



# Neuropsychiatric Consequences of Viral Infections-Focus on SARS2 and other Coronaviruses



Robert Yolken

E Fuller Torrey

Faith Dickerson

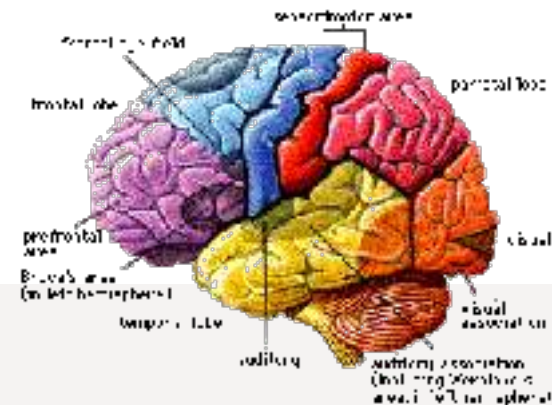
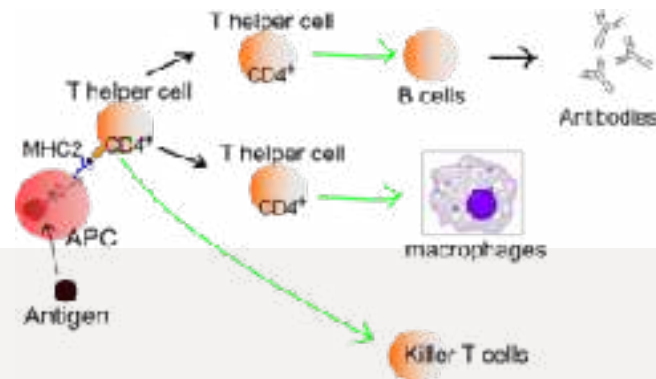
Johns Hopkins School of Medicine

Stanley Medical Research Institute

No Conflicts to Declare  
No Unapproved Medications

# The Origin of Immune Activation in Psychiatric Disorders

- Inflammation is a major component of schizophrenia and other serious psychiatric disorders
- The immune response of the periphery and central nervous system are somewhat interrelated
- Crucial Questions:
  - What is the source of the inflammatory process?
  - How can the inflammatory response be modulated to benefit patients?



# Schizophrenia and Bipolar Disorder

## Clinical Features

- Positive and Negative Symptoms
- Altered Mood
- Cognitive Impairment

## Brain Abnormalities

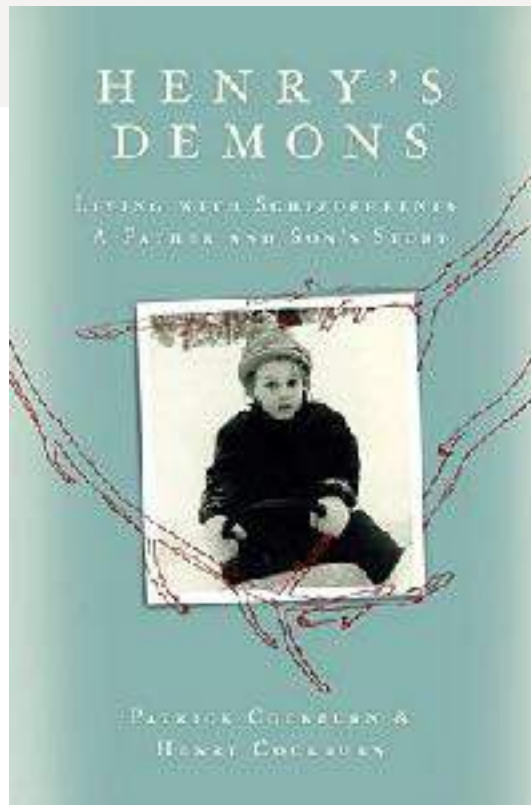
- Dopamine and other neurotransmitters
- Ion Channels
- Inflammatory Pathways

## Massive social and economic consequences

- Individual
- Family
- Society

## Risk factors

- Genetic
- Infectious Exposures
- Gene-Environmental Interactions



Henry Cockburn was born in London and raised in Canterbury, where he attended King's School and won several awards for his artwork. In 2002, during his first year of studying art at Brighton University, he was diagnosed with schizophrenia.

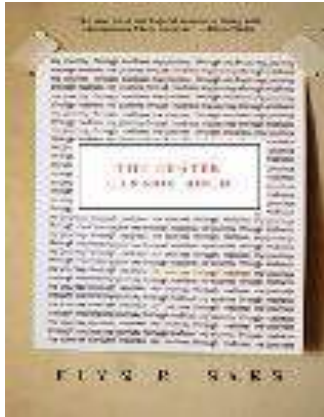




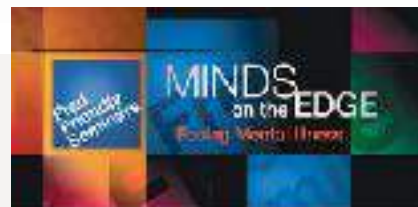
LIVES RESTORED

## Expert on Mental Illness Reveals Her Own Fight

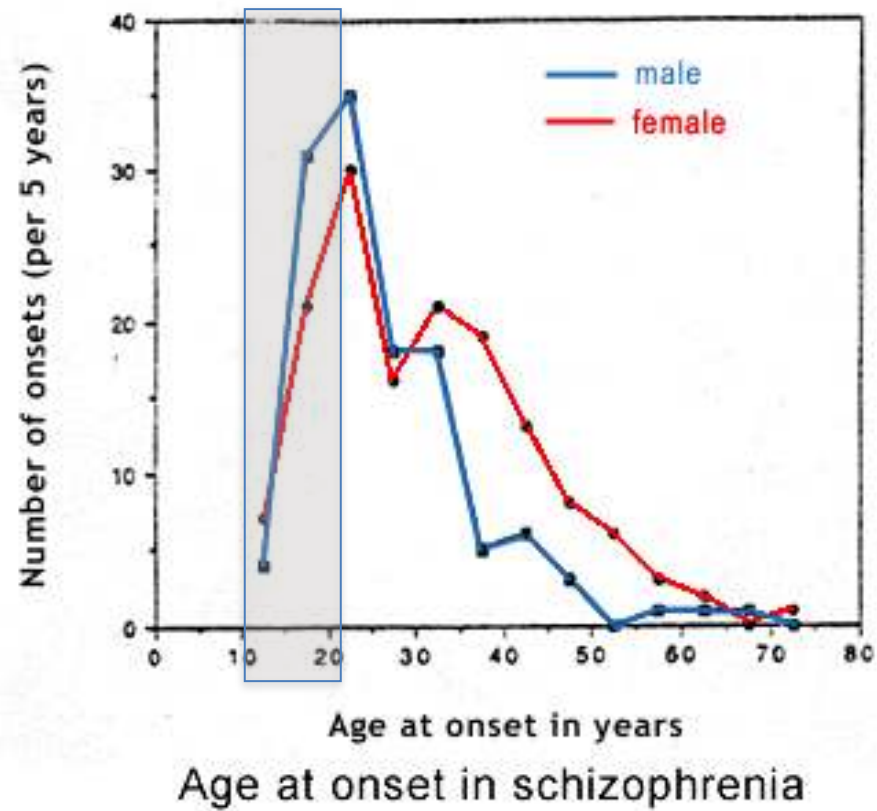
The Power of Rescuing Others: Marsha Linehan, a therapist and researcher at the University of Washington who suffered from borderline personality disorder, recalls the religious experience that transformed her as a young woman.



Psychologist Frederick Fiese accepted that he was schizophrenic and learned to control the disease with medication after he'd already experienced several psychotic breaks. One-third of the nation's estimated 400,000 homeless people suffer from schizophrenia, but refuse to take medication because they don't think they're ill, Fiese said.

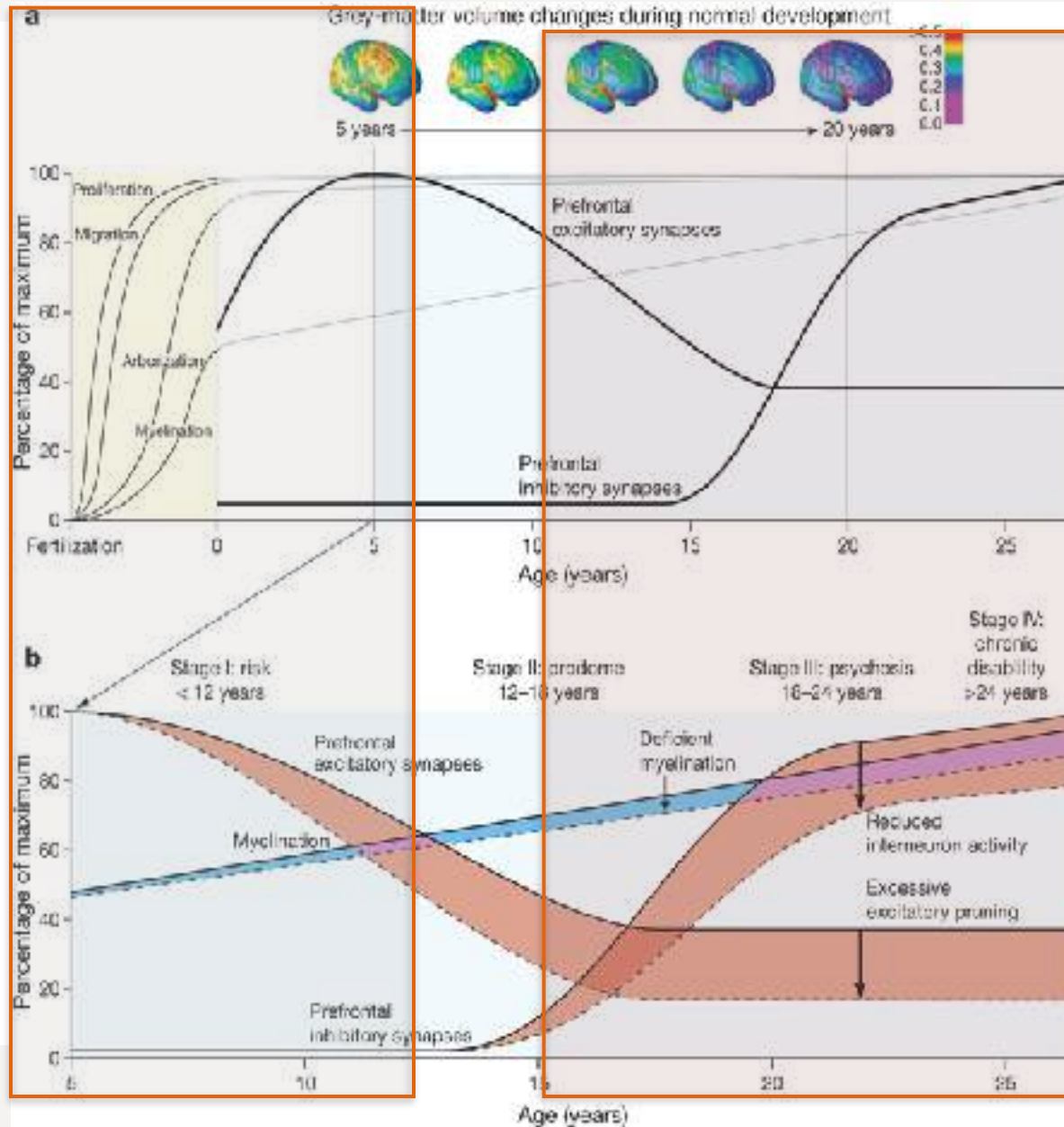


# Schizophrenia-An adult disease?

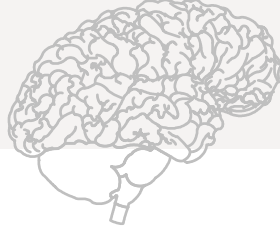


# Neurodevelopmental Concept of Disease

Exposures



Symptoms



# Schizophrenia in the Human Population

## *Aspects Not Consistent with Simple Genetics*

- **Environmental events during pregnancy and birth**
  - Seasonality (Increased rates during winter)
  - Urban birth
  - Maternal Fever/Infection
  - Famine
- **Discordance among monozygotic twins**
- **Common occurrence of disorders in individuals without an affected first degree relative**
- **Evolutionary persistence of a trait associated with low rates of reproduction**
- **Extensive genetic studies have found many genomic regions of small effect but few genes of large effect**



# Complex Human Diseases

## Beyond Koch and Mendel



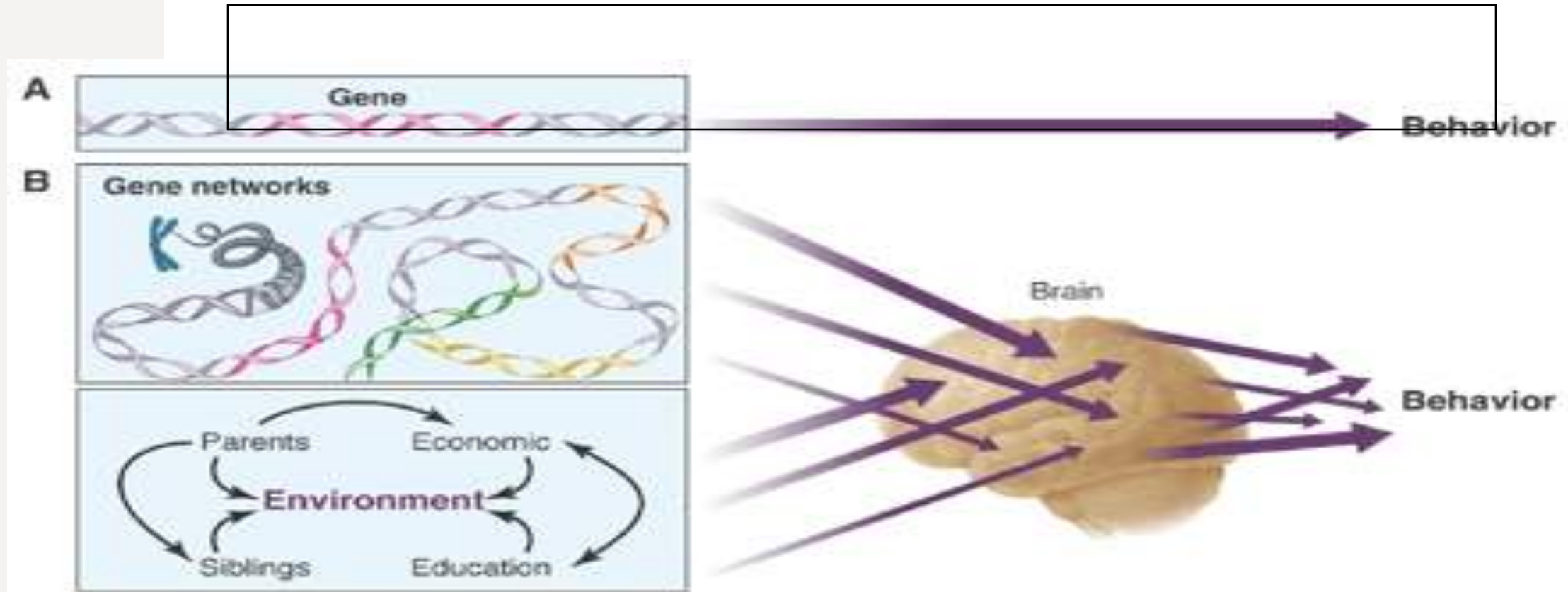
Mendel-Human traits are determined by **individual** genes which function independently of other genes and of environmental influences

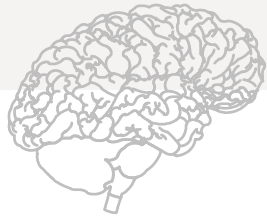


Koch-Many human diseases are caused by **specific** microbes which exert their effect **independently** of other microbes, environmental factors and genes

# Human Brain Diseases

## *Gene-Environmental Interactions*





# Infectious Agents and Animal Behavior

## Mechanisms that increase transmission

- Toxoplasma gondii*
  - Altered fear response
- Malaria/Leishmania
  - Listlessness
- Rabies Virus
  - Increased aggression
- Herpesviruses/Retroviruses
  - Sexual transmission
- Respiratory viruses
  - Coughing
  - Droplet transmission
  - ? Altered cognition and behavior



Influenza  
RSV  
Coronaviruses



> *Schizophr Bull.* 2011 Jan;37(1):101-7. doi: 10.1093/schbul/sbp052. Epub 2009 Jun 2.

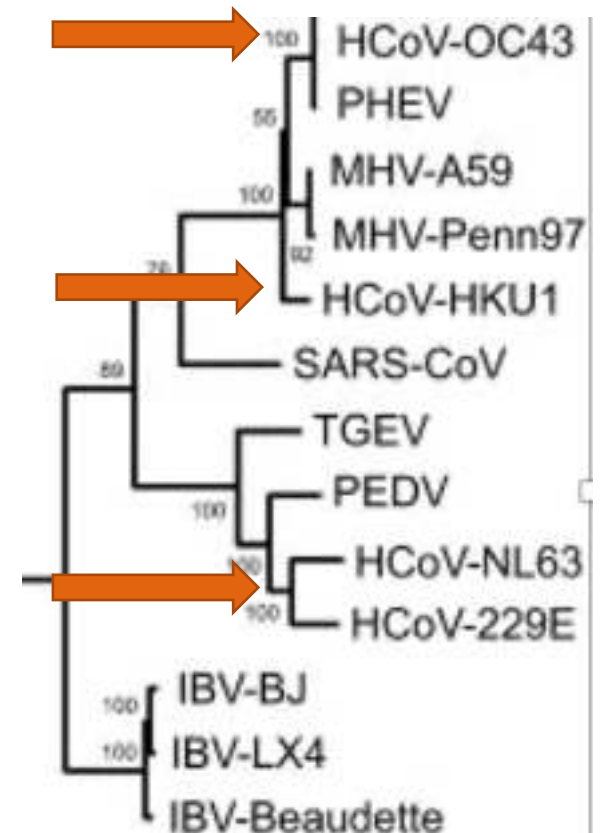
## Coronavirus immunoreactivity in individuals w recent onset of psychotic symptoms

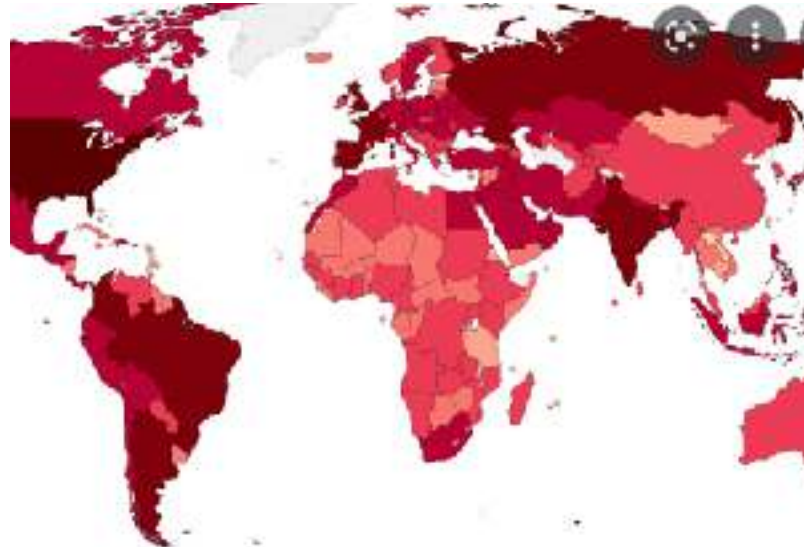
Emily G Severance<sup>1</sup>, Faith B Dickerson, Raphael P Viscidi, Ioannis Bossis, Cassie R Stallings,  
Andrea E Origoni, Anne Sullens, Robert H Yolken

> *J Affect Disord.* 2011 Apr;130(1-2):220-5. doi: 10.1016/j.jad.2010.09.029. Epub 2010 Oct 27.

## Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts

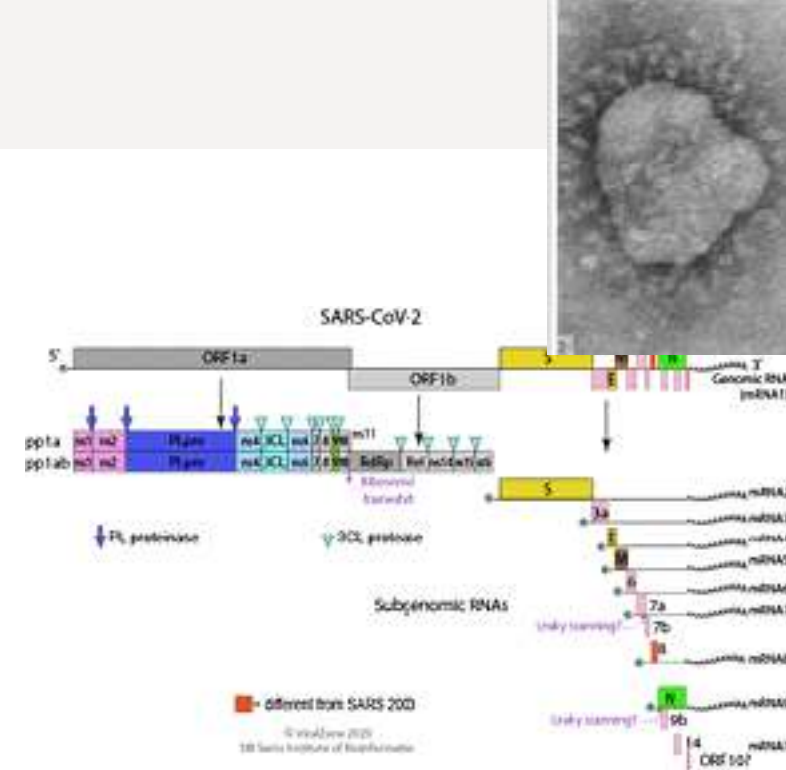
Olaoluwa Okusaga<sup>1</sup>, Robert H Yolken, Patricia Langenberg, Manana Lapidus, Timothy A Arling,  
Faith B Dickerson, Debra A Scrandis, Emily Severance, Johanna A Cabassa, Theodora Balis,  
Teodor T Postolache





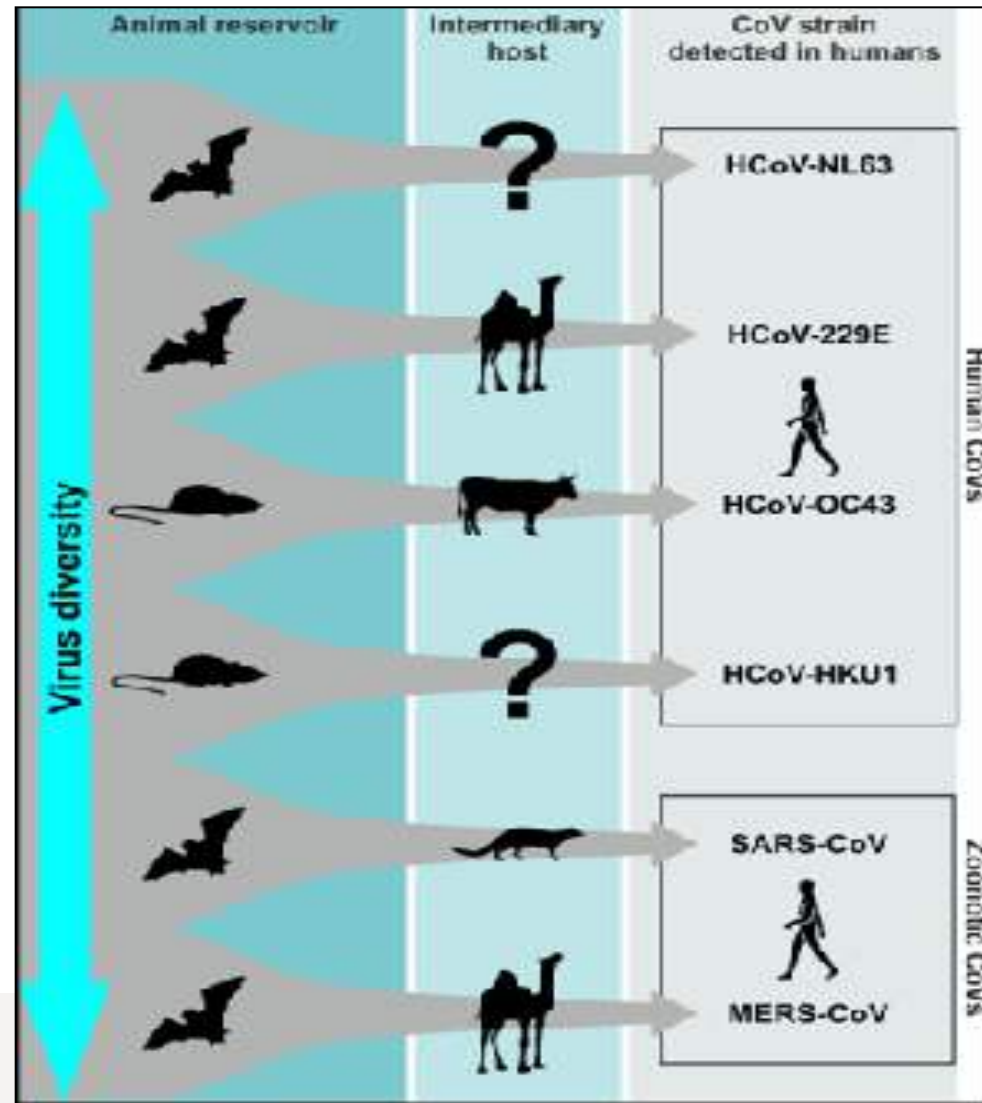
# Coronaviruses

- ◆ Widespread in the animal kingdom
- ◆ Single-stranded RNA genome (positive sense)
- ◆ Large genome size allows for accessory proteins
  - ◆ Modulate host immune response
  - ◆ Adapt to different hosts and environmental conditions
- ◆ Varying degrees of infectivity and pathogenicity
- ◆ Capable of cross-species transmission and adaptation
- ◆ Many non-SARS strains cause common cold symptoms
- ◆ Capable of replicating in different tissues, including CNS



# Animal Groups and Intermediate Hosts for Coronaviruses which Infect Humans

From: Corman et al, *Advances in Virus Research*, 2018



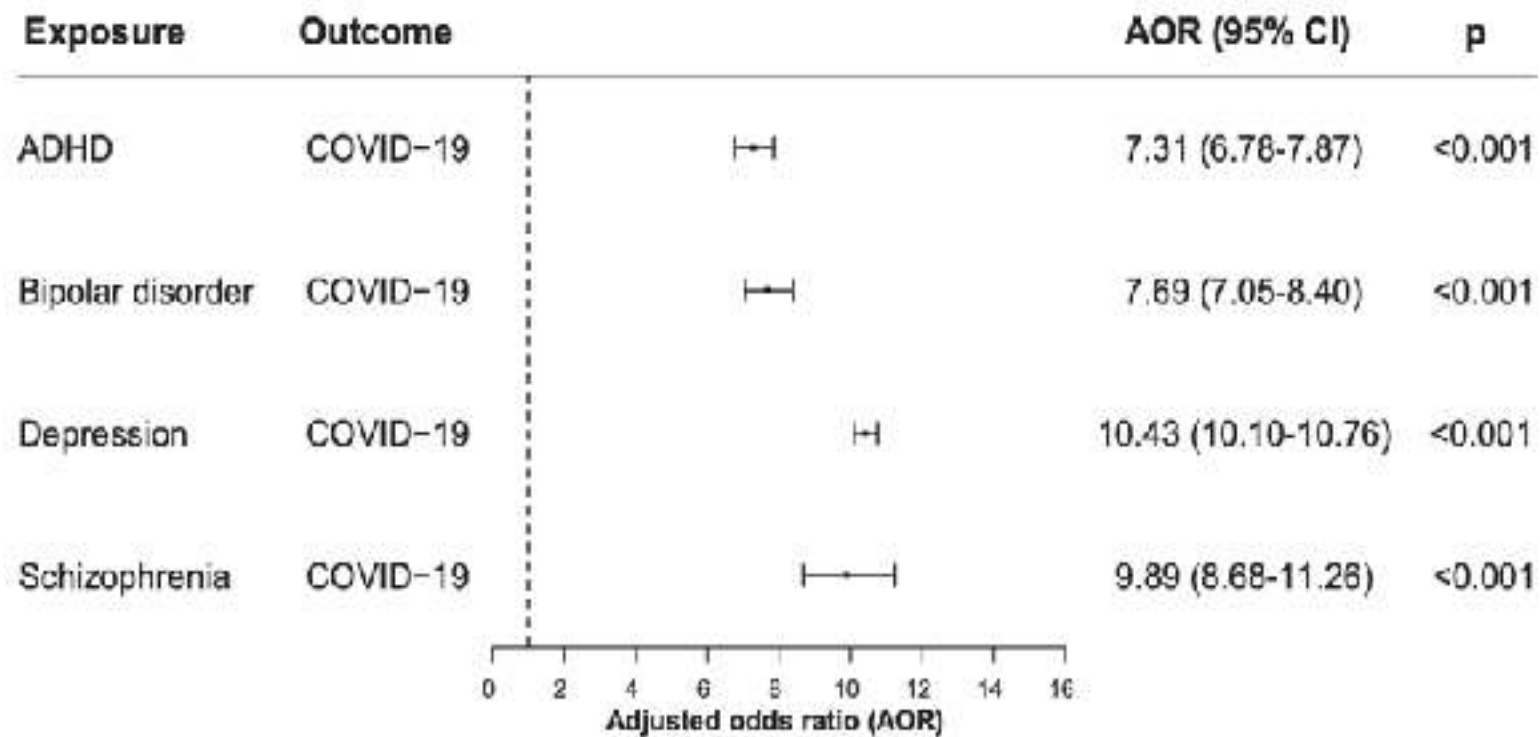
**SARS-CoV-2?**

Exotic food animals  
Bats  
Rodents  
Cats  
Dogs  
Isolated Humans

World Psychiatry Posted Oct 6,  
2020

## Increased risk of COVID-19 infection and mortality in people with mental disorders: analysis from electronic health records in the United States

QuanQiu Wang<sup>1</sup>, Rong Xu<sup>1</sup>, Nora D. Volkow<sup>2</sup>

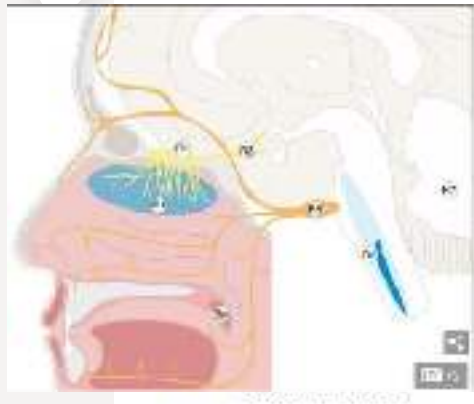


1.5-2 fold increase of **death** from Covid-19 infection as compared to age-matched populations. Increased mortality rates in women and African Americans



# Covid-19 and Brain Disorders-Potential Mechanisms

Lancet Neurology Oct 2020 53%



ROUTE OF ENTRY

olfactory nerve → piriform cortex



EARLY SYMPTOM

anosmia

SPREAD

CNS

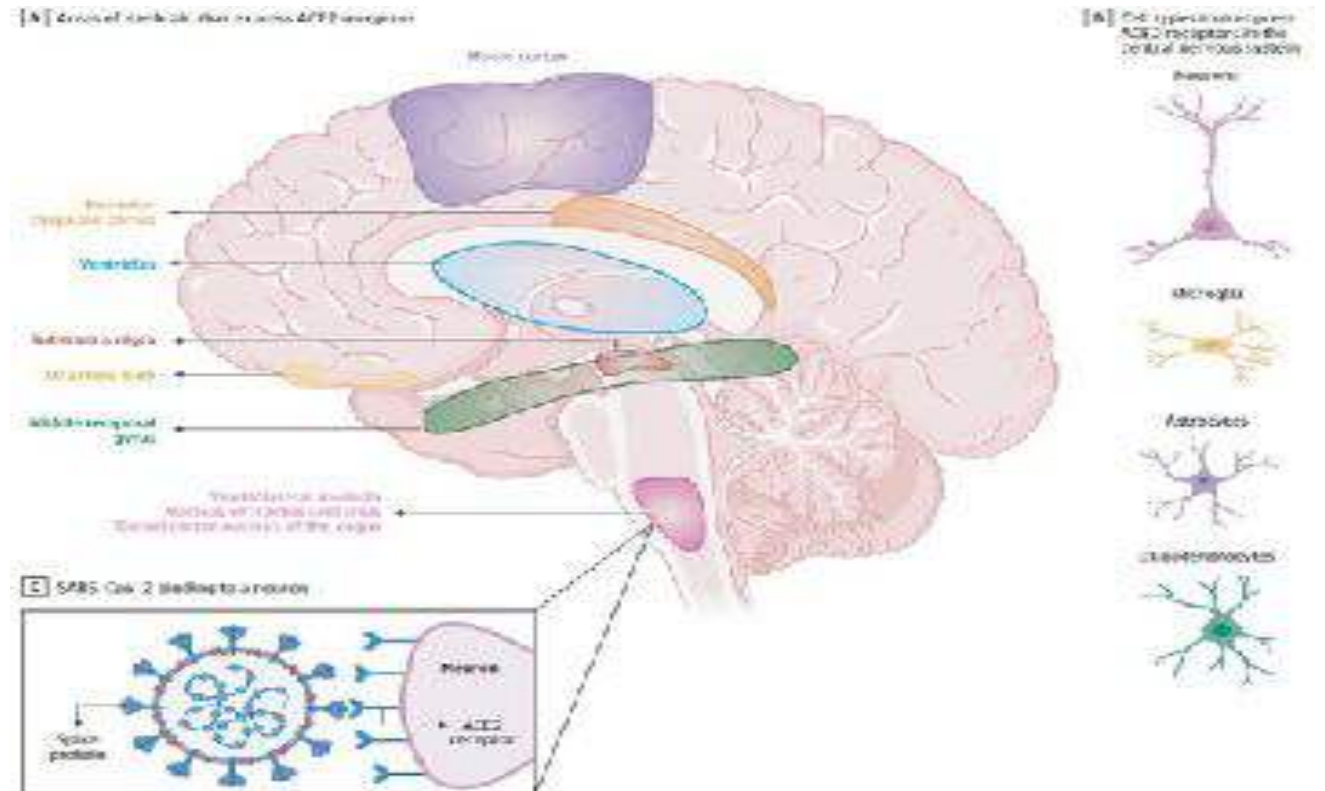
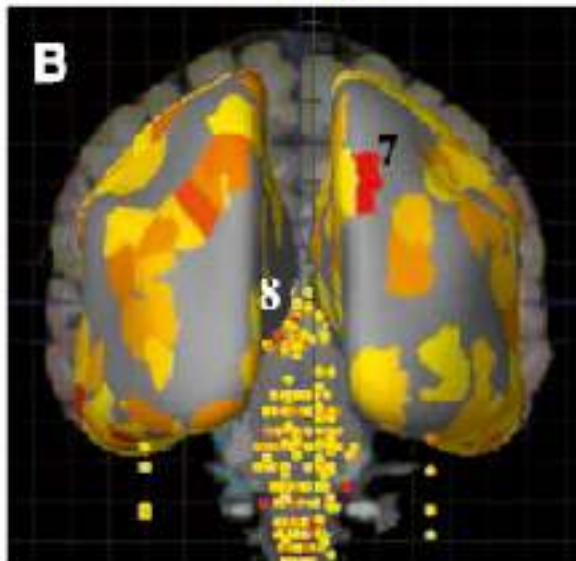
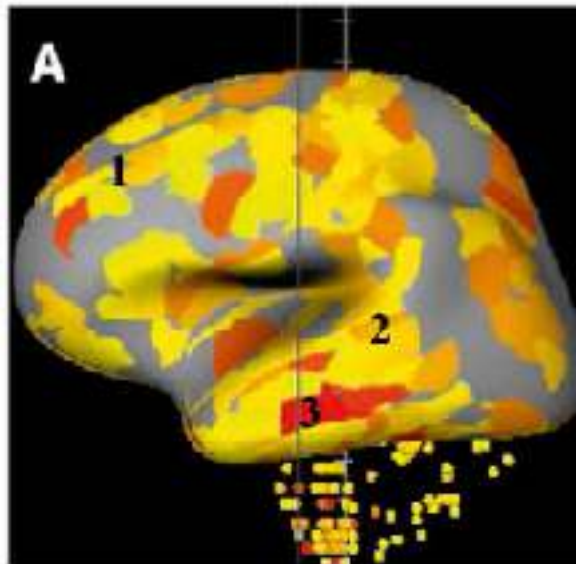


SYMPTOMS of CNS DIRECT INVASION



# ACE2 Receptor Distribution in The Brain

1. Motor Cortex
2. Auditory Cortex
3. Temporal Gyrus
4. Hippocampus
5. Caudate Nucleus
6. Hypothalamus
7. Somatosensory Cortex
8. Lateral Ventricle
9. Medula
10. Brainstem



[Genes \(Basel\)](#), 2020 Jul; 11(7): 741.

Published online 2020 Jul 3. doi: [10.3399/genes11070741](https://doi.org/10.3399/genes11070741)

PMCID: PMC7397

PMID: 32635

## Analysis of ACE2 Genetic Variability among Populations Highlights Possible Link with COVID-19-Related Neurological Complications

[Claudia Strafala](#)<sup>1,2,\*</sup>, [Valerio Caputo](#)<sup>1,2</sup>, [Andrea Termine](#)<sup>2</sup>, [Shila Parati](#)<sup>2</sup>, [Stefano Gambardella](#)<sup>3,4</sup>, [Paola Ronjani](#)<sup>3</sup>, [Caro Callagirone](#)<sup>5</sup>, [Giuseppe Novelli](#)<sup>1,3</sup>, [Emiliano Giardina](#)<sup>1,2,†</sup> and [Raffaella Cascola](#)<sup>1,6,†</sup>

Zubair et al, JAMA Neurol. doi:

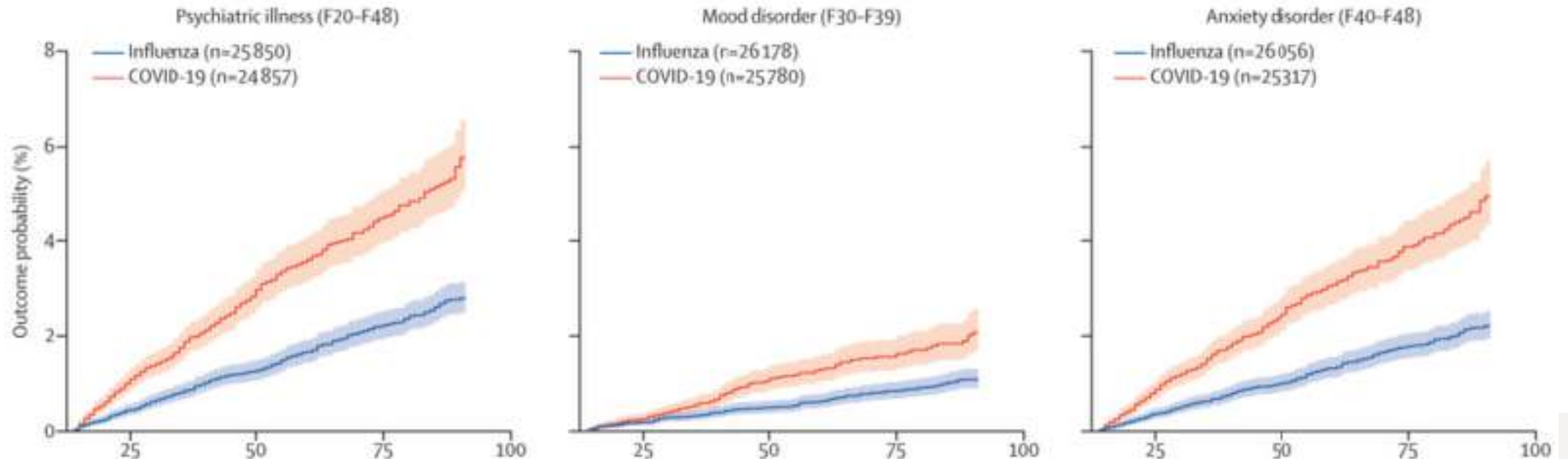
10.1001/jamaneurol.2020.2065

Slide courtesy of Scott Letendere UCSD

# Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA

Individuals with psychiatric disorders had increased rates of serious Covid-19 infections (and increased psychiatric symptoms.)

Individuals with Covid-19 infections had increased rates of **newly recognized** psychiatric disorders



# Covid-19 and Psychiatric Disorders

- ◆ Increased rates of infection and death in some individuals with established disorders
- ◆ Increased rate of newly recognized symptoms following infection
  - ◆ Psychosis
  - ◆ Mania
  - ◆ Depression/Anxiety
  - ◆ Cognitive Decline
  - ◆ Suicide Behaviors
- ◆ Possible mechanisms
  - ◆ Viral infection of the brain
  - ◆ CNS immune activation
  - ◆ Stress
  - ◆ Social isolation



12002 publications as  
of May 13 ,2022

# The Experiences of Persons with Serious Mental Illness during the COVID Pandemic: **Background**

- Presents an unprecedented source of stress
- Might be particularly problematic in individuals with serious mental illness
  - Limited resources
  - Small social networks
  - Reliance on health care agencies whose services may be disrupted
  - Pre-existing anxiety may be exacerbated
  - Loneliness and depression may be increased by social isolation
  - Increased prevalence of risk factors such as smoking, obesity
- Effects on outpatients with serious mental illness not well characterized

# Experiences during the COVID Pandemic: **Methods**

- Previous research participants in cohort studies
- Adults with Schizophrenia, Bipolar Disorder, Major Depressive Disorder, Non-psychiatric comparison group
- Contacted by phone, email, US mail
- Individual interview (in period July 2020 – Jan 2021) by video or telephone focused on
  1. Infection with COVID-19
  2. Mental distress and suicidal thoughts
  3. The impact of the pandemic on day-to-day life and the degree of worry
  4. Current use of tobacco and alcohol and changes in their use
  5. Changes in access to medical care and recent missed medical visits and medications

Dickerson et al., Psychiatr Serv.  
2022 Feb 1;73(2):133-140.

# COVID Survey Sample (N=195)

## Diagnostic groups

- Schizophrenia: n=50
- Bipolar Disorder: n=51
- Major Depressive Disorder: n=29
- Non-psychiatric comparison group: n=65

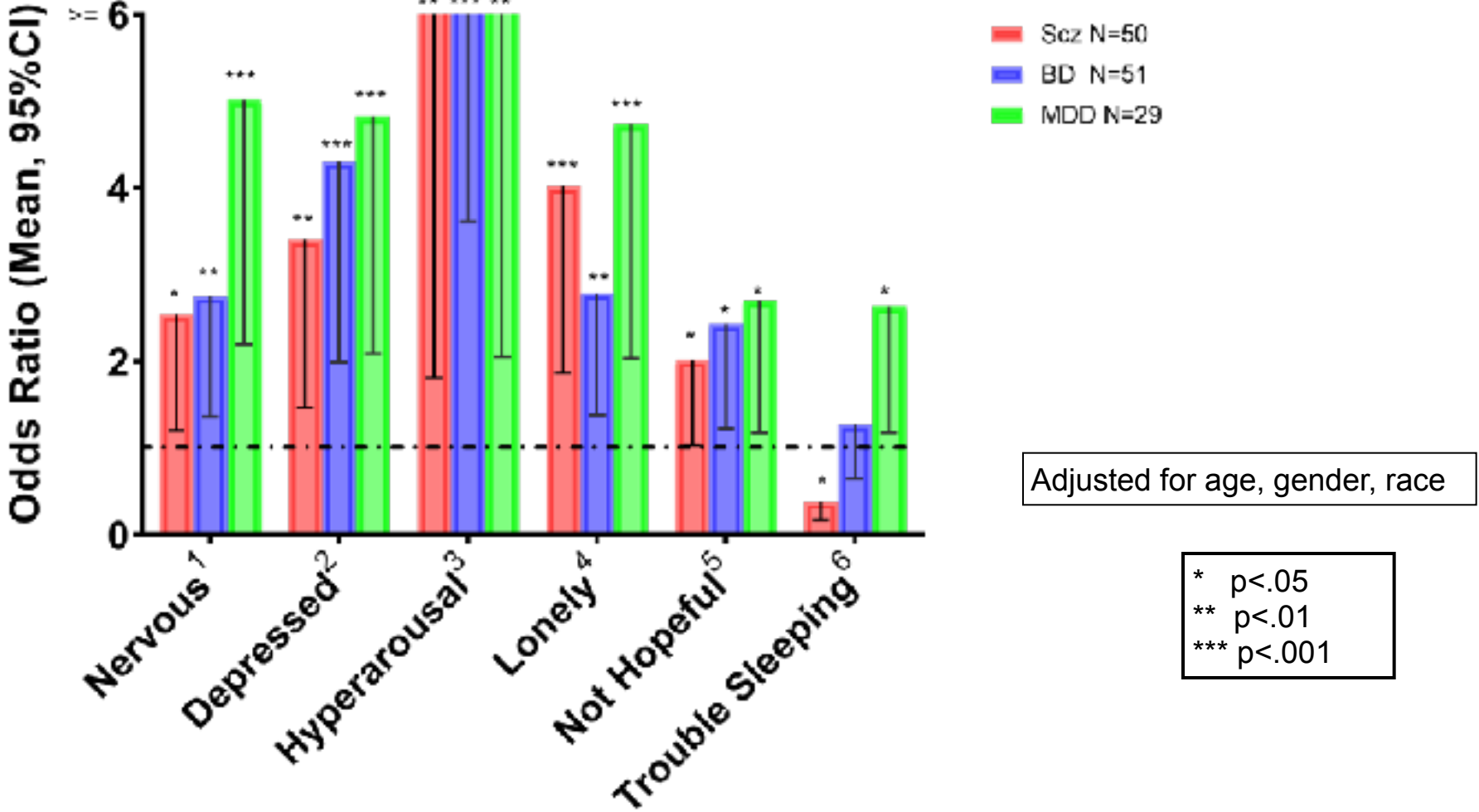
Mean age: 41.0 years ( $\pm$  13.3), range 19-72

Gender: 83 (43%) Male

Race: 126 (65%) White, 46 (24%) Black, 23 (12%) Other

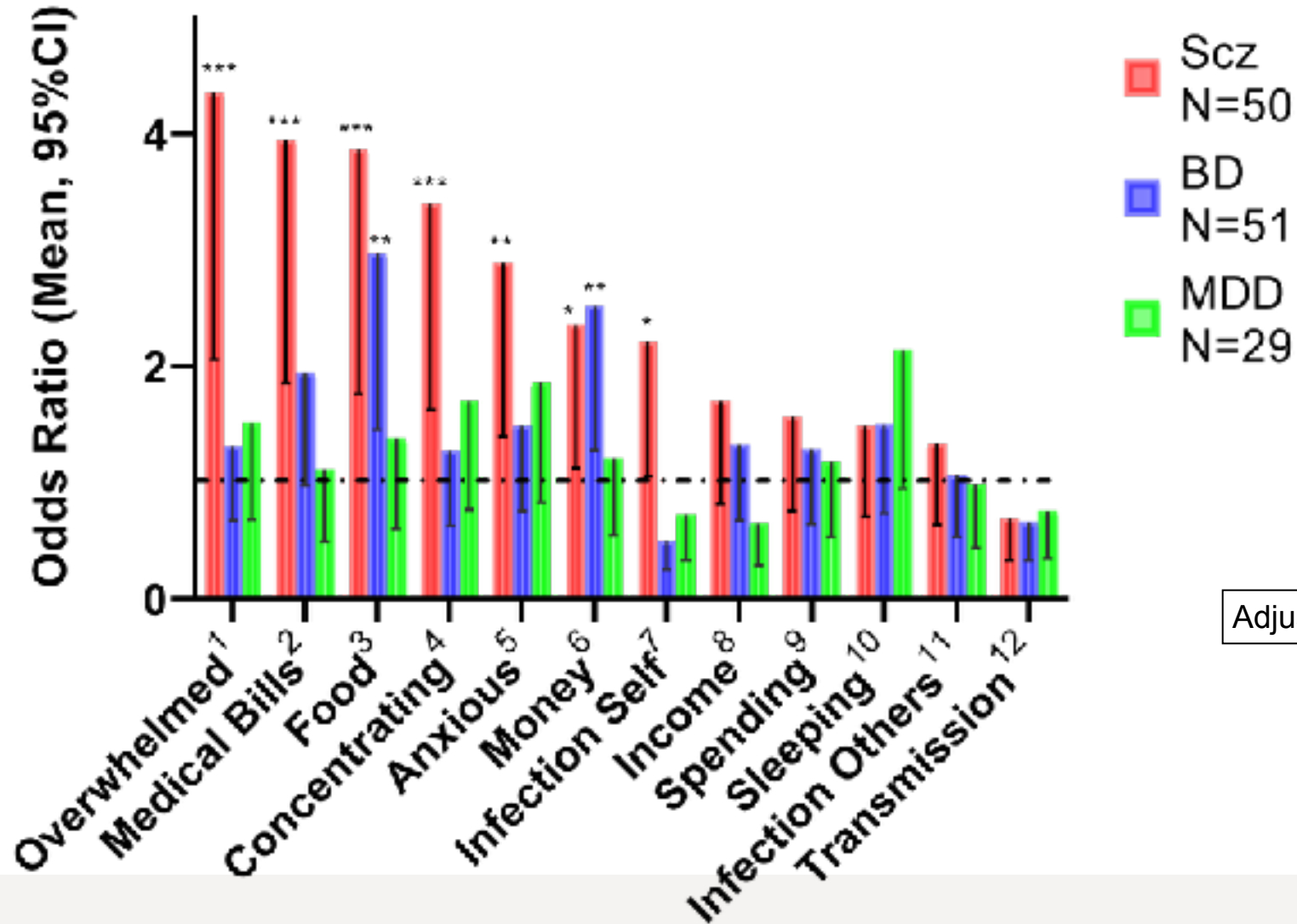
Perceived infection with COVID-19: 17 (9%)

# Frequency of Mental Distress: Comparison between Psychiatric Groups and Non-psychiatric Group





# COVID-related Concerns: Comparison between Psychiatric Groups and Non-psychiatric Group



Adjusted for age, sex, race

\* p<.05  
\*\* p<.01  
\*\*\* p<.001

# Participant Comments

“I feel really paranoid, I've never been closed in like this.”

"I really enjoyed the day program. I want to go back. I miss going, I really like interacting with peers. I love being around people."

“I am just with clients at the house; they're not going out as much; their anxiety is high which causes a lot of stress.“

"I'm always worried that my medications will run out."

“I am pretty stressed out, always on my mind. I am constantly thinking, ‘What can I buy to protect myself?’”

“[I have been smoking more] because I'm home more. I try not to but it's hard because I don't have a hobby or something to do. I'm going to play video games."

"I have a lot of social anxiety; I isolate myself on purpose. I liked that I wasn't expected to leave the apartment.“

## Covid-19 Vaccine Utilization in Individuals With Psychiatric Disorders

**COVID-19** hospitalisation, mortality, **vaccination**, and postvaccination trends among people with **schizophrenia** in Israel: a longitudinal cohort study.

Tzur Bitan D, Kridin K, Cohen AD, Weinstein O.

Lancet Psychiatry. 2021 Oct;8(10):901-908. doi: 10.1016/S2215-0366(21)00256-X. Epub 2021 Aug

Comment > Prim Care Companion CNS Disord. 2021 Nov 4;23(6):21br03028.

doi: 10.4088/PCC.21br03028.

### **COVID-19 Vaccine Hesitancy Among Patients With Psychiatric Disorders**

**Association of Psychiatric Disorders With Incidence of SARS-CoV-2 Breakthrough Infection Among Vaccinated Adults.**

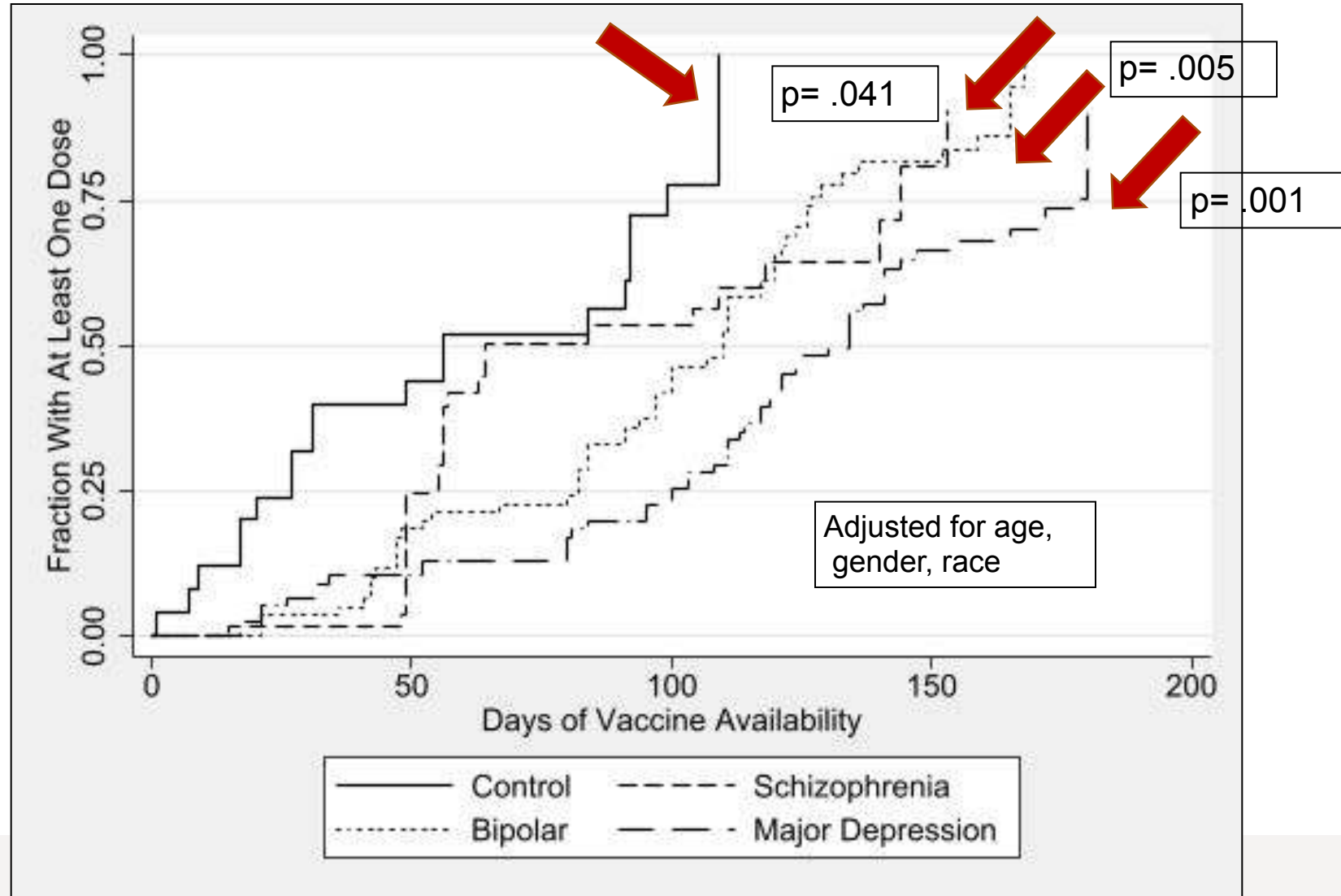
Nishimi K, Neylan TC, Bertenthal D, Seal KH, O'Donovan A.

JAMA Netw Open. 2022 Apr 1;5(4):e227287. doi: 10.1001/jamanetworkopen.2022.7287.

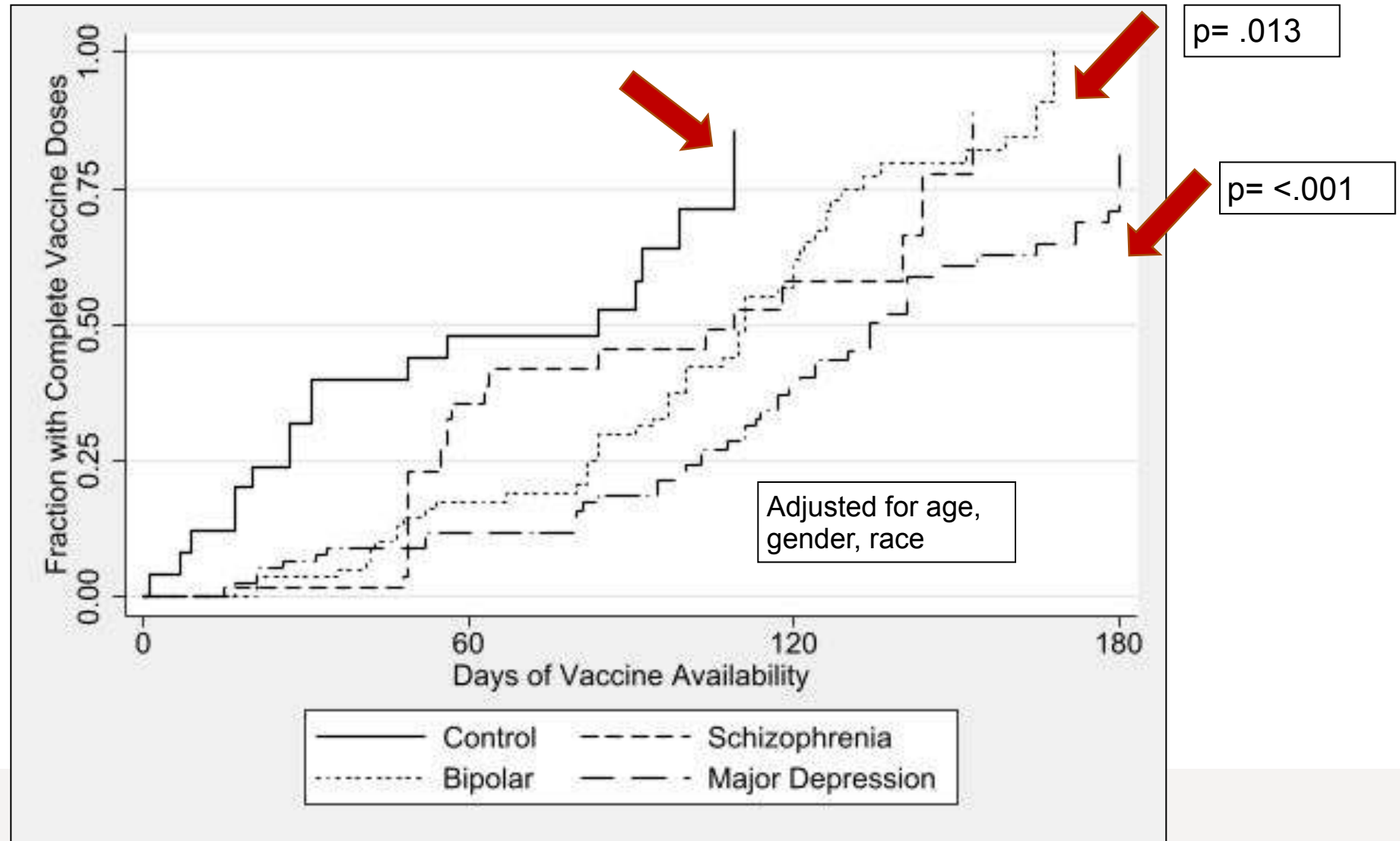
# Response to the COVID Vaccine: **Methods**

- Sample: Previous research participants
  - Assessed in period December 12, 2020 – Feb 22, 2022; before and after vaccine doses
- Vaccine information: Date(s) and type of COVID-19 vaccine
- Previous COVID infection
- Laboratory measures by chemiluminescent immunoassays from blood samples
  - IgG antibodies to 3 antigens on the SARS-2 virion surface (Spike, S1 RBD, S1 NTD) and SARS-2 nucleoprotein
  - IgG antibodies to 4 non-SARS coronaviruses
  - Circulating levels of 19 cytokines
- Data analysis: Mixed effects models with relevant covariates

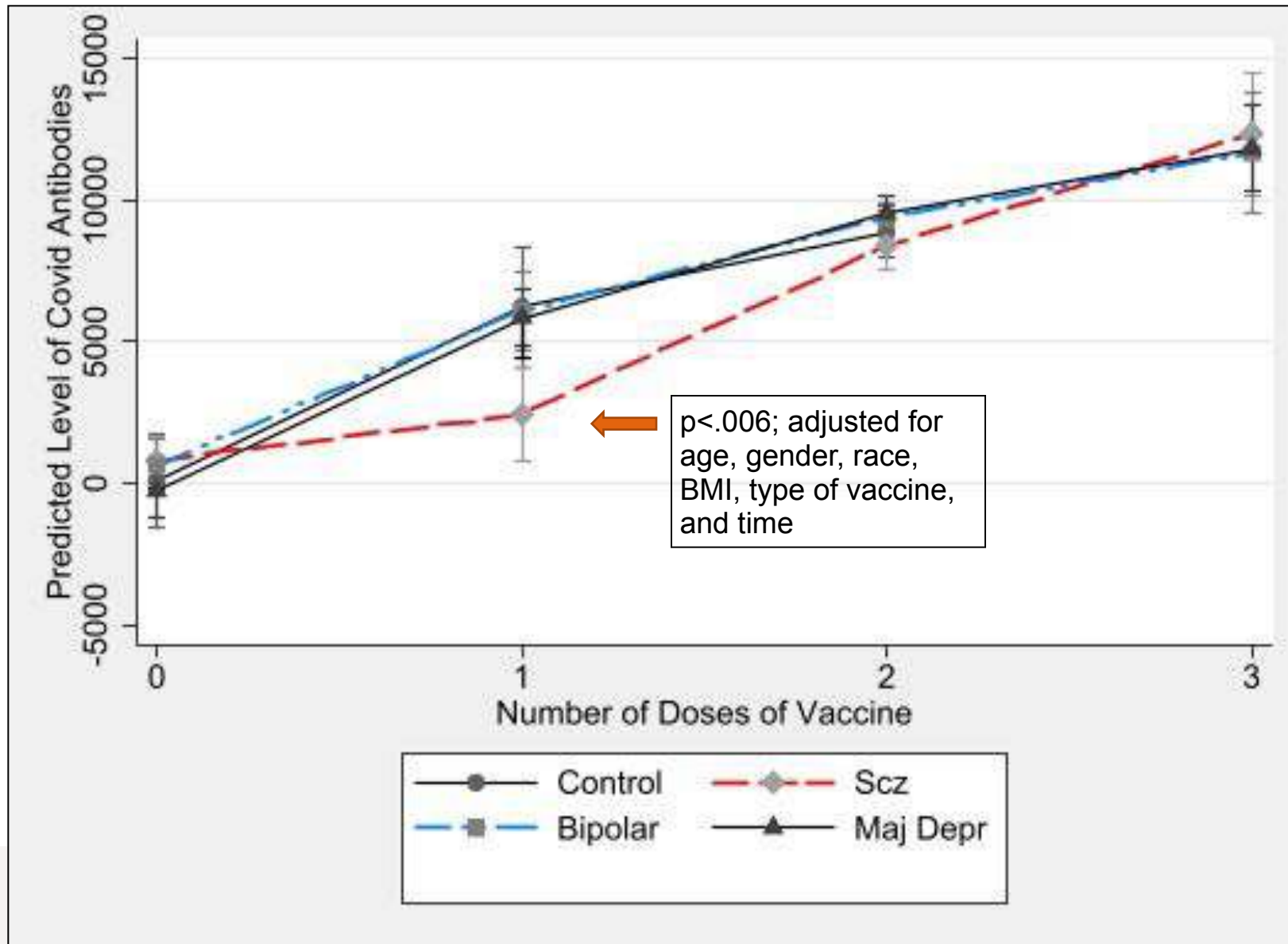
# Receipt of First Dose of COVID-19 Vaccine by Diagnostic Group



# Receipt of Complete Doses of COVID-19 Vaccine by Diagnostic Group



# Levels of COVID-19 Antibodies to SARS-Cov-2 Spike Protein Following Immunization



doi: 10.1007/s00406-020-01231-x. Epub 2021 Jan 5.

# Repurposing of CNS drugs to treat COVID-19 infection: targeting the sigma-1 receptor

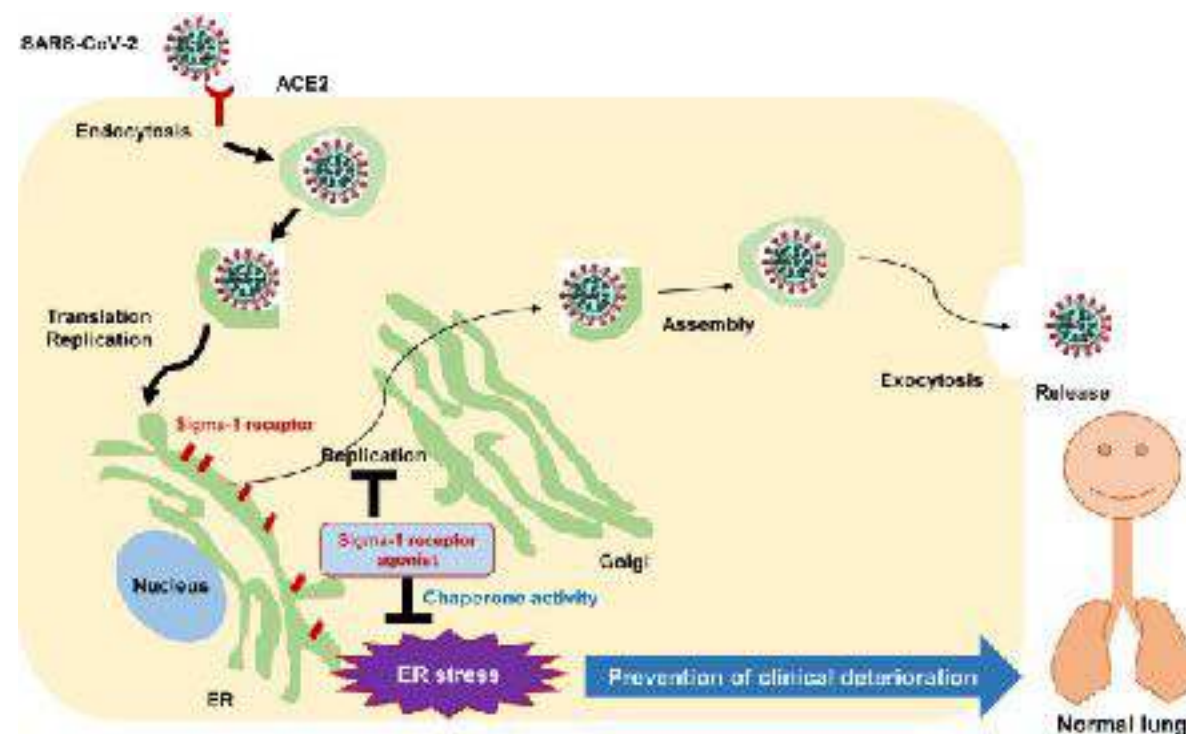
Kenji Hashimoto<sup>1</sup>

&gt; JAMA Netw Open. 2021 Nov 1;4(11):e2133090. doi: 10.1001/jamanetworkopen.2021.33090.

## Mortality Risk Among Patients With COVID-19 Prescribed Selective Serotonin Reuptake Inhibitor Antidepressants

Tomiko Oskotsky<sup>1,2</sup>, Ivana Maric<sup>3</sup>, Alice Tang<sup>1,2,4</sup>, Boris Oskotsky<sup>1,2</sup>, Ronald J Wong<sup>5</sup>, Nima Aghaee-pour<sup>3,5,6</sup>, Marina Sircu<sup>1,2</sup>, David K Stevenson<sup>3,7</sup>

Affiliations: 1, 2, 3, 4, 5, 6, 7





## Sulforaphane exhibits antiviral activity against pandemic SARS-CoV-2 and seasonal HCoV-OC43 coronaviruses in vitro and in mice

Alvaro A. Ordonez<sup>1,2</sup>, L. Korin Bullen<sup>3,4</sup>, Andres I. Villabona-Hueta<sup>5</sup>, Elizabeth A. Thompson<sup>6,7</sup>, Mitchell L. Turner<sup>8,9</sup>, Vanessa F. Merino<sup>9</sup>, Yu Yan<sup>9</sup>, John Kim<sup>9</sup>, Stephanie L. Davis<sup>9,10</sup>, Oliver Komm<sup>9,4</sup>, Jonathan D. Powell<sup>6,7</sup>, Franco R. D'Alessio<sup>9</sup>, Robert H. Yolken<sup>10</sup>, Sanjay K. Jain<sup>9,9</sup>, Francisco J. Alvarez-Branda<sup>11</sup>

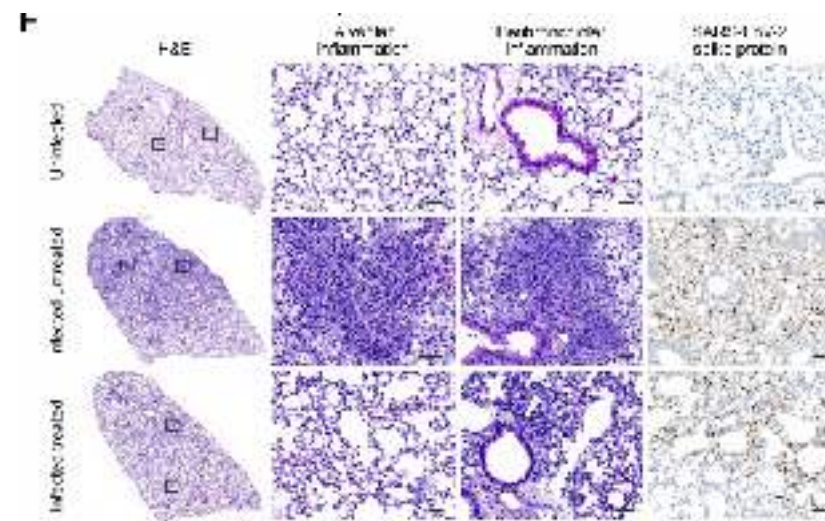
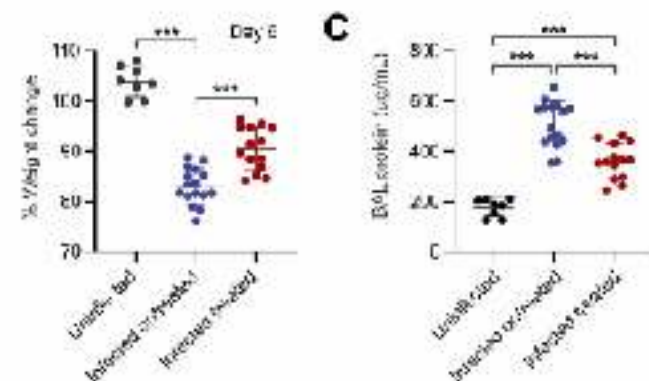
COMMUNICATIONS BIOLOGY

### Chemical Found in Leafy Greens Shown to Slow Growth of COVID-19 and Common Cold Viruses

03/23/2022



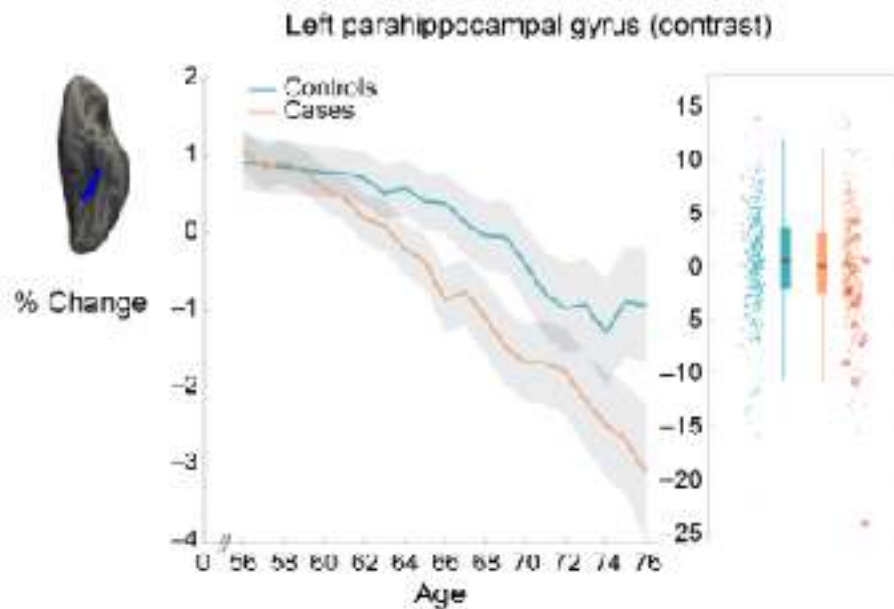
A Johns Hopkins Children's Center-led study finds sulforaphane could help prevent and treat illnesses caused by some coronaviruses, including COVID-19.



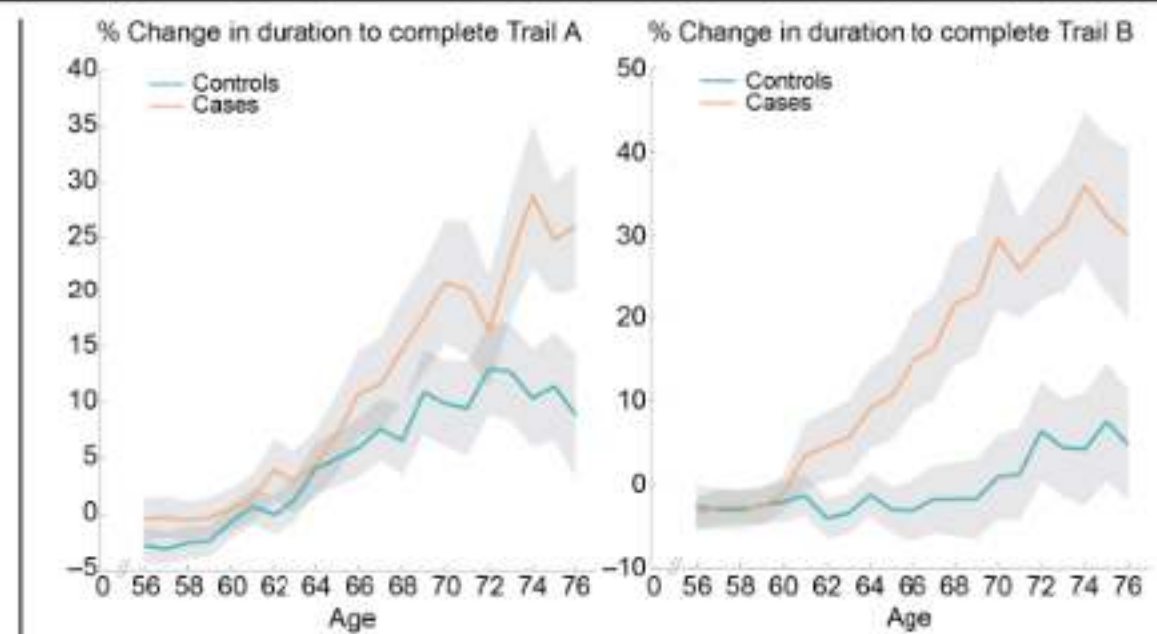
# Mild Covid Infection is Associated with Alterations in Brain Volume and Cognitive Functioning in Previously Healthy Adults

• [Nature 07 March 2022](#)

Decreased Limbic  
Brain Volume



Decreased Performance on Cognitive Testing



## Psychiatric Effects of Covid Infections in Infants and Children



**Psychiatric** problems during the **COVID-19** pandemic in **children** with autism spectrum disorder.

Vasa RA, Singh V, Holingue C, Kalb LG, Jang Y, Keefer A.

Autism Res. 2021 Oct;14(10):2113-2119. doi: 10.1002/aur.2574. Epub 2021 Jul 7.

**Exacerbation of obsessive compulsive disorder symptoms in children and adolescents during COVID-19 pandemic.**

Tanir Y, Karayagmurlu A, Kaya İ, Kaynar TB, Türkmen G, Dambasan BN, Meral Y, Coşkun M.

Psychiatry Res. 2020 Nov;293:113363. doi: 10.1016/j.psychres.2020.113363. Epub 2020 Aug 3.

PMID: 32798931 **Free PMC article.**

**Comment:** > J Am Acad Child Adolesc Psychiatry. 2021 Jan;60(1):5-7.

doi: 10.1016/j.jaac.2020.08.436. Epub 2020 Sep 2.

**School Closures and Social Anxiety During the COVID-19 Pandemic**

# The Effect of Covid-19 on Neonates, Infants, and Children

- ◆ Study Populations
  - ◆ Covid-19 Infected mothers and their neonates
  - ◆ Infants Age 1-2
  - ◆ Children 8-9
- ◆ Long Term Evaluation of Neurodevelopment
  - ◆ Cognitive
  - ◆ Neurological
  - ◆ Behavioral (Autism)
- ◆ Possible Mechanisms
  - ◆ Direct Infection
  - ◆ Multisystem immunopathy
  - ◆ Social Isolation
  - ◆ Interrupted Medical Care and Education



Review

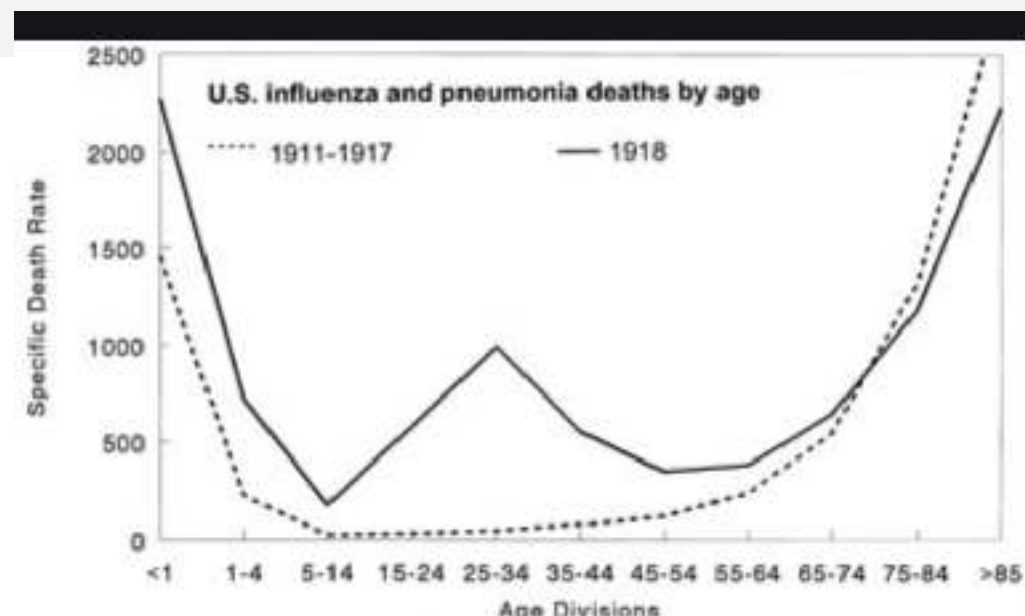
> [Front Psychiatry](#). 2020 Feb 26;11:72. doi: 10.3389/fpsy.2020.00072.

eCollection 2020.

# Schizophrenia and Influenza at the Centenary of 1918–1919 Spanish Influenza Pandemic: Mechanisms of Psychosis Risk

Adrianna P Kępińska<sup>1</sup>, Conrad O Iyegbe<sup>1</sup>, Anthony C Vernon<sup>2 3</sup>, Robert Yolken<sup>4</sup>, Robin M Murray<sup>1</sup>, Thomas A Pollak<sup>1</sup>

## Rampant Lies, Fake Cures and Not Enough Beds: What the Spanish Flu Debacle Can Teach Us About Coronavirus



VOL. V.

APRIL, 1926.

No. 4.

## AMERICAN JOURNAL OF PSYCHIATRY

INFLUENZA AND SCHIZOPHRENIA.

AN ANALYSIS OF POST-INFLUENZAL "DEMENTIA PRECOX,"  
AS OF 1918, AND FIVE YEARS LATER.

FURTHER STUDIES OF THE PSYCHIATRIC ASPECTS OF INFLUENZA.\*

By KARL A. MENNINGER, M. D., TOPEKA.

Review > [Front Psychiatry](https://doi.org/10.3389/fpsyt.2020.00072). 2020 Feb 26;11:72. doi: 10.3389/fpsyt.2020.00072.

eCollection 2020.

## Schizophrenia and Influenza at the Centenary of the 1918–1919 Spanish Influenza Pandemic: Mechanism of Psychosis Risk

Adrianna P Kępińska<sup>1</sup>, Conrad O Iyegbe<sup>1</sup>, Anthony C Vernon<sup>2,3</sup>, Robert Yolken<sup>4</sup>, Robin M Murray<sup>1</sup>, Thomas A Pollak<sup>1</sup>

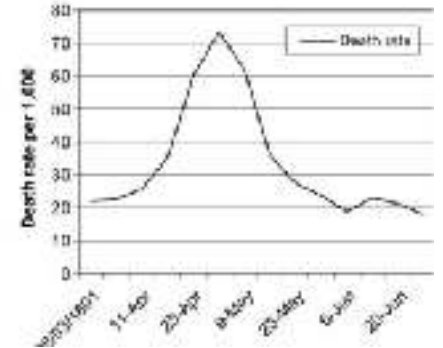
## 1918 H1N1 Influenza Pandemic

- Killed 650,000 people in the US and an estimated 50 million worldwide
- Young adults between the ages of 20 and 40 were at greatest risk for mortality, possibly because...
  - Hemagglutinin had been adapting to humans in years leading up to 1918
  - Others had been previously exposed to a prior H1 influenza
  - Encephalitis lethargica: somnolence, oculogyric crisis, and behavior disorders



# “Russian Flu” 1889-1892

- ◆ First epidemic in Europe in 47 years
- ◆ Followed containment of cholera, typhoid, and other life-threatening infections
- ◆ Followed path of new railway system from Russia to England. Then to US.
- ◆ Approximately 100,000 deaths in England More than 1,000,000 worldwide
- ◆ Most mortality in the elderly
- ◆ Initial denial and slow response from governments
  - ◆ Until illness affected political and religious leaders
- ◆ Extensive coverage in news media with contradictory advice (Quinine)
- ◆ Conspiracy theories (Electricity)
- ◆ Psychiatric consequences
  - ◆ Mood disorders (“Neurasthenia”)
  - ◆ Psychosis
  - ◆ Suicide





# Did a coronavirus cause the pandemic that killed Queen Victoria's heir?

Technology & Ideas

## Our Coronavirus Predicament Isn't All That New

The Russian flu pandemic of 1889 might have actually been caused by a foe that has become all too familiar.

[J. Virol.](#) 2005 Feb, 79(3): 1595-1604.

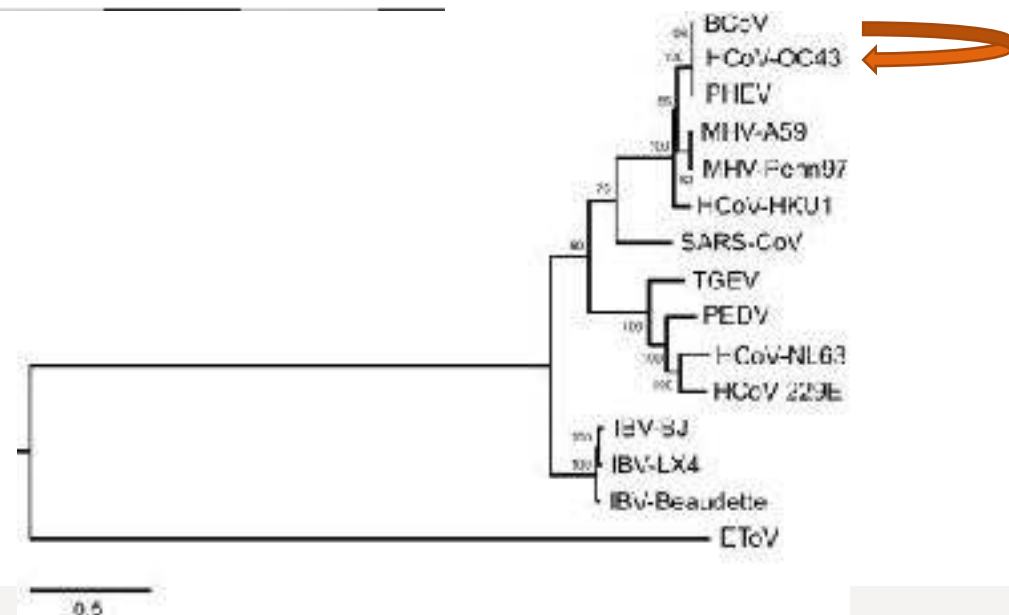
doi: [10.1128/JVI.79.3.1595-1604.2005](https://doi.org/10.1128/JVI.79.3.1595-1604.2005)

PMCID: [PMC544107](https://pubmed.ncbi.nlm.nih.gov/15850185/)

PMID: [15850185](https://pubmed.ncbi.nlm.nih.gov/15850185/)

Complete Genomic Sequence of Human Coronavirus OC43: Molecular Clock Analysis Suggests a Relatively Recent Zoonotic Coronavirus Transmission Event

[Leon Vignou, Elis Kovanis, Ellen Moss, Inge Thoren, Elke Wollants, Philippe Lemey, Anne Mieke Vandamme, and Marc Van Ranst](#)



Estimated time of OC43 origin ~1890

# SARS-COV-2-Likely Future Scenarios

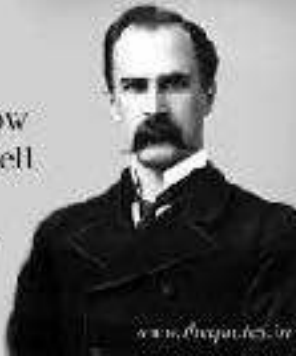
Current SARS2 strains will become endemic

- ◆ Pandemics with novel Coronavirus strains likely
- ◆ Individuals with psychiatric disorders remain at increased risk
- ◆ Infections will lead to an increased rate of psychiatric disorders in previously unaffected individuals
- ◆ Critical needs
  - ◆ Vaccines to keep up with Coronavirus mutations
  - ◆ Vaccine strategies directed at individuals with psychiatric disorders.
  - ◆ Increased mental health resources due to increased rates of psychiatric disorders
    - ◆ Children
    - ◆ Young adults
    - ◆ Older individuals

1849-1919

The best preparation for tomorrow  
is to do today's work superbly well

*William Osler*





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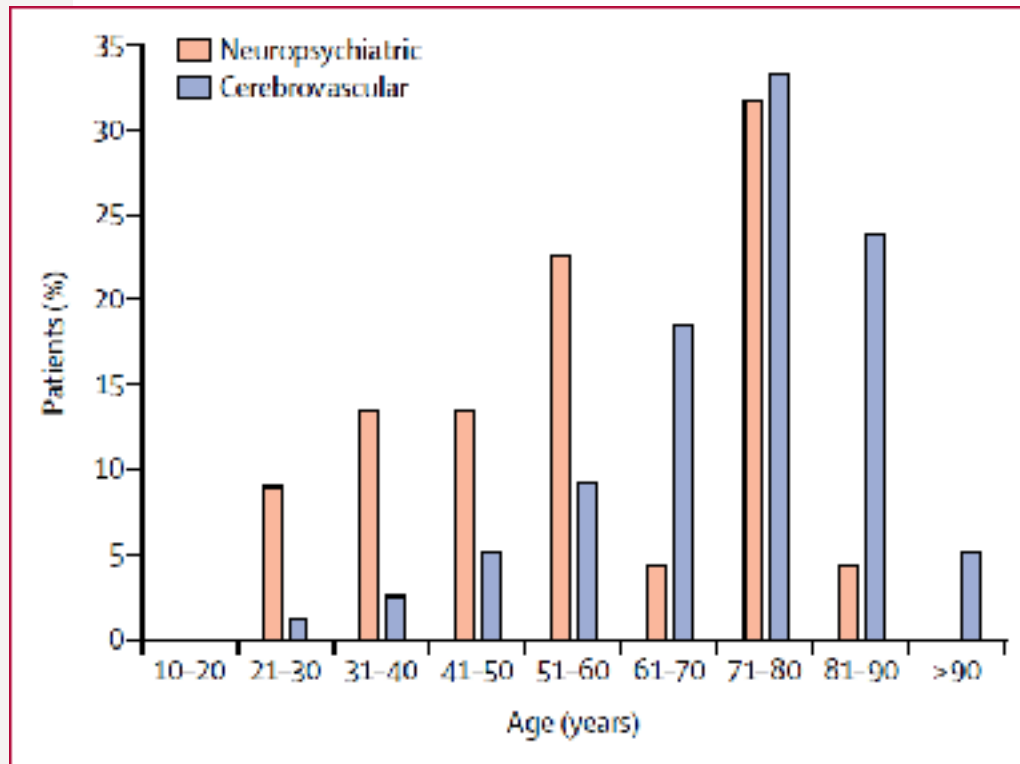


Maree Webster  
E Fuller Torrey

# Extra Slides

# Neuropsychiatric Complications of Covid-19

+Case series 153 Covid+ pts with neurological OR new and acute neuropsychiatric complications



39 altered mental status:

- 7 encephalitis
- 9 encephalopathy
- 23 neuropsychiatric disorder
  - 10 psychosis
  - 6 neurocognitive
  - 7 other

Varatharaj et al. Lancet Psy2020