Long COVID

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Long COVID

- ✓ **Definitions and Background**
- ❑ Death Trends
- ❑ Long COVID in Non-Hospitalized Patients
- ❑ Most Common Sites for Long COVID
  - Lungs
  - Heart
  - Brain
- ❑ PAI-1 Levels and COVID; Underwriting Conclusions

COVID-19: Definitions/Background

- Coronavirus Disease – 2019 (COVID-19) is a viral respiratory illness caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome – Coronavirus – 2); origin has yet to be determined
- SARS-CoV-2 enters human cells mainly by binding to the ACE 2 enzyme, which is highly expressed in the lungs, cardiac muscle tissue, kidney, gastrointestinal lining and the inner cellular lining of arteries, veins and capillaries
- Prior, similar viruses include:
  - SARS-CoV-1, which caused the 2002 to 2003 SARS epidemic, believed to have started in southern China and resulting in 8,000 confirmed cases with an estimated fatality rate of 9 to 11%*
  - MERS-CoV (Middle East Respiratory Syndrome Corona Virus), currently endemic to the Arabian Peninsula, with an estimated 36% fatality rate*
- This compares to a fatality rate of approximately 1.1% for COVID-19

*American Journal of Emergency Medicine 2021 Feb; 40: 188-192

COVID-19 – Thrombotic Disease

- Thrombotic Disease = Blood clots in veins and arteries
- COVID-19 predisposes its victims to thrombotic disease because of:
  - Excessive inflammation
  - Platelet activation
  - Constriction, rather than dilation, of large, surface heart blood vessels
- COVID spike protein can change clotting protein to insoluble, small microclots that damage blood vessels and block blood flow to many different organs throughout the body.

Long COVID-19

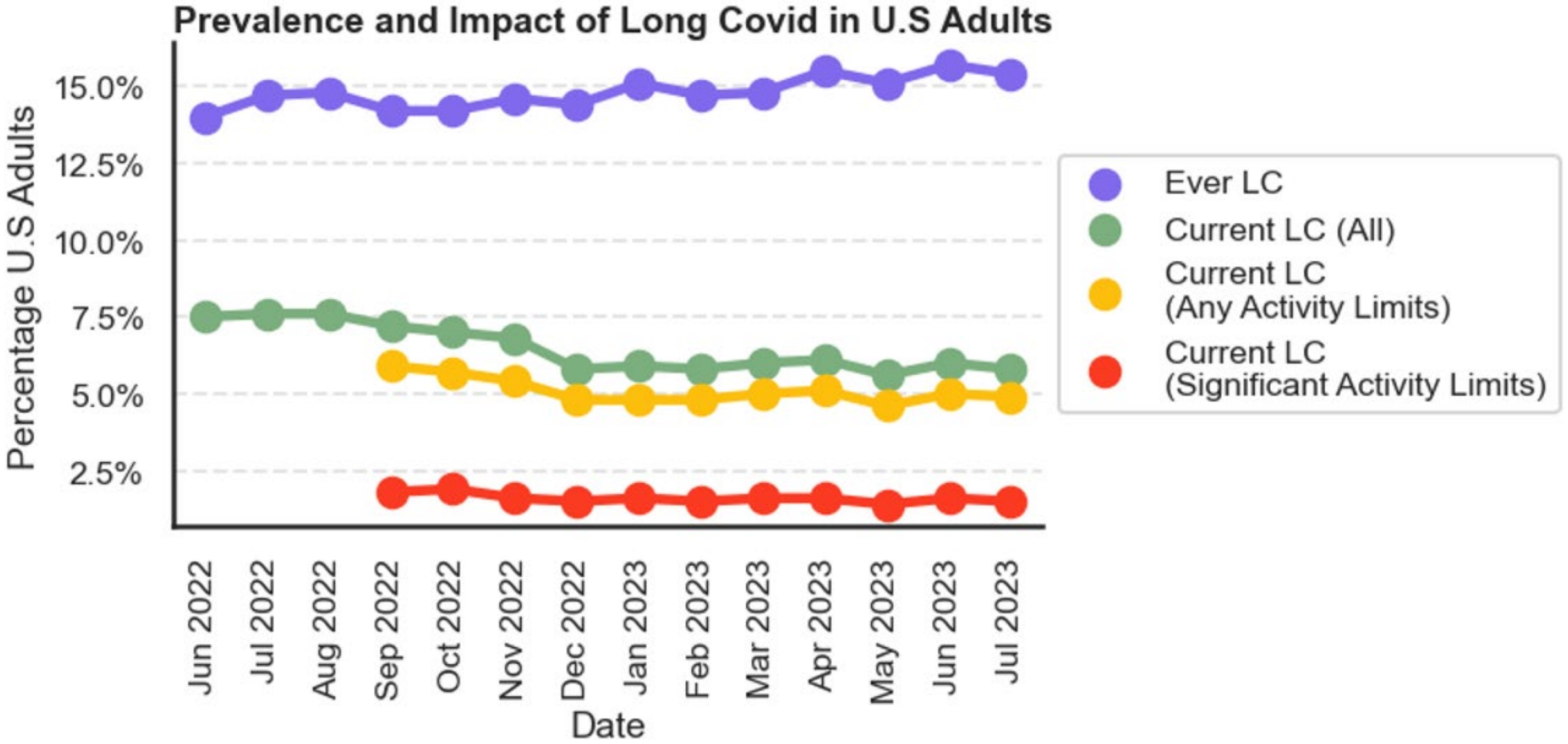
- Most patients totally recover from acute COVID within 3-4 weeks after onset of infection
- Long COVID has been reported in 10% to 30% of those with COVID-19
- More common in women, non-whites, hospitalized versus non-hospitalized and those with COPD and/or smoking history
- Reinfection poses additional risk, although less severe than initial COVID

Post COVID-19 Syndrome*

- Individuals with history of probable or confirmed SARS-CoV-2 infection
- Experience symptoms impacting everyday life, such as fatigue, shortness of breath and cognitive dysfunction
- Symptoms usually are present 3 months from onset of acute COVID-19 symptoms
- Symptoms last for at least 2 months and can't be explained by alternative diagnosis
- Most with post-COVID syndrome are PCR negative, i.e., biologically recovered**

*Source: World Health Organization

**Clinical Research & Reviews, 15(3), 869-875

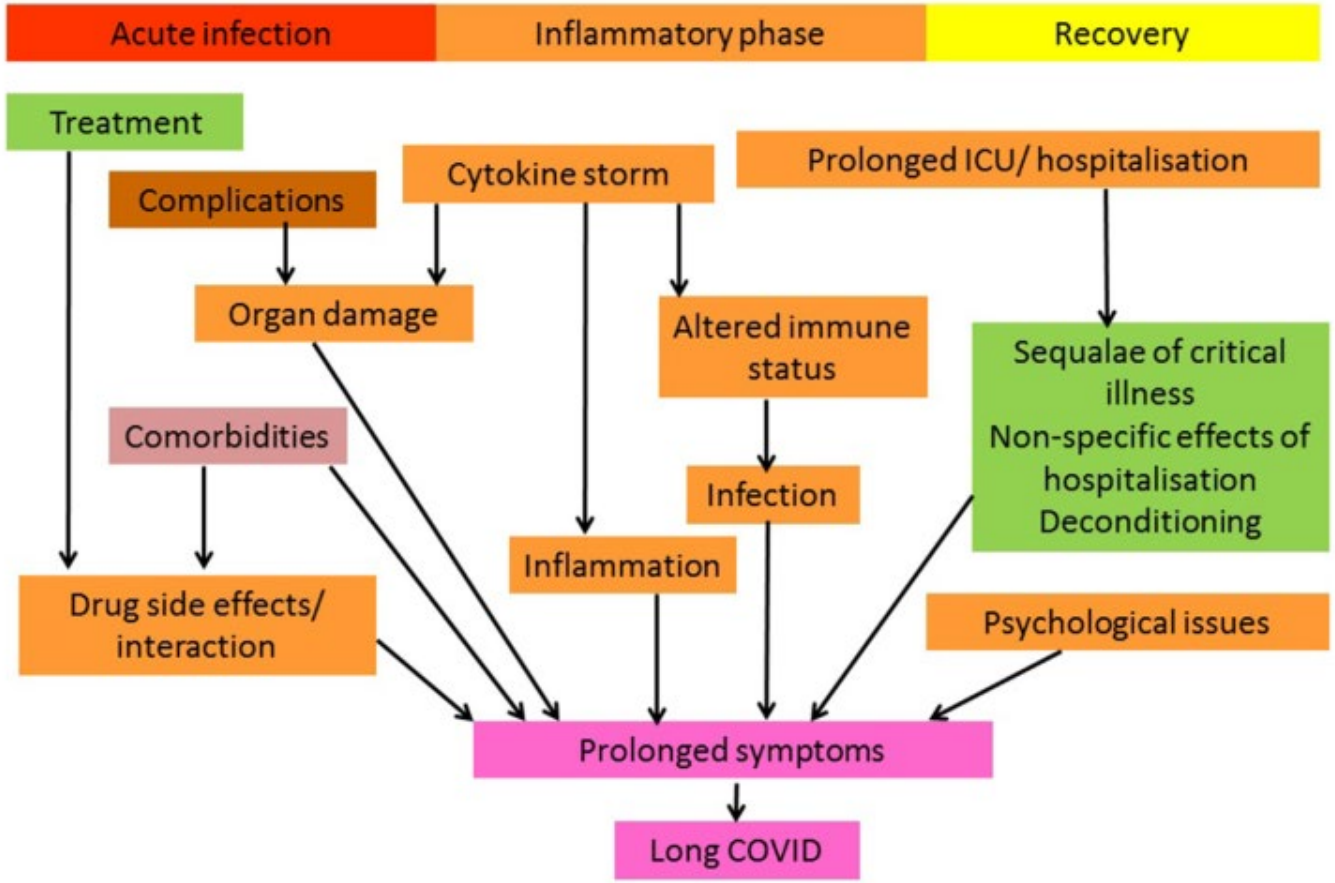

Prevalence and Impact of Long Covid in U.S Adults
Percentage U.S Adults
15.0%
12.5%
10.0%
7.5%
5.0%
2.5%
Jun 2022
Jul 2022
Aug 2022
Sep 2022
Oct 2022
Nov 2022
Dec 2022
Jan 2023
Feb 2023
Mar 2023
Apr 2023
May 2023
Jun 2023
Jul 2023
Date
Ever LC
Current LC (All)
Current LC (Any Activity Limits)
Current LC (Significant Activity Limits)

Source: CDC

Three Categories of Long COVID

- Patients who do not recover completely and have ongoing symptoms due to direct cell damage from the virus
- Patients with symptoms related to chronic hospitalizations, such as being bed bound for an extended period
- Patients with symptoms that appear after recovery

How Long COVID Evolves



Source: Clinical Research & Reviews 15 (2021) 869-875

Note: Cytokine storm is a physiological reaction in which the immune system causes an uncontrolled and excessive release of pro-inflammatory signaling molecules (cytokines) that normally are part of the body's immune response to infection

Incidence of Long COVID: Hospitalized versus Non-hospitalized

Cohort	**Range – Long COVID**
Non-hospitalized patients	10% – 30%
Hospitalized patients	50% - 70%
Vaccinated	10% - 12%

Source: Nature Reviews Microbiology; Volume 21; March 2023; 133-146

COVID-19 versus Influenza:
Relative Risk of Developing Medical Conditions Post Hospitalization

Condition	**Hazard Ratio**
Venous thromboembolism	1.77
Dementia	0.95
Stroke	0.86
Seizure	0.55
Parkinson's	0.39

Source: JAMA *Intern Med.* Doi:10:100/jamamainternmed.2023.2228

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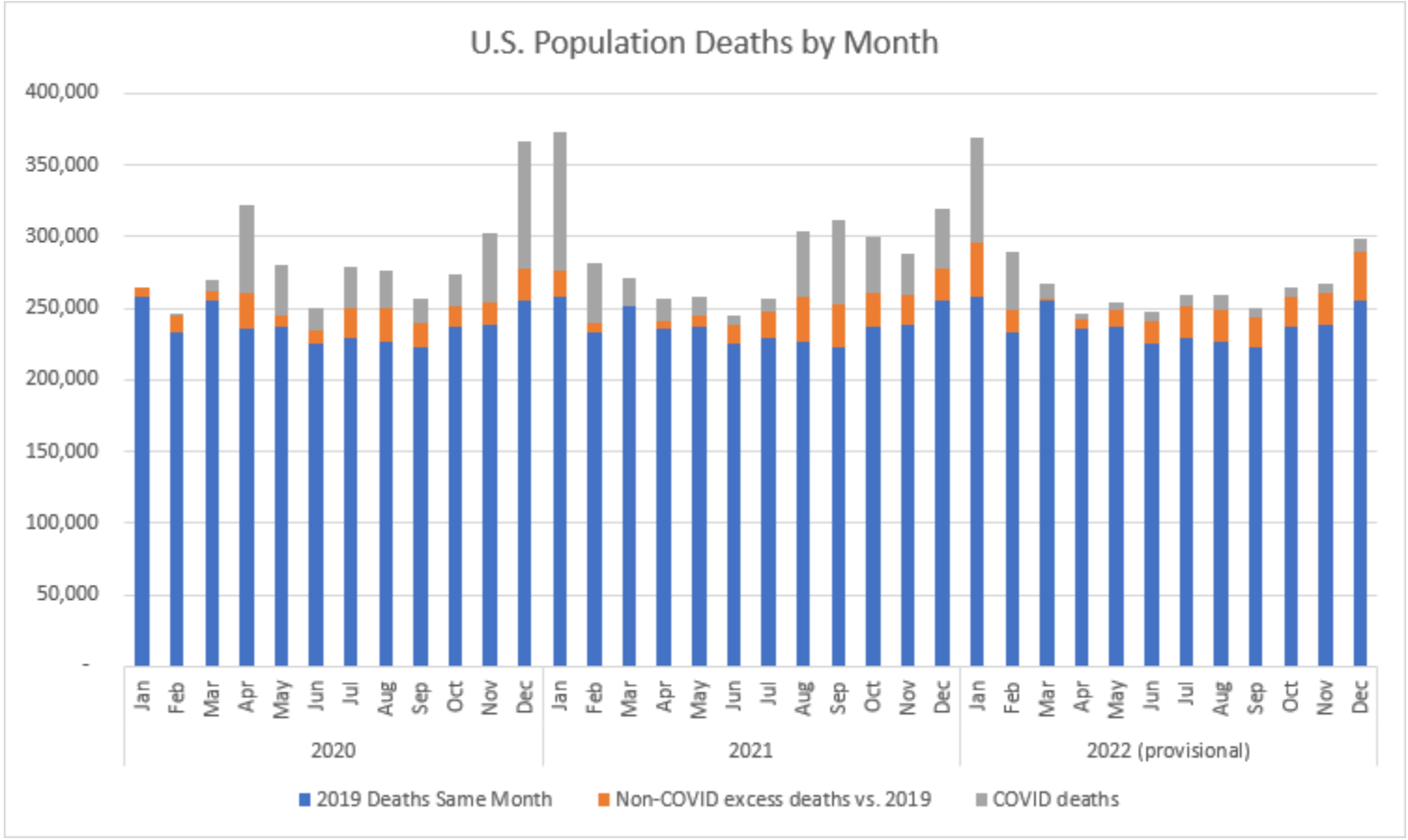
U.S. Death Trends

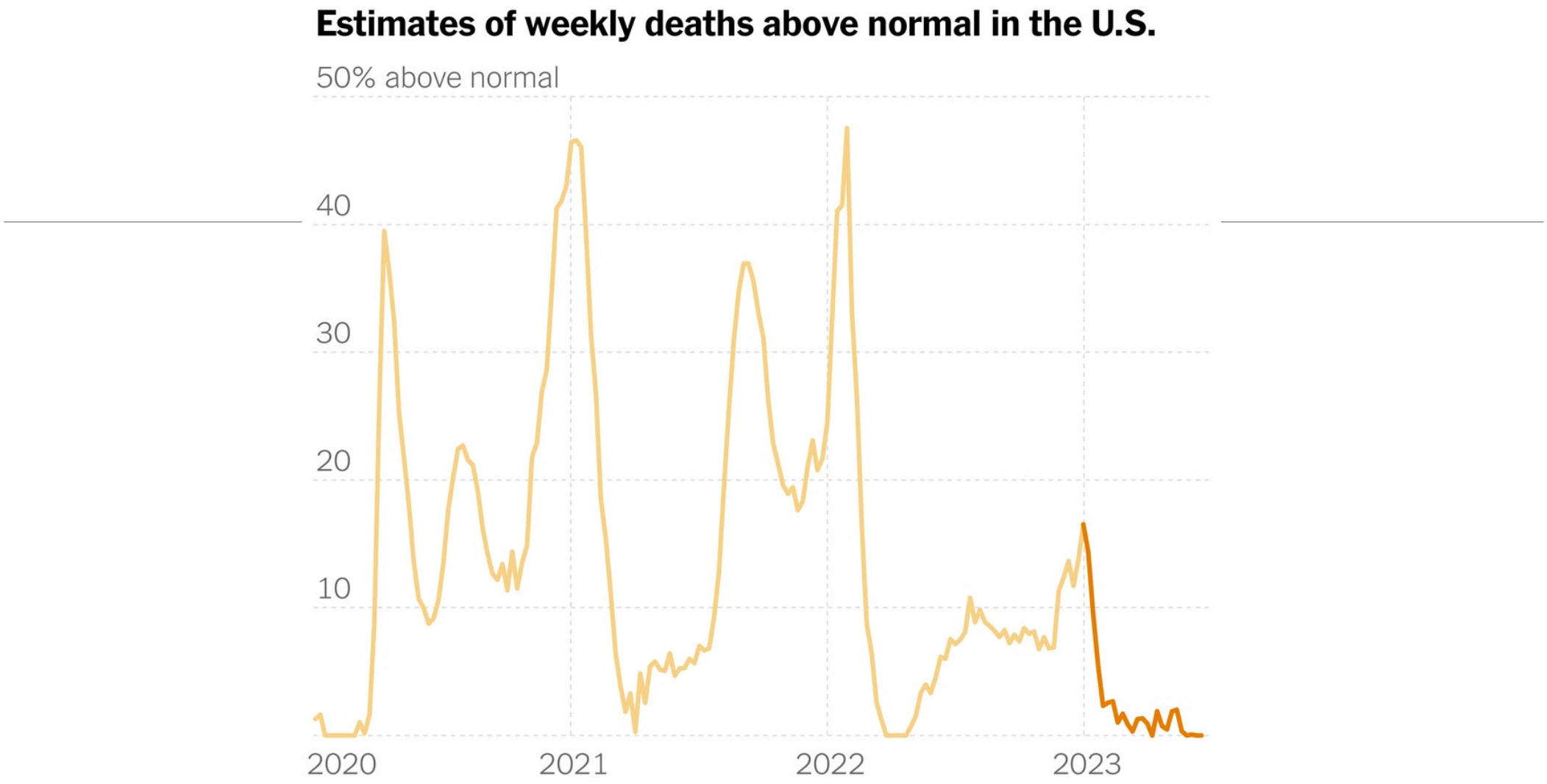
	Number of Deaths:		% to Total:		Rank:	
	2021	2022	2021	2022	2021	2022
Heart Disease	695,547	699,659	20.1%	21.4%	1	1
Cancer	605,213	607,790	17.5%	18.6%	2	2
COVID-19	416,893	186,702	12.0%	5.7%	3	4
Accidents	224,935	218,064	6.5%	6.7%	4	3
All Other	1,521,643	1,561,491	43.9%	47.7%		
Total	3,464,231	3,273,705	100.0%	100.0%		

Source: CDC

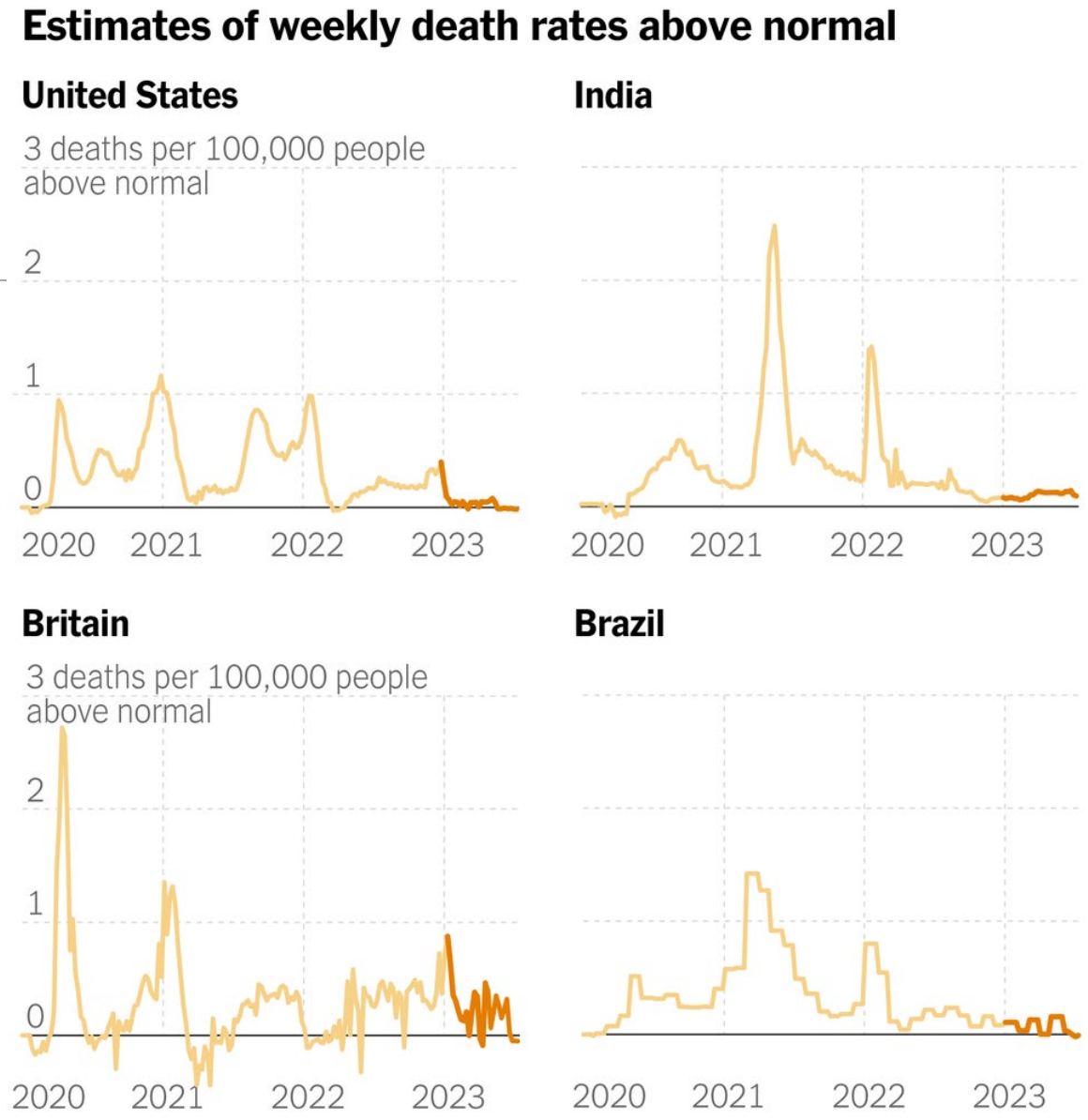
U.S. Population: Total and Excess Deaths, 2020 - 2022



Source: Longevity Holdings, based on CDC data



Source: New York Times



Source: New York Times

Long COVID Mortality Rates Over Time: Hazard Ratio of Infected versus Uninfected

Overall	**2.01**
Days 0 – 90	6.36
Days 91 – 180	1.18
Days 181 – 365	0.92
Days 366 – 730	0.89

Source: *JAMA Intern Med.* Doi 10.1001/jamainternmed.2023.3587; with censoring, weighted

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Long COVID in Non-Hospitalized Patients

- Large UK study comparing 486,149 adults with confirmed SARS-CoV-2 infection to 1,944,580 adults with no recorded evidence
- Symptoms were scored a minimum of 12 weeks after infection
- Risk factors for long COVID also were evaluated

UK Study* - Relative Incidence of Symptoms 12 weeks after infection

	SARS-COV-2 Infected	Uninfected Group	Hazard Ratio
1 symptom	5.6%	4.7%	1.19
2 symptoms	3.6%	2.9%	1.24
≥ 3 symptoms	4.9%	4.0%	1.24

- Relative incidence of SARS-CoV-2 symptoms was greater at 4-12 weeks and greatest at 0-4 weeks, reflecting decreased symptoms with the passage of time

*_Nature Medicine_, Volume 28, pages 1706-1714 (2022)

Symptoms with high relative SARS-CoV-2 incidence after 12 weeks:

Symptom	**Hazard Ratio**
Loss of Smell	6.49
Hair Loss	3.99
Sneezing	2.77
Reduced Libido	2.36

*Source: *Nature Medicine*, Volume 28, pages 1706-1714 (2022)

UK Study* – Long COVID Risk Factors

- Women were 1.52x more likely than men to develop long COVID
- Blacks were 1.21x more likely than whites
- Smokers were 1.12x more likely than never-smokers
- People with BMI > 30 were 1.10 more likely than people with normal weight (BMI of 18.5 – 25)
- Increased age, after adjusting for comorbidities, did not correlate with increased Long COVID (in non-hospitalized patients)

**Nature Medicine*, Volume 28, pages 1706-1714 (2022)

UK Study* - Comorbidities Associated with Increased Risk of Long COVID

Disease	Hazard Ratio
COPD	1.55
Fibromyalgia	1.37
Anxiety	1.35
Multiple Sclerosis	1.26

*_Nature Medicine_, Volume 28, pages 1706-1714 (2022)

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Respiratory System

- Primary target of COVID-19; how it gets into the body
- Symptoms include dyspnea and cough, as well as lung function abnormalities
- 80% of COVID-19 cases confined to upper airway; 20% reach the alveoli – tiny air sacs that move O_2 and CO_2 in and out of blood stream – leading to the formation of pulmonary infiltrates, which often result in pneumonia

Hospitalization and Long-Term Respiratory Symptoms

- Interstitial pneumonia is the leading cause of COVID hospitalization
- Most cases of pneumonia are mild to moderate; progression to severe respiratory failure and acute respiratory distress syndrome (ARDS) occurs in 5% to 10% of cases
- Wuhan, China study found persistent interstititial lung abnormalities in 54% of hospitalized patients 6 months after discharge, dropping to 42% at 1 year, and leveling off to 39% at 2 years
- High prevalence of functional impairment in ICU patients

Long COVID: Symptoms, Disease Incidence & Mortality Risk

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Cardiovascular Impairment

- Involves both acute phase and post-recovery phase
- Conditions include heart attack, myocarditis, cardiomyopathy, tachycardia and heart failure
- Heart injury may be direct from viral infection or indirect from inflammatory response
- Palpitations and chest pain are the most common subjective findings

Post COVID Cardiovascular Disease: TriNetX Global Health Research Network

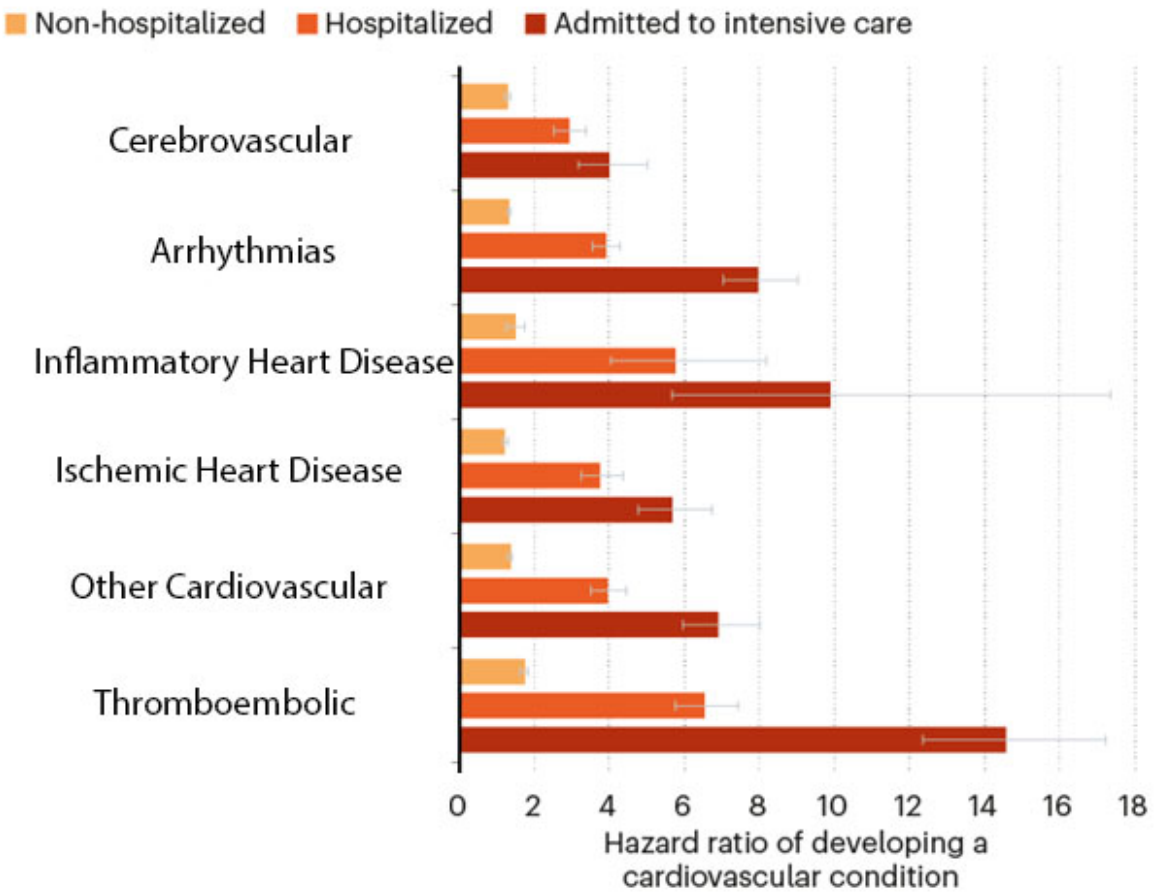
- Drawn from a cohort of 4.1 million unvaccinated people who underwent COVID-19 testing
- Study Period: 30 days to 12 months after COVID-19 test
- 690,892 COVID-19 positive versus 690,892 COVID-19 negative – matched by age, gender, race, socioeconomic status, comorbidities and lab results
- Statistically rigorous study
- COVID positive survivors had 1.6 times the risk of cardiovascular disease and 1.6 times greater mortality risk
- Risk of mortality higher in older (≥ 65) COVID survivors

TriNetX Study: Disease Incidence, COVID-19 Positive vs Negative 12 Months Post Infection

Disease	Hazard Ratio
Myocarditis	4.4
Pulmonary Embolism	2.6
Atrial Fibrillation	2.4
CAD/Heart Attack	2.0
Stroke	1.6
Any Cardiac Outcome	1.6
Mortality	1.6

*Source: www.thelancet.com Vol 53 Month, 2022

Cardiovascular & Cerebrovascular Disease Incidence — Non-Hospitalized vs Hospitalized vs ICU Patients



**Nature Medicine*, 28, 583 – 590 (2022)

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Brain Involvement

- Generally, arises during acute phase; but neurologic/psychiatric symptoms are also frequent during post-COVID phase
- Symptoms include muscle pain, dizziness, headaches, fatigue, loss of smell and taste, brain fog and ataxia
- More than one third of COVID patients develop neurologic symptoms during the acute phase of illness
- Roughly one third of hospitalized patients had dysexecutive syndrome at discharge

History of Neurotropic Respiratory Viruses Resulting in Chronic Brain Disease

- Spanish Flu believed to be the underlying cause of sleeping sickness. Spanish Flu survivors also had a 70% higher risk of Parkinson's disease after 10 years and a 90% higher risk after 15 years*
- Herpes Simplex Virus 1 believed to be associated with molecular processes in Alzheimer's Disease
- One in five survivors of 2002 and 2012 corona virus pandemics reported depressed mood, insomnia, anxiety, irritability and fatigue

**JAMA Neurology* 2021; 78(12): 1461

Longer Term Neurologic Issues

- Multiple studies have found neurologic symptoms after COVID recovery
- Symptoms can be due to inflammatory response or direct damage to cerebral tissue
- Recent Lancet study found long term cognitive deficits greatest for people with COVID symptoms ≥ 12 weeks (-0.22 sd from mean) or hospitalized (-0.31 sd from mean)
- Those reporting full recovery showed no deficits

Dutch Study*: Presence of at least Moderate Neurologic Symptoms 90 - 150 days post-COVID

	COVID-19 Positive	Not Infected	Hazard Ratio
Loss of Smell	8.1%	0.8%	10.1
Dyspnea	3.5%	0.9%	3.9
Muscle Pain	13.5%	8.7%	1.6
Headaches	8.5%	5.5%	1.5
Dizziness	2.4%	2.1%	1.1
All Symptoms	40.7%	29.3%	1.4

*www.thelancet.com Vol 400 August 6, 2022

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Thanks to the Amish: Potentially Good News on the Horizon!

- Genetic mutation discovered in a small Indiana Amish community has been associated with lower PAI-1 protein levels
- Those with lower PAI-1 lived about 10% longer than others in the community and also had less morbidity
- This has led to a new experimental drug to lower PAI-1 levels and hopefully reduce morbidity and mortality in general, and with COVID-19 patients specifically

How PAI-1 Levels Relate to COVID

- High PAI-1 levels are associated with increased arterial blood clotting which is a leading driver of damage to the lungs, heart and brain experienced by COVID patients
- COVID patients tested had PAI-1 levels that were 10 times higher than normal and far higher than levels in non-COVID patients
- By reducing PAI-1 levels, the newly developed drug (TM5614) will hopefully reduce the blood clotting in COVID patients and thereby also reduce both short term and long-term damage to lungs, heart and brain

Underwriting Conclusions

- Risk of Long COVID is significantly greater with hospitalized than non-hospitalized survivors and most significant with ICU patients
- Length of symptoms also matters
- Comorbidities matter – particularly COPD
- Ultimate mortality impact is unknown at this time, and will depend on the trend of disease incidence rates over time
- Deaths from primary COVID trending down; some evidence to suggest that long COVID mortality also trending down

Thank You!

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