COVID as a Natural Resilience Experiment: The COVID-19 Virus (and Vaccine) as Stressor

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Disclosures

- Nothing to disclose

Outline

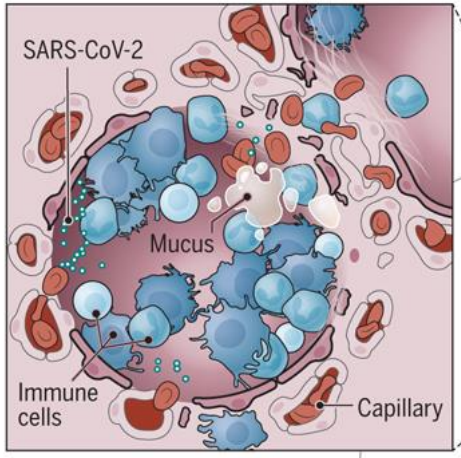
- Magnitude of COVID-19 as health stressor
- COVID-19 patient case report and population data
- How COVID-19 fits in resilience conceptual models
- Papers related to COVID-19 and resilience
- Knowledge Gaps
- Research opportunities

COVID-19
A RAMPAGE THROUGH THE BODY

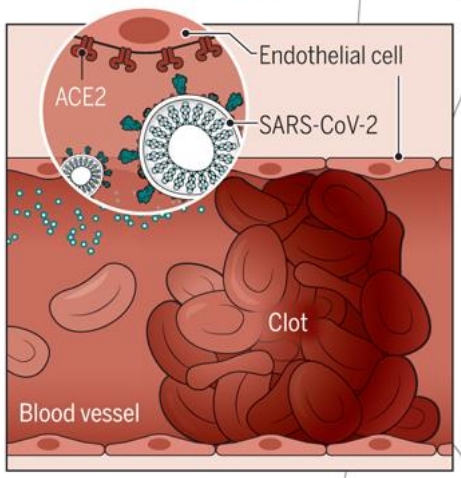
An invader's impact

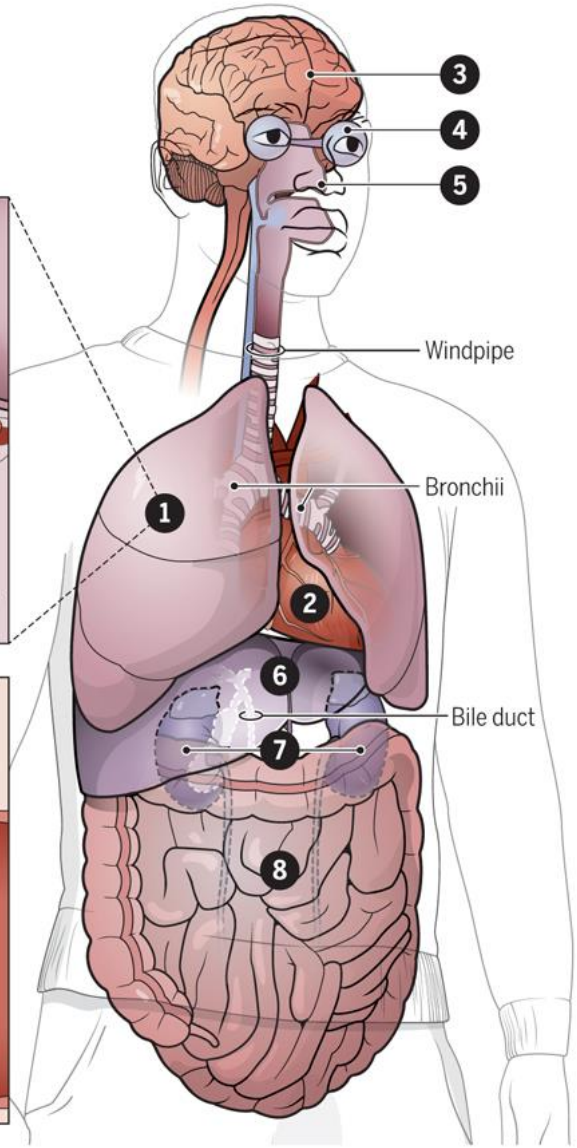
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

1 Lungs
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.



2 Heart and blood vessels
The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.





3 Brain
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

4 Eyes
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

5 Nose
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose's nerve endings and damage cells.

6 Liver
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

7 Kidneys
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

8 Intestines
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.

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Patient Presentation

- 86 yr. old male rehabilitation facility resident
- Past medical history: diabetes mellitus with nephropathy and neuropathy, diabetic foot wound complicated by necrotizing fasciitis requiring left below knee amputation, atrial fibrillation, hypertension, mild cognitive impairment
- Independent basic ADLs, assistance IADLs
- 10 prescription medications; 5 prn
- Developed dry cough and nasal congestion
- Triggered COVID screening, PCR positive for SARS-CoV-2
- Exam: BP 120/64; P 90; R 18; T 97.6; O2 sat 95%; oriented, pleasant, conversant, normal heart and lung exams
- Symptoms resolved in 2 days; no change in functional status; discharged to community residence, living with sister

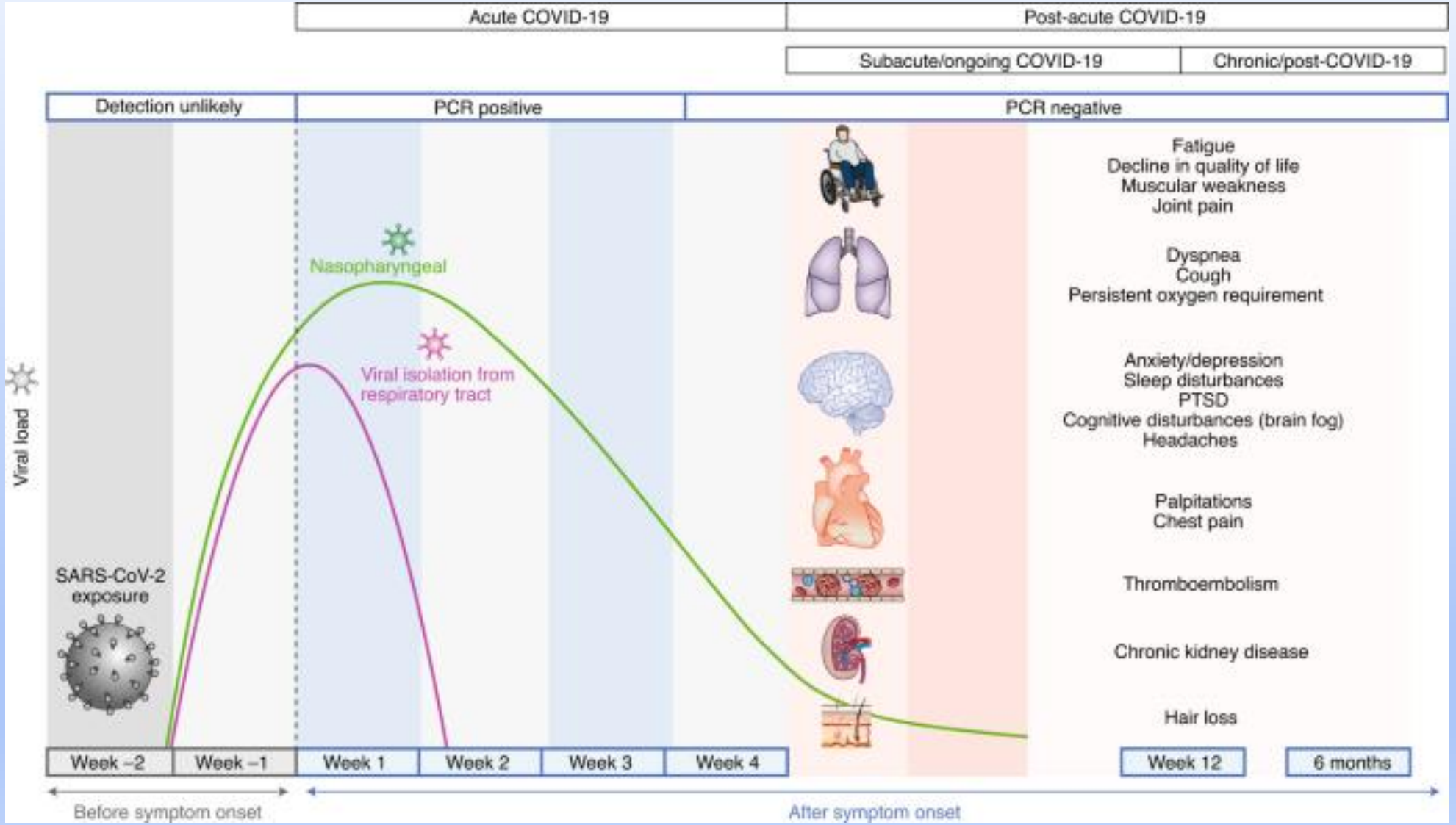
COVID-19 Cases, Hospital Admissions, Deaths per 100,000 Population Dec 12, 2020

Age Group (years)	Cases	Hosp*	Deaths
65-74	323	7.4	14.5
75+	366	17.4	58.0

*Hosp = new hospital admission; age 60-69 and 70+

CDC COVID Data Tracker: Hospital Admissions
CDC COVID Data Tracker: Case & Death Trends by Demographics

Post-Acute COVID-19 Syndrome



Nalbandian A et al. Nature Medicine | VOL 27 | April 2021 | 601–615

Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years

United States, March 2020–November 2021

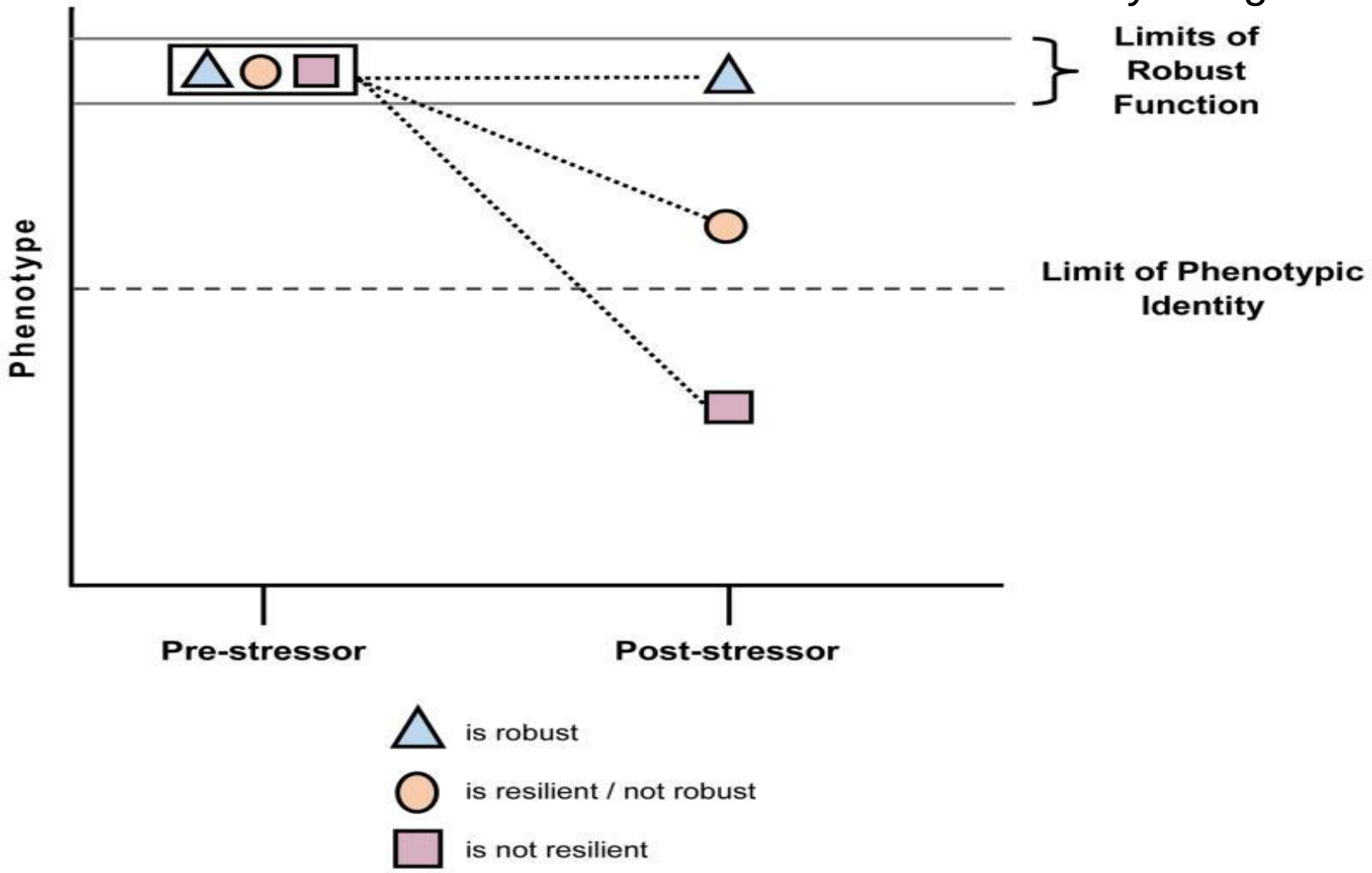
Age group, yrs	No. of patients (column %)		No. of patients with ≥1 incident condition (column %*)		Absolute risk difference†	No. of COVID-19 survivors with a post-COVID condition§
	Case-patients	Control patients	Case-patients	Control patients		
18–64	254,345 (72.0)	1,051,588 (64.1)	90,111 (35.4)	154,011 (14.6)	20.8	1/5
≥65	98,819 (28.0)	589,188 (35.9)	44,840 (45.4)	108,850 (18.5)	26.9	1/4

* Percentage of COVID-19 case-patients or control patients with ≥1 incident condition divided by the total study COVID-19 cohort or control cohort row's age group total.
† Percentage point difference between COVID-19 case-patients and control patients (e.g., the value 20.8 is calculated as 35.4 minus 14.6).
§ Number of COVID-19 survivors who experienced a post-COVID condition estimated as the inverse of the absolute risk difference.

Bull-Otterson L, Baca S, Saydah S, et al. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021. MMWR Morb Mortal Wkly Rep 2022;71:713–717

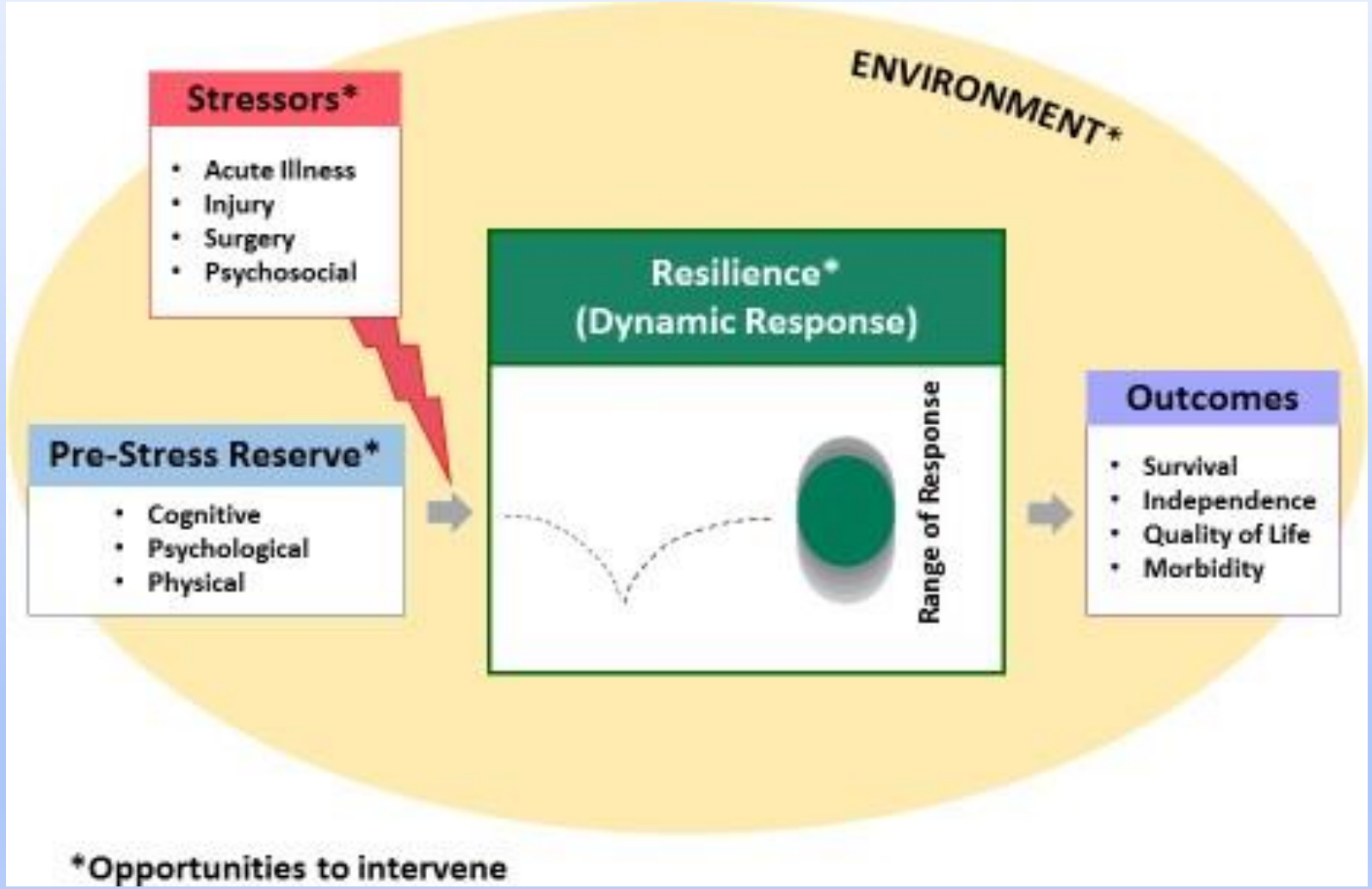
Resilience Conceptual Model
Johns Hopkins Pepper Center

Pre-Stressor and Post-Stressor Levels of Function in a Physiological System



Varadhan R, Walston JD, Bandeen-Roche. Can Physical Resilience and Frailty in Older Adults be Linked by the Study of Dynamical Systems. J Am Geriatr Soc. 2018;66(8):1455-1458.

Resilience Conceptual Model
Duke Pepper Center



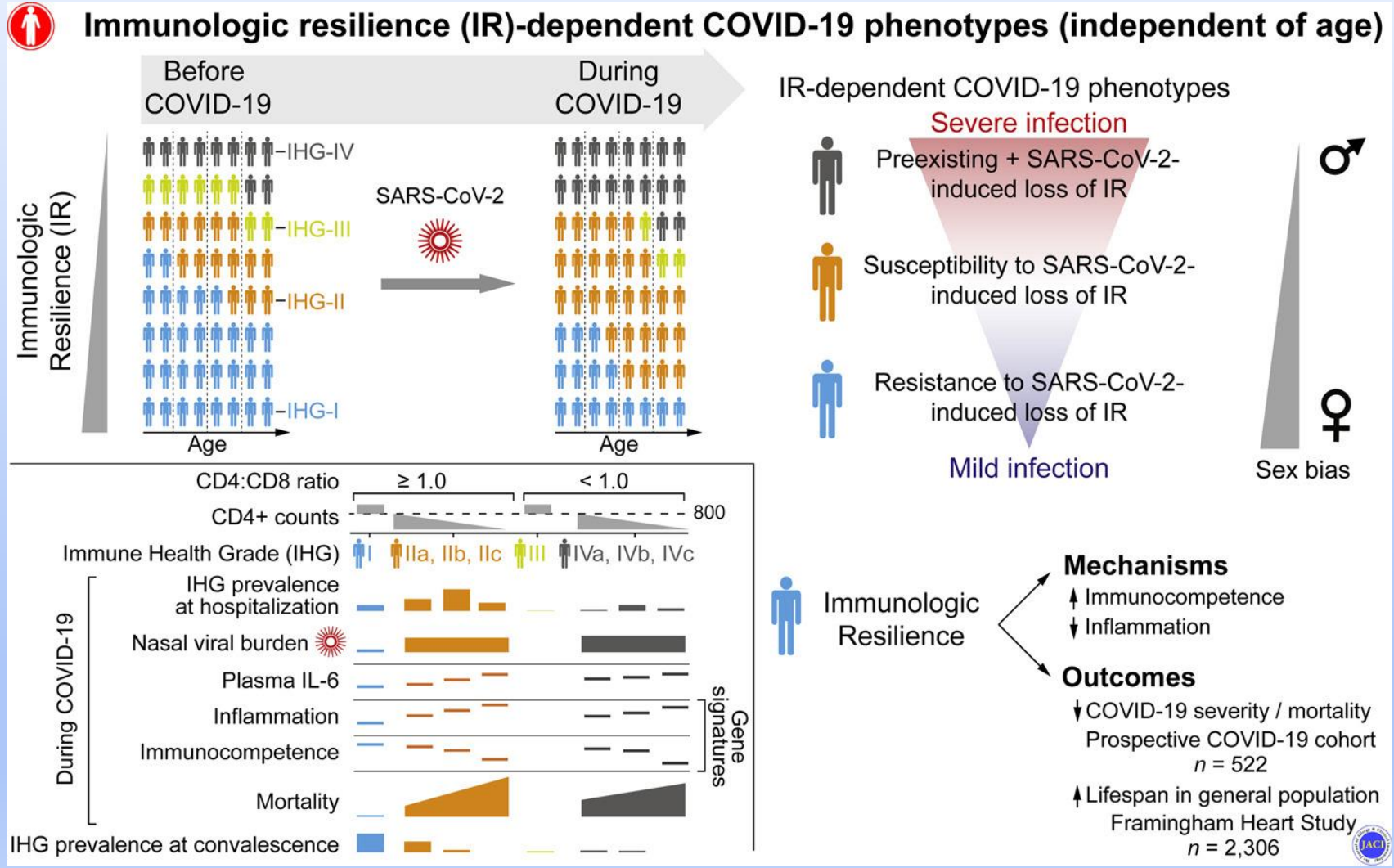
Whitson, H.E., Crabtree, D., Pieper, C.F., et al. A template for physical resilience research in older adults: Methods of the PRIME-KNEE study. J Amer Geriatr Soc. 2021;69: 3232-3241

Examples of Stressors, Resilient Responses and Regulatory Factors*

Stressor	Potential Adverse Consequences of Stressor	Resilient Clinical or Functional Response	Example Systems Influencing Level of Resilience
Exposure to Infectious Agent	-Septicemia -Restricted activity -Accelerate lean body mass loss -Mortality	-Avoidance of infection -Rapid recovery from infection	-Immune -Pulmonary -Genitourinary -Dermatologic

*Modified Table 1 from Hadley EC, Kuchel GA, Newman AB; Workshop Speakers and Participants. Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging. J Gerontol A Biol Sci Med Sci. 2017 Jul 1;72(7):980-990.

Immunologic Resilience and COVID-19 Survival Advantage



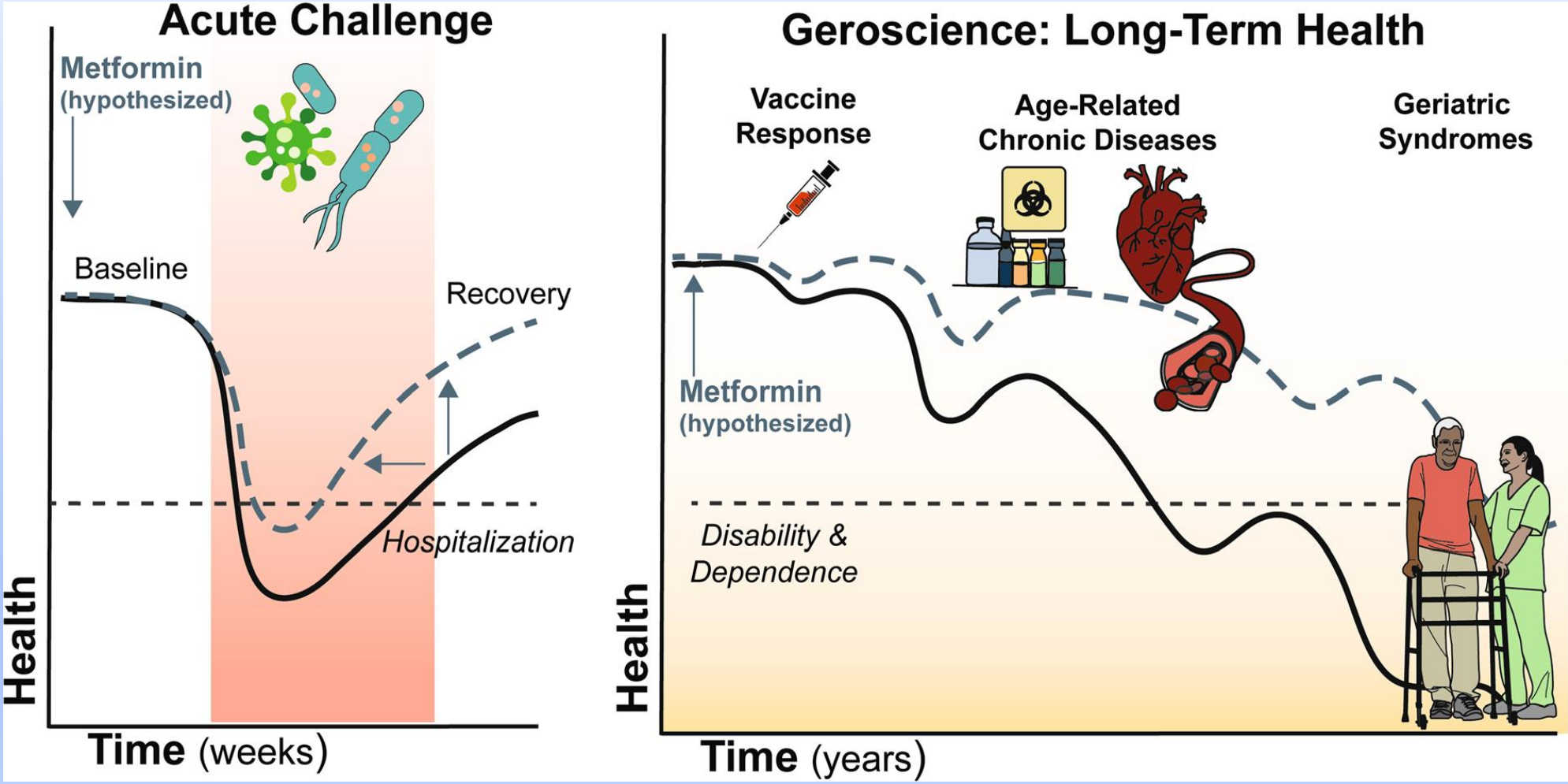
Lee GC, Restrepo MI, Harper N. Immunological resilience and COVID-19 survival advantage
J Allergy and Immunology. 2021;148:1176-1191

Selected Examples of Potential Influences of Biologic Aging-Related Mechanisms on Types of Resilience

Mechanisms	Type of Resilience Affected
Cell senescence	Immune responses, cancer chemotherapy tolerance, wound healing
Impaired stem/progenitor cell function	Resistance to infections, wound healing, cancer chemotherapy tolerance
Dysregulation of inflammatory factors	Infection resistance and recovery, wound healing, avoiding postsurgical MI, cancer chemotherapy intolerance
Inadequate DNA repair	Cancer chemotherapy tolerance
Impaired mitochondrial function	Ability to meet bioenergetic demands posed by stressors (eg, for averting falls, mounting febrile responses)

Table 3 from Hadley EC, Kuchel GA, Newman AB; Workshop Speakers and Participants. Report: NIA Workshop on Measures of Physiologic Resiliencies in Human Aging. J Gerontol A Biol Sci Med Sci. 2017 Jul 1;72(7):980-990.

Geroscience and Immune Resilience: Acute and Long-Term Health



Justice JN et al. A geroscience perspective on immune resilience and infectious diseases: a potential case for metformin
GeroScience (2021) 43:1093–1112

Animal Models in COVID Research

nature

Article

Virus-induced senescence is a driver and therapeutic target in COVID-19

Science AAAS

CORONAVIRUS

Senolytics reduce coronavirus-related mortality in old mice




Chu H et al. Animal models in SARS-CoV-2 research. Nat Methods 2022;19:392–394
Lee S et al. 2021;599:283 Camell et al. Science 2021;373:295

Knowledge Gaps

- Older patient and population level characteristics associated with a resilient response to acute and post-acute COVID-19
- Molecular and immunological mechanisms underlying reserve and resilience with aging to acute and post-acute COVID-19
- Optimal analytical approaches to address questions regarding resilience and COVID-19
- Factors and mechanisms underlying long-last immunity to COVID-19 vaccination in older adults
- Interventions at points before, during or after COVID-19 to augment reserve and resilience and improve health outcomes

Research Opportunities

- Observational studies (cohorts, database)
  - RECOVER: Researching COVID to Enhance Recovery **About the Initiative | RECOVER COVID**
  - Homepage - COVID-19 Research Database (covid19researchdatabase.org)
  - Open-Access Data and Computational Resources to Address COVID-19 | Data Science at NIH - NIH Office of Data Science Strategy
- Clinical research
  - Clinical measures (battery) of resilience before, during, and after infection
  - Geroscience based clinical trials
  - Enhancement of duration of vaccine efficacy
- Laboratory based research (cell, animal model, translational)
  - Immunological – mucosal immunity, innate and adaptive immune response with aging for infection and vaccine response
  - Mechanisms of SARS-CoV-2 cell entry and replication in older cells
- Computational and informatics methods (e.g., artificial intelligence) integrating emerging multi-modal data for COVID-19 diagnosis, prevention, and treatment in older adults.
- NOT-AG-21-016: Notice of Special Interest: Neurological and Neurocognitive Sequelae from SARS-CoV-2 Infection and COVID-19 in Aging and Age-Related Neurodegeneration