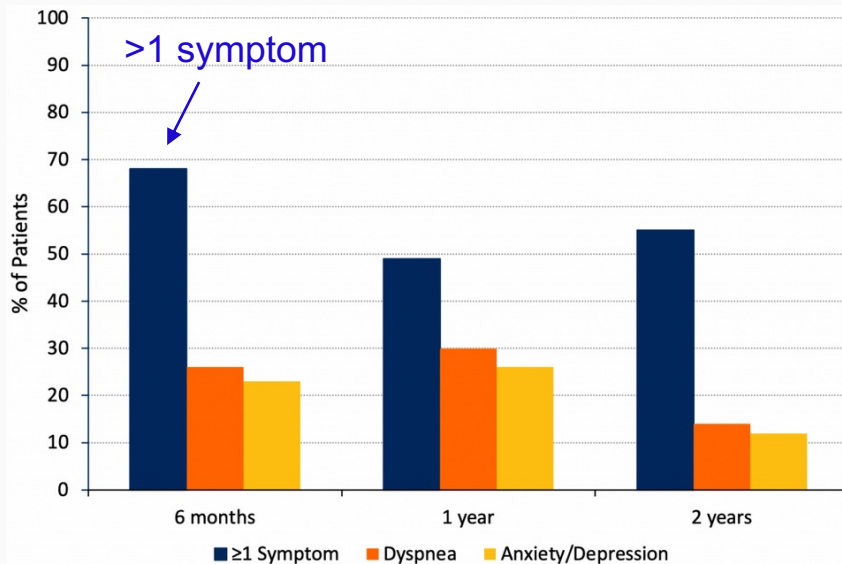
^aDepartment of Pediatrics and Congenital Cardiac Surgery and Cardiology, Ospedali Riuniti, Ancona, Italy

^bDepartment of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, Modena, Italy; National Institute for Cardiovascular Research - INRC, Bologna, Italy

^cCardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, United States



Prevalence of Long COVID in China



- Over 1,000 individual who survived hospitalization due to COVID-19
- More than half report symptoms 2 years later
- Close to 30% suffer anxiety and depression one year later



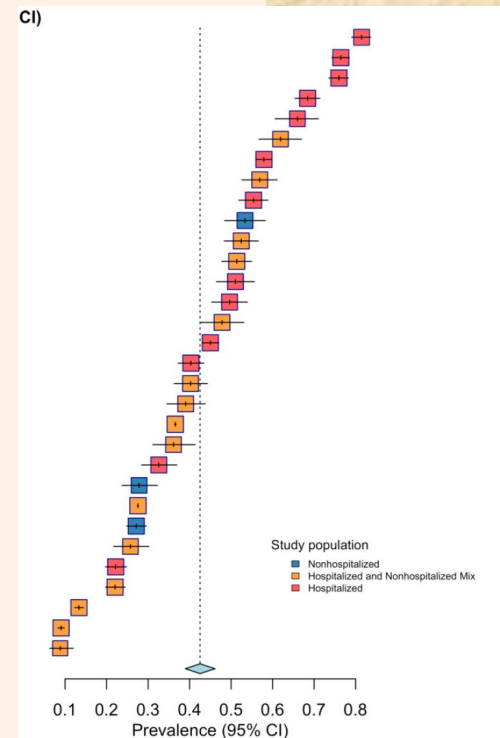
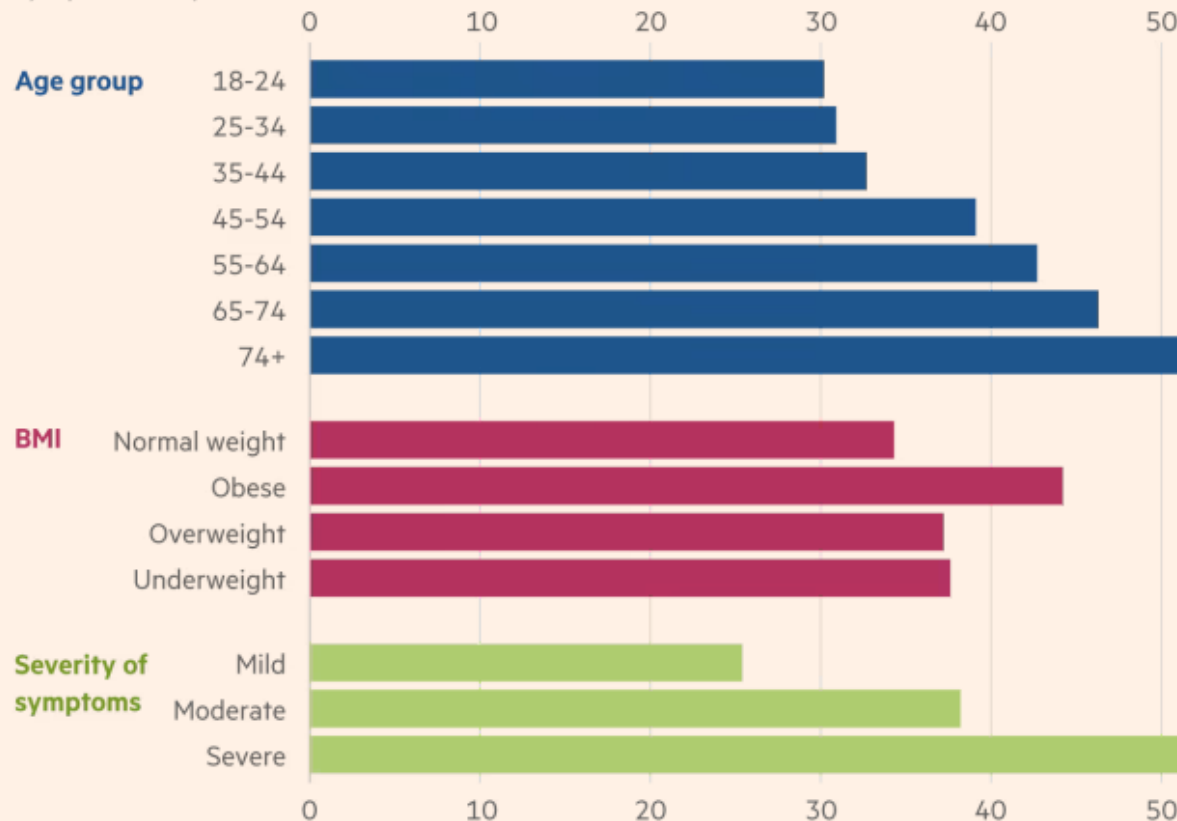
World-wide Estimates of Long COVID

Most common estimate: 25%-40% of patients show more than one symptom four months post-infection




























Long Covid also affects the young and fit

4 months post-infection

% of symptomatic patients



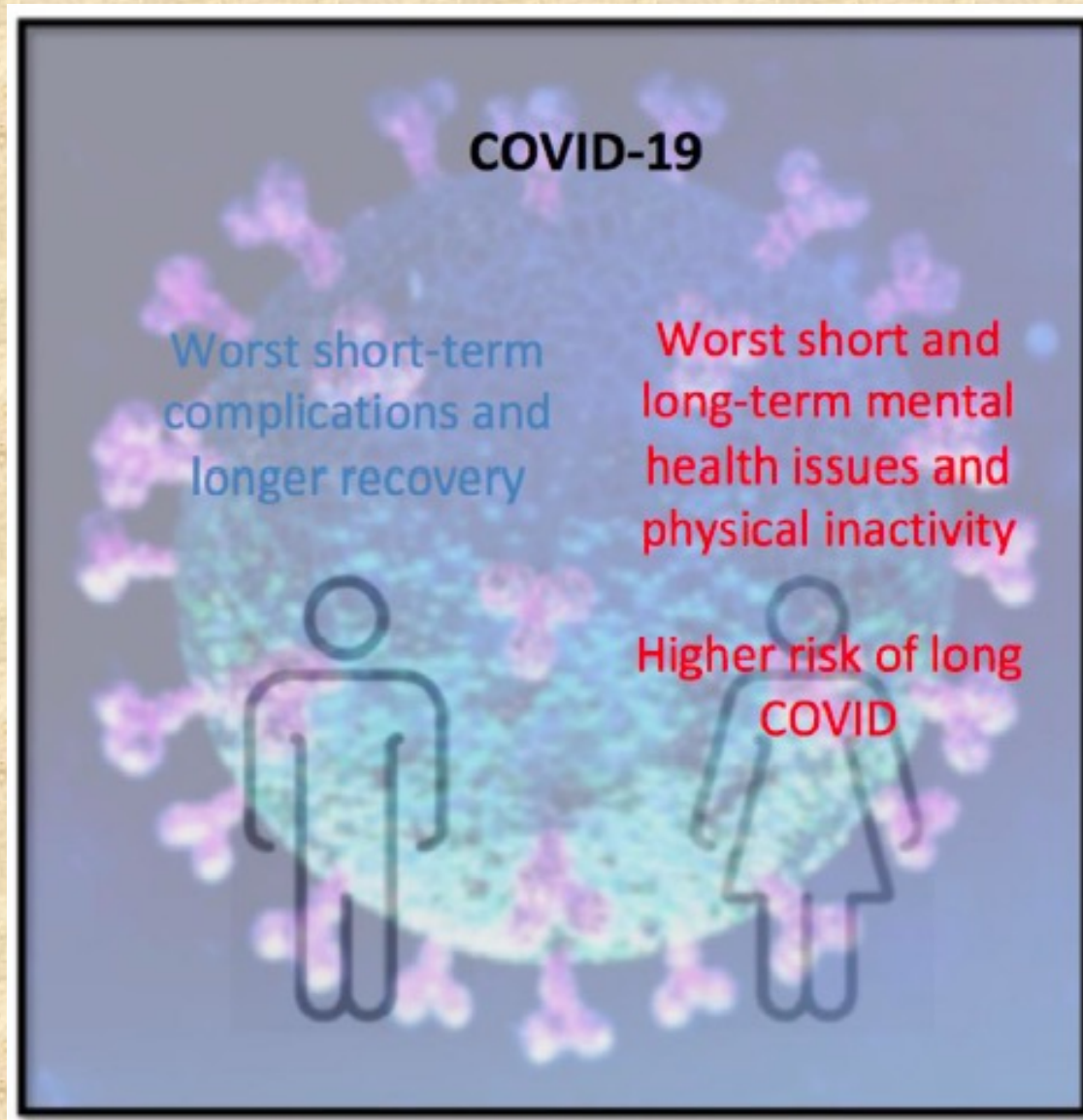
Characterizing Long COVID

	SYMPTOM FREQUENCY IN POST-			
	<5%	5-15%	15-30%	>30%
GENERAL		 New UTI  Sweating		 Fatigue
NEURO-PSYCH		 Difficulty Concentr  Memory Deficits  Dizziness	 Sleep Disorder  Anxiety  Depression	
HEAD & NECK	 Voice Change	 Headache  Visual Impairmt  Smell Disorder  Taste Disorder  Hair Loss		
RESP		 Cough  O2 Use	 Shortness of Breath	
CARDIAC		 Palpitatns  Chest Pain		
GASTRO-INTESTINAL	 Nausea / Vomiting	 Lack of Appetite  Diarrhea  Abdominal Pain		
MUSCULO-SKELETAL		 Decreased Mobility  Joint Pains  Muscle Pains		

- > 200 symptoms associated with Long COVID
- cognitive deficits are centered on frontal lobe function
- similar patterns of cognitive and affective symptoms reported with SARS and MERS infection

- Over 50 studies separating prevalence of individual symptoms

Predictors of Long COVID



- males often experience worse short-term effects and longer recovery from COVID
- females experience worse short- and long-term mental health effects of COVID and have higher risk for long COVID
- asthma is strong predictor of respiratory problems in long COVID but doesn't link to mental health symptoms
- ongoing debate whether vaccines protect against long COVID

Predicting Long COVID

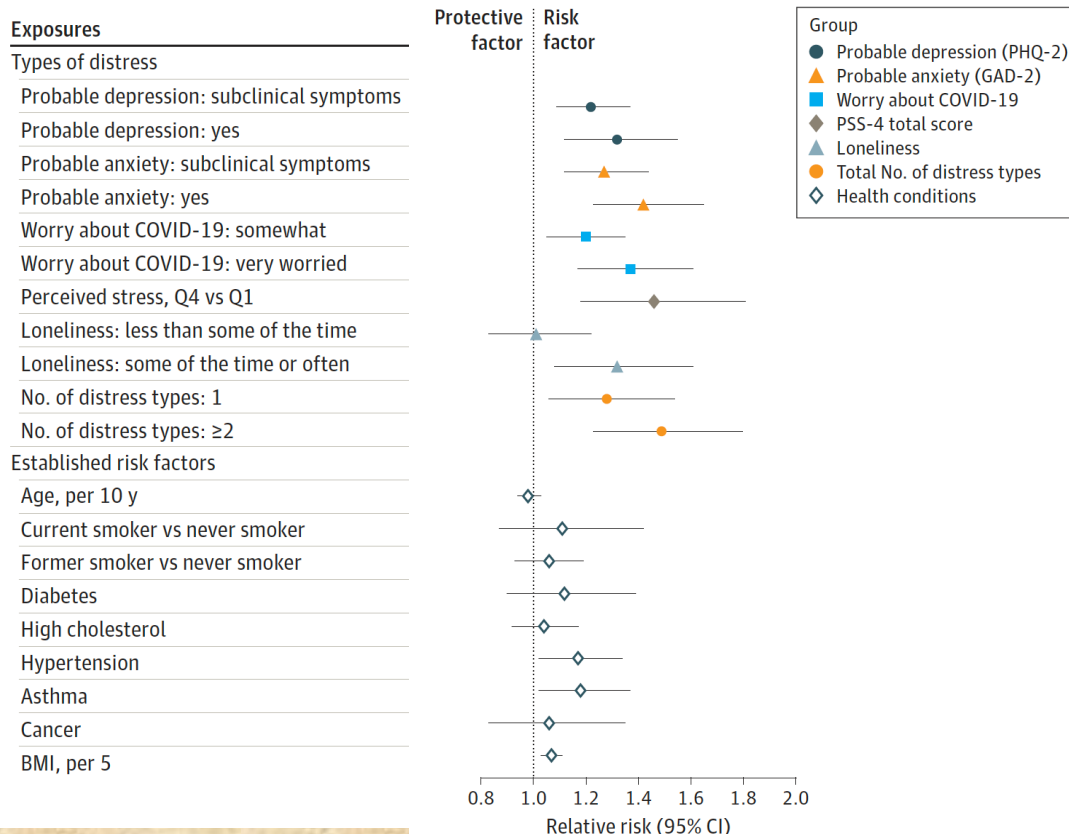
JAMA Psychiatry | Original Investigation

Associations of Depression, Anxiety, Worry, Perceived Stress, and Loneliness Prior to Infection With Risk of Post-COVID-19 Conditions

Siwen Wang, MD; Luwei Quan, BA; Jorge E. Chavarro, ScD; Natalie Slopen, ScD; Laura D. Kubzansky, PhD; Karestan C. Koenen, PhD; Jae Hee Kang, ScD; Marc G. Weisskopf, PhD; Westyn Branch-Elliman, MD; Andrea L. Roberts, PhD



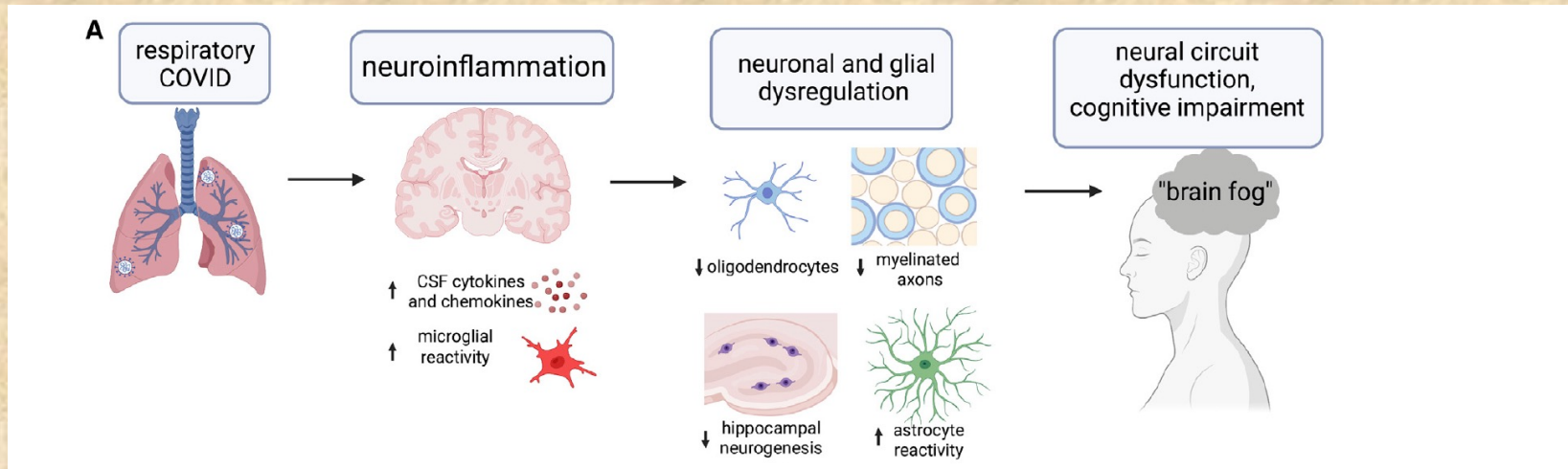
Over 60 000 individuals surveyed from April 2020 to Sept. 2021



- Pre-infection psychological distress associated with increased risk of long COVID
- significantly impact on daily activities
- Increased stress may explain the higher proportion of women that develop long COVID

Stress-induced Susceptibility to Long COVID

“Inflammation and immune dysregulation may link psychological distress with long-term COVID.”



- Chemo-fog is produced by immune system dysregulation
- Gender differences in long COVID presentation disappear with age



Social isolation

- alters immune function
- reduces function of reward system





Steve Lamontagne

Michael Smith Foreign
Study Supplement

Diego Pizzagalli
McLean Hospital
Harvard Medical School



Queen's University

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Catherine Normandeau
Arianna Norwickyi
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David De Sa Nogueira
Pascal Romieu

Adam Sunavsky
Daryl Wilson
Makaila Winters
Lihua Xue