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The Importance of Cognitive Health for Pandemic Survival and Future Longevity

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The Importance of Cognitive Health for Pandemic Survival and Future Longevity

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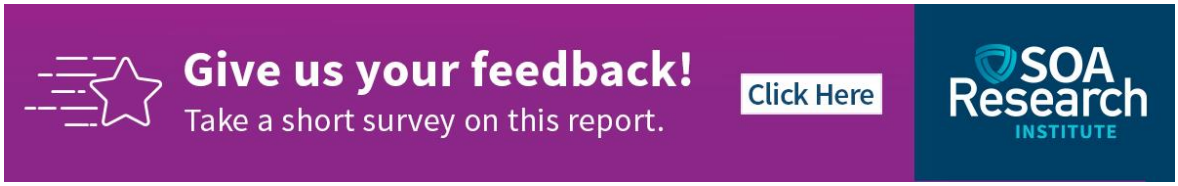

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The Importance of Cognitive Health for Pandemic Survival and Future Longevity

ABSTRACT

Gerontologists have established that successful aging includes maintenance of high cognitive and physical function, as well as sustained engagement in social and productive activities, having close personal relationships with family and friends. COVID-19, with its multiple lockdowns, stay-at-home injunctions and social distancing, has made it hard for the maintenance of successful aging. Furthermore, the numerous and burdensome societal restrictions, necessary for flattening the pandemic curve, have served to increase the prevalence of frailty, which is a biological state of decreased reserve and resistance to stressors, resulting from declines across multiple physiological systems. Cognitive health is important for longevity in general, and for pandemic survival in particular. A public health issue is the large number of those infected who have symptoms of illness months after pandemic recovery. Surveying the long COVID risk horizon, there is societal concern over the widespread prevalence of chronic fatigue and cognitive dysfunction. However, the prospect of nonreversible neuronal injury stands out as the most significant unresolved concern, highlighted by 2022 research findings. Longitudinal studies over a number of years would be needed for a scientific evaluation of the impact of long COVID in a large population. However, nonreversible neuronal injury scenarios would provide valuable insight into the future lifespan legacy of long COVID.

1. COVID-19 AND THE BRAIN

As with influenza pandemics, the COVID-19 pandemic is primarily a respiratory disease, as is evident from the name of the underlying virus, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2. However, COVID-19 affects multiple organ systems, including the kidneys, gastrointestinal tract, heart and brain. Overt cerebrovascular events during acute COVID-19 often occur in those with vulnerabilities to vascular disease, such as advanced age and cardiac disease. Increases in blood markers of vascular inflammation as well as thrombosis and infarction in other tissues can also be found in patients with COVID-19 and stroke. System-wide vascular dysfunction can characterize severe acute COVID-19 and has the potential to contribute to manifestations of organ system failure and systemic inflammation in those most severely ill. Microscopic blood clots in the brain may lead to neurologic symptoms even in the absence of clinically apparent stroke (Spudich and Nath 2022).

It was originally suggested that the underlying virus, SARS-CoV-2, might be neurotropic, that is, capable of invading and replicating inside neuronal cells. Many patients with acute COVID-19 lose their sense of smell, indicative of possible viral interference with the olfactory neurons, which may represent a potential route of entry into the proximal central nervous system. However, analysis of cerebrospinal fluid from living patients with neuropsychiatric symptoms has almost uniformly failed to detect viral RNA (Spudich and Nath 2022).

From a large number of subsequent observations of clinical practice, it seems that SARS-CoV-2 does not directly infect the central nervous system (Butler et al. 2022). One factor affecting the brain is the impact of COVID-19 on blood vessels. Multiple studies have found abnormal clotting, which can cause stroke in patients with severe cases of COVID-19. Autopsies have revealed damage to brain blood vessels, the walls of which have become thinner and may leak proteins, so triggering an immune response.

The emerging neurobiology from studies of cerebrospinal fluid and brain tissue places emphasis on inflammatory effects of COVID-19, responsible for many of the neuropsychiatric complications of the illness. Immune activation and inflammation within the central nervous system are the primary drivers of neurologic disease in acute COVID-19.

Studies of cerebrospinal fluid from people with COVID-19 have found changes in immune cells, including a higher production of chemicals that can be toxic to brain cells. Understanding of the mechanisms driving these immune responses may involve drawing a parallel with the body's response to chemotherapy (Hamzelou 2022). Patients with cancer who receive chemotherapy may mount an inadequate immune response to COVID-19 vaccinations.

Even mild cases of COVID-19 may lead to a loss of cognitive function and a reduction in brain volume equivalent to at least one year of normal aging. This is a recent finding from brain scans taken both before and, on average, 4.5 months after coronavirus infection (Douaud et al. 2022). A key open question is whether this brain tissue damage resolves in the longer term.

1.1 COVID-19, THROMBOSIS AND STROKE RISK

A large Swedish thrombosis study was conducted by Katsoularis et al. (2022) of a million people who tested positive for SARS-CoV-2, with about four million matched control participants. They found an increased risk of a first deep vein thrombosis up to three months after COVID-19; pulmonary embolism, that is, a blood clot in the lungs, up to six months; and a bleeding event up to two months, with the risk of pulmonary embolism in the acute phase being especially high. For pulmonary embolism, there were 1,761 cases, of

whom 281 (16%) died. This contrasts markedly with 169 cases among the fourfold more numerous control participants, of whom 22 died.

The association between COVID-19 and risk of venous thromboembolism (VTE), that is, blood clots in veins, has been studied by Tong, Yang, and Merritt (2022) among almost a quarter of a million Medicare beneficiaries, aged 65 and older. All had been hospitalized with an acute ischemic stroke between April 2020 and November 2021. VTE was most common (4.4%) among those who had been hospitalized with COVID-19, was less common (3.1%) among those with COVID-19 who did not need hospitalization, and least common (2.6%) among those with no history of COVID-19. Underlying conditions of stroke patients can overlap with VTE risk factors, such as prolonged immobility and obesity.

Cognitive impairment and memory loss are common after a stroke. Between 30% and 80% of all stroke survivors exhibit some form of cognitive impairment, and a substantial fraction (Al-Qazzaz et al. 2014) of stroke patients develop dementia within a year of stroke onset. Poststroke dementia, particularly vascular dementia, reflects the vascular risk factors that are most correlated with cerebral vascular disease.

1.2 COGNITIVE RESERVE

Reserve is a characteristic of brain structure and function that moderates the relationship between brain pathology and its clinical manifestation. The concept originated to explain differences in clinical outcomes between people with similar degrees of brain pathology or damage, particularly Alzheimer's disease.

The role of cognitive reserve as an emerging concept in stroke recovery has been assessed by Rosenich and Hordacre (2020). With the global incidence of stroke increasing, and set to rise with an aging population, cognitive reserve shows promise in reducing the burden of disability. The higher an individual's cognitive reserve is, the better the preservation of neural resources and cognitive and behavioral abilities. Compensatory mechanisms of stroke recovery may be influenced by cognitive reserve.

Cognitive reserve is an active process, along with neural compensation or neuroplasticity, that may moderate the manifestations of brain pathology and injury. Flexibility and adaptability of cognitive networks allow the brain to resist the effects of age- or disease-related changes. Neural reserve and compensation operate to utilize and optimize cognitive-processing strategies to maximize performance when neural networks are compromised by neuropathology such as stroke, and recruit alternate neural networks not normally used to compensate for neurologic disruption.

Cognitive reserve describes resistance to impairment in cognitive processes, such as memory, reasoning and attention (Woo and Bruce 2014). It may be thought of as an asset that can be accumulated throughout life, education, work or leisure activities involving physical or cognitive exertion. This asset can be used throughout life to maintain well-being in response to stress and environmental challenges. Cognitive reserve and resilience are key to preserving cognitive health. Those having higher cognitive reserve can withstand injury longer (Rosenich and Hordacre 2020).

Cognitive dysfunction following COVID-19 infection is a notable component of long COVID. Potential biological mechanisms contributing to cognitive impairment include hypoxia, hyperinflammation, hypercoagulability, blood brain barrier disruption, uremia, septic encephalopathy and autoimmune mechanisms. Sociodemographic factors also modulate cognitive outcomes and recovery following hospitalization (Valdes et al. 2022).

In a study conducted in New York City six months after COVID-19 hospitalization, Valdes et al. (2022) found a higher likelihood of cognitive impairment among patients with fewer years of formal education,

consistent with a well-established relationship between low educational attainment and cognitive impairment. Social and economic disparities contribute to observed cognitive differences. Patients with less education tend to achieve lower scores in attention, memory and executive function. Education builds cognitive reserve, which helps sustain a larger degree of brain pathology before cognitive impairment becomes apparent. Long-term monitoring would be needed to assess the likelihood of progression to other neurodegenerative disorders.

1.3 COGNITIVE HEALTH AND FRAILTY

Frailty is a condition characterized by weakness, progressive decline in physiologic function and diminished strength, and reduced resilience to stressors, with an increased risk of adverse outcomes. An increase in frailty is associated with a decrease in resilience, which represents a state of adequate reserve and resistance to stressors.

The functional state and frailty of those aged 65 years or older can be determined on the Clinical Frailty Scale (CFS). Those on CFS levels 1 to 3 are fit; those on CFS level 4 are vulnerable, slowing down and being tired during the day. The higher levels correspond to states of increasing frailty. Those on CFS level 5 are mildly frail, needing help with high-order daily activities such as finances, transportation, housework and medication. Those on CFS level 6 are moderately frail, needing help with all outside activities and with housekeeping. Those on CFS level 7 are severely frail and are completely dependent for personal care because of physical or cognitive issues. Beyond these seven levels, two additional levels correspond to those very severely frail, unable to recover even from a minor illness, and the terminally ill with a life expectancy less than six months.

As a consequence of decline in multiple physiological functions, older and frail people are at increased risk of adverse outcomes when they have an acute illness. Frailty is related to loss of muscle mass, a poor nutritional status and underlying inflammation, all of which predispose an individual to a poorer COVID-19 immune response.

Frailty increases with age and is related to multimorbidity. Various European studies (Tehrani et al. 2021) have found CFS to be strongly associated with death in older patients with COVID-19, and that CFS level appears to be a better predictor of outcomes in adult hospitalized patients with COVID-19 than age and comorbidities. Frail patients have a significantly higher incidence of admission to intensive care, compared with fit patients (Sablerolles et al. 2021).

Cognitive health is an integral part of frailty avoidance, maintaining independence of daily living, and making optimal personal health and well-being decisions. In the absence of adequate cognitive health, any activity is liable to lead to some misjudgment, without due attention and assistance from others. This underlines the importance of having a social support network in resilient aging. Long COVID, although not unique to people who have been living with frailty, might serve to prompt closer attention to specific clinical measures thus far not studied.

Frailty is generally characterized by issues such as reduced muscle strength and fatigue. Around 10% of people over 65 live with frailty. It can be envisioned as a disorder of energy balance and availability, which mimics the exhaustion of the metabolic reserves of an individual. The long-term deleterious effects of the pandemic might negatively affect the accumulation of the biological reserves of an individual. Survivors of the pandemic might thus have a high prevalence of frailty, which would be detrimental to longevity. Among the frail are those with dementia, who are often multimorbid and have low functional reserves (Rolland et al. 2022).

2. COVID-19 AND NEUROLOGICAL DISEASE

The neurological manifestations of COVID-19 are recognized as an important component of the disease, even in cases without respiratory symptoms (WHO 2021). The neurological manifestations range from mild to critical and can present both during and after acute COVID-19 infection. Reported neurological signs and symptoms in the acute phase include headache, dizziness, impaired taste or smell, delirium, stroke, seizures and coma.

Regarding medical interventions, some COVID-19 medications used, such as corticosteroids, may have neurological side effects that can manifest and persist during the acute or postacute phase of illness (Joshee et al. 2022). In accordance with WHO recommendations, systemic corticosteroids, including dexamethasone, have been used for patients with severe and critical COVID-19, but not in patients with nonsevere COVID-19.

2.1 DEMENTIA

Those suffering from dementia face daily challenges to their well-being and are especially vulnerable because of their dependence on others for their survival. With more than 50 million people having dementia globally, dementia is the pandemic of an aging society. The arrival of a global infectious disease pandemic creates an unprecedented perfect storm crisis. COVID-19 is the greatest infectious disease pandemic since the influenza pandemic of 1918, which emerged only about a decade after the scientific discovery of dementia.

Behavioral and psychological symptoms of dementia cover a wide range, including depression, anxiety, agitation and psychosis, and may be exacerbated under COVID-19 restrictions (Gedde and Husebo 2022). For those with dementia, COVID-19 has increased the stress of everyday living, with the need to comprehend, execute and remember basic public health guidelines on minimizing infection spread. Under the intense pressure of COVID-19, nonessential health services have been cut back, affecting essential visits by dementia patients for laboratory tests and neuroimaging, and delaying the diagnosis of new onset dementia and the monitoring of rapidly progressive dementia.

To insulate care home residents from infection, strict confinement measures were introduced during the pandemic. These included a ban on visitors and group activities and isolation within one room. In China staff in care homes suffered from exhaustion and burnout after just a month of lockdown of facilities (Wang 2020).

Many older people in western countries live at home alone and may become withdrawn and feel abandoned. Isolation and stimulus deprivation are antithetical to what is therapeutically desirable for someone living with dementia. Loneliness and social isolation are risk factors for the development and progression of cardiovascular disease and functional decline, as well as dementia. Before the pandemic, the U.S. prevalence of loneliness and social isolation was estimated to range from 40% to 60% (Curelaru et al. 2021).

Lack of social and sensory stimulation increase vulnerability to boredom and worsen neuropsychiatric symptoms, increasing apathy, anxiety, agitation and depression, as well as hastening cognitive decline, with deteriorating concentration, memory and communication. Those with mild dementia and mild cognitive impairment have benefited from television-based assistive integrated cognitive stimulation services (Paplikar et al. 2022). Maintenance of activities such as exercise and hobbies can alleviate apathy. Anxiety can be relieved by preserving daily routines. Interventions aimed at supporting people with dementia should be multifactorial, involving both cognitive and physical activities, including aerobic and nonaerobic

exercise (Curelaru et al. 2021). In an Asian dementia study, it was found that animal-assisted interventions improved well-being, cognitive abilities, affective and behavioral aspects, decreasing depression and shortening stays in institutions (Batubara et al. 2022).

2.2 BRAIN CHANGES OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60% to 80% of cases. AD is a slowly progressive brain disease that begins many years before symptoms emerge. The hallmark pathologies of AD are the accumulation of beta-amyloid plaques outside neurons in the brain and twisted strands of tau proteins inside the neurons. These changes are accompanied by the death of neurons and damage to brain tissue.

Plaques and smaller accumulations of beta-amyloid, called oligomers, may contribute to the damage and death of neurons by interfering with the neuron-to-neuron communication at synapses. Inside neurons, tau protein tangles block the transport of nutrients essential for neuron survival. Beta-amyloid plaques may begin accumulating before abnormal tau proteins, and increasing beta-amyloid accumulations are associated with subsequent increases in these proteins. Other brain changes linked with AD include inflammation and decreased brain volume. Such atrophy occurs because of cell loss. Toxic beta-amyloid accumulation and tau proteins activate cells that attempt to clear the toxic proteins. Partial clearance may lead to chronic inflammation.

Normal brain function is further compromised by reduction in ability to metabolize glucose. These brain changes are biomarkers of AD. The majority of the people with the brain changes of AD also have the brain changes of a second cause of dementia. Such mixed dementia is common at advanced ages.

There is an AD continuum with three phases: preclinical AD, mild cognitive impairment due to AD and dementia due to AD, which can be mild, moderate or severe. The length of each phase of the continuum is influenced by age, genetics and gender. When biomarker tests indicate that a person with mild cognitive impairment has the brain changes of AD, that person is deemed to have mild cognitive impairment due to AD.

In the preclinical AD phase, people have measurable brain changes that indicate the earliest signs of AD, but they have not yet developed symptoms such as memory loss. Examples of AD biomarkers include abnormal levels of beta-amyloids as shown on PET scans. When the early changes of AD occur, the brain adjusts so as to allow for normal cognitive function.

Not all people having evidence of Alzheimer's related brain changes develop symptoms of mild cognitive impairment or dementia due to AD. Indeed, some people have beta-amyloid plaques at death without having had cognitive problems. This is an enigma of AD, which is part of the puzzle of finding effective AD treatments.

2.3 EXCESS DEMENTIA DEATHS ATTRIBUTABLE TO COVID-19

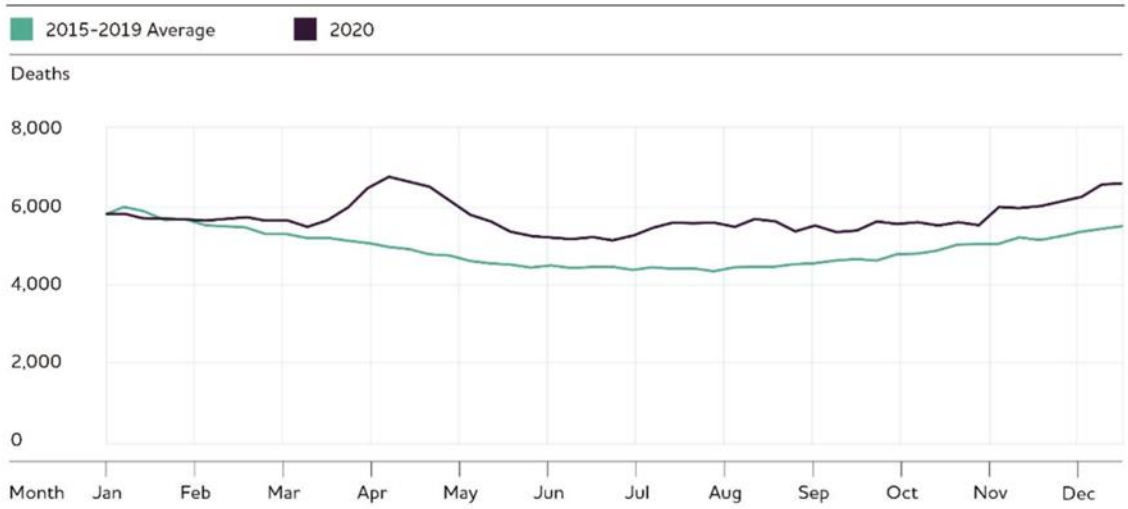
Data from the CDC indicate that in 2020 there were 44,729 more U.S. deaths from AD and other dementias in 2020 (17% more than expected), compared with the five-year average (see Figure 1). For 2021 the corresponding additional number of U.S. deaths from AD and other dementias compared with the five-year average was at least 11,000 (Alzheimer's Association 2022).

Those suffering from dementia have been among the most vulnerable groups in society during the pandemic. Shielding from social contact has not been such a safe option because of the negative psychological and sociological impacts of isolation.

Furthermore, in 10% of death certificates listing COVID-19 as the primary cause of death, AD was also listed as one of the multiple causes of death. Among people aged 85 or older who died of COVID-19, AD or another dementia was listed as a multiple cause of death on 24% of death certificates.

Figure 1

U.S. DEATHS DUE TO DEMENTIA IN 2020, COMPARED WITH PREVIOUS YEARS.



Alzheimer's Association (2021).

In CDC official statistics, if a death certificate lists AD as the underlying cause of death, then the deceased is deemed to have died from AD. Those with experience of looking after AD patients are all too familiar with the dangerous and hazardous pathways down which AD can lead; just forgetting to take essential medication can be fatal. COVID-19 is just another of these pathways; forgetting to take hygiene or social distancing precautions can be fatal. It was found that 4.72% of those in the COVID-19 cohort who had encephalopathy received a first diagnosis of dementia within six months.

2.4 DEATHS FROM ALZHEIMER'S DISEASE

The remarkably rapid success of mRNA vaccine development for COVID-19 renews optimism over the potential for great advances in medical science. But even with outstanding dedicated scientists, serendipity and good fortune have always played a significant part in medical progress over recent decades, including COVID-19 vaccine development. Counterfactually, had the pandemic emerged just two years earlier, BioNTech's board would not have entertained the idea of building a vaccine (Miller 2021).

Life actuaries and other longevity modelers making future projections of U.S. population mortality improvement need to scan the research horizon to estimate the potential reduction in mortality associated with the future availability of effective AD treatments. This can be achieved through a counterfactual analysis, imagining an alternative realization of history. A counterfactual analysis can estimate how many deaths might be indirectly attributable to AD.

This is a lengthy and painstaking undertaking, requiring a longitudinal study of thousands of seniors, covering a period of several decades from the 1990s. U.S. longevity analysts are fortunate that there have been two diligent longitudinal cohort studies: the Religious Orders Study of older Catholic nuns, priests and brothers from across the U.S. and the Rush Memory and Aging Project of older persons living in Illinois (Bennett et al. 2018). Both studies required brain and tissue donations, with the autopsy rate being almost 90%. Accordingly, the ascertainment of mortality was mostly complete and dates of death reliable.

The pooled analysis included 2,566 persons who did not have dementia at baseline. Over an average 8.0 years of follow-up, AD was diagnosed in 21.8% of the participants. The mean age of incident AD diagnosis was 86.53 years. Also during follow-up, 72% of those who developed AD died, as did 34.5% of those who did not develop AD. The median survival time from diagnosis to death was 3.8 years overall. Importantly, in persons aged 75–84, the rate of mortality was more than four times higher after a diagnosis of AD; in persons aged 85 and older, the rate of mortality was nearly three times higher.

An associated population-attributable risk analysis (James et al. 2014) estimated that as many as 503,000 deaths in Americans aged 75 and older were attributable to AD in 2010. This would elevate AD to being the third leading cause of death after heart disease and cancer. This is a factor of six greater than the 84,000 deaths that the CDC attributed to AD in 2010. In 2019 official death certificates recorded 121,499 deaths from AD, an increasing trajectory further advanced by COVID-19. In 2020 the number increased 10.5% to 134,242.

The number of Americans aged 65 or older with AD is projected to reach 12.7 million by 2050 in the absence of AD medical breakthroughs (Alzheimer's Association 2022). By 2050 the population of Americans aged 65 or older is projected to grow from 58 million to 88 million. The incidence rate of Alzheimer's appears to be declining (ibid.), which has been attributed to improvements in Alzheimer's risk factors. It is unknown how COVID-19 will affect the U.S. prevalence of AD (ibid.).

A future effective treatment for AD should leverage a degree of mortality improvement very much greater than indicated just by the AD mortality rates. Consequently, in setting health care priorities, AD research should be well supported, as COVID-19 vaccine development has been in 2020 and 2021. With the large number of latent deaths already attributable to AD, there is further concern over the prospect of long-term neurological consequences of COVID-19. AD research has been slowly making progress. On January 6, 2023, the U.S. Food and Drug Administration approved Leqembi for the treatment of AD. Leqembi is the second of a new category of medications approved for AD that target the fundamental pathophysiology of the disease.

2.5 COVID-19 AND PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting approximately 6 million people worldwide. Symptomatic treatments are available, but these have limited effect as the disease progresses. The annual cost of PD to individuals, families and the U.S. government is about $52 billion (McFarthing et al. 2021).

In the 1960s studies of those who were born between 1888 and 1924, who were young at the time of the 1918 influenza pandemic, indicated that they had been two to three times more likely to develop PD at some period, compared with those born at different times. Many of the patients exhibited viral encephalitis. This finding supplements other evidence from survivors of outbreaks of HIV, West Nile virus, Japanese encephalitis, Western equine virus and Epstein-Barr virus. Each of these viruses is capable of crossing into the brain, with the potential to damage the structures controlling movement coordination, and starting the degeneration process leading to PD.

Since the coronavirus pandemic emerged, numerous case studies have been done of patients who had COVID-19 and who developed acute Parkinsonism, with symptoms such as tremors, muscle stiffness and impaired speech. As a caveat, cases of acute Parkinsonism could be those already in the early stages of PD, for whom COVID-19 infection accelerated or exposed the symptoms. However, Rao et al. (2022) have closely assessed three specific cases of post-COVID Parkinsonism who had no features of Parkinsonism, nor any history suggestive of Parkinsonism, before the onset of COVID-19. Albornoz et al. (2022) have found that the SARS-CoV-2 virus activates the same inflammatory response in the brain as neurological diseases such as Parkinson's. According to this study, the spike protein of the SARS-CoV-2 virus was enough to start the inflammatory process, and although all cells reacted strongly to this virus across all brains examined, the process was further aggravated in those with existing proteins in the brain linked to Parkinson's.

In addition to direct brain injury, the possible pathophysiology of postinfectious Parkinsonism includes neuroinflammation and hypoxic brain injury in the context of encephalopathy. As with the 1918 influenza pandemic, it is conceivable that decades after the arrival of COVID-19, a higher PD incidence may emerge as a future health span and lifespan concern. There is scope for optimism over the PD treatment horizon. Despite the coronavirus pandemic, which forced the withdrawal of two PD trials, in 2020 considerable activity took place in the clinical development of novel and improved drug-based therapies for PD. The agents investigated included both those that alleviated the features of the condition and those that attempted to address the underlying biology of PD. As of February 2021, 19 agents were in 28 trials in phase 3 (McFarthing et al. 2021). Looking through the bright lens of COVID-19 vaccine R&D, which resulted in the rapid development of multiple effective vaccines, hope for an effective PD treatment is more than an expression of human cognitive bias.

2.6 COVID-19 AND DELIRIUM

Delirium originated as a diagnosis many centuries ago, and its definition has evolved to its current usage to describe acute fluctuations in attention, awareness or orientation. In the U.S. the annual health care costs for delirium are $152 billion (Arnold 2020).

The onset of delirium is often precipitated by influences on preexisting chronic risks (e.g., infection in an AD patient). Approximately 40% to 60% of people with dementia in residential care facilities experience behavioral and psychological symptoms such as agitation and psychosis. A study in Italy (Poloni et al. 2021) found a high prevalence of delirium as an onset manifestation of COVID-19 in elderly residential patients with dementia. Residents with delirium-onset COVID-19 had higher mortality than those who did not manifest delirium at onset (Wang 2020).

Beyond age and frailty, poor prognosis in older adults with COVID-19 is associated with delirium. This clinical predictor for poor prognosis is a disorder with a fluctuating course of altered consciousness or cognitive function, which commonly affects hospitalized older adults. Altered consciousness (e.g., confusion, delirium, stupor and coma) as a neurological consequence of COVID-19 occurs in nearly 15% of hospitalized COVID-19 patients. The prevalence increases with age. For those critically ill, the proportion rises to more than half (Arnold 2020).

Altered consciousness may depend on the direct effects of coronavirus infection, viral invasion of the central nervous system and other factors. Neurotransmitter imbalance, pro-inflammatory cytokines, tissue hypoxia and sleep deprivation are factors in the pathomechanism of delirium. Comorbidities such as excessive Body Mass Index, hypertension, cardiovascular and chronic kidney disease raise a patient's risk of admission to an Intensive Care Unit.

Delirium may be caused by the impacts of acute respiratory distress syndrome. Poor communication with health care staff in protective equipment may be detrimental to mental state assessment and delirium diagnosis. Another potential mechanism is the development of a secondary encephalopathy through the hyperactivation of immune response and cytokine storm. Systemic inflammatory response, hyperactivity, agitation and restlessness are other neuropsychiatric manifestations linked with delirium. When the brain is unable to compensate for a stressful situation, as with severe COVID-19, delirium easily occurs (Arnold 2020).

3. LONG COVID

A sizeable proportion of those who have recovered from COVID-19 may experience some lingering symptoms, which may last for months. The most common of these are shortness of breath, cognitive dysfunction and fatigue. But there are numerous other symptoms, including anxiety, depression, muscle aches and loss of smell and taste. These are aggregated as Post-Acute Sequelae of SARS-CoV-2 infection (PASC). Long COVID, as PASC is popularly known, is the first patient-identified illness rooted in a social media network; an American patient who became ill in March 2020 initiated a Facebook group that she named Survivor Corps (Horwitz et al. 2022). As the pandemic continued, it became clear that Survivor Corps members were struggling with symptoms for weeks and months (Khullar 2021).

Cognitive impairment appears to persist long after COVID-19. Examination of individuals (154,068 diagnosed with COVID-19 from March 2020 to January 2021 compared to 5,638,795 contemporary controls and 5,859,621 historical controls) in the U.S. Veterans Affairs national health care database revealed elevated risk of cognitive and memory disorders (hazard ratio 1.77) and of a diagnosis of Alzheimer's disease (hazard ratio 2.03) in the 12 months following SARS-CoV-2 infection (Monje and Awasaki 2022). Risk of cognitive disorders was evident in all subgroups analyzed regardless of age, sex, obesity, hypertension, smoking history or area deprivation index (Xu, Xie, and Al-Aly 2022).

Cohort studies based on U.S. veterans health care databases also provide evidence that the one-year burden of cardiovascular disease in survivors of acute COVID-19 is substantial (Xie et al., 2022). The focus here is on neurological issues. Individuals who have recovered from COVID-19 perform worse on a range of cognitive tests than would be expected given their age and demographic profiles. For those who had ventilator treatment, the score reduction was worse than the average 10-year decline (Hampshire et al. 2021). Severe COVID-19 illness is associated with significant objectively measurable cognitive deficits that persist into the chronic phase (Hampshire et al., 2022).

A high rate of failed neuropsychological tests among the elderly has shown that COVID-19 is capable of eliciting persistent measurable neurocognitive alterations, particularly in the areas of attention and working memory (Lauria et al. 2022). These effects, which degrade basic social and living skills, may represent an early stage of cognitive impairment in the elderly and give rise for concern about an increased prevalence of dementia among the elderly.

Between 10% and 30% of those recovered from COVID-19 suffer from slow or sluggish thinking, known as brain fog (Fong 2022). For the U.S., with more than 100 million cases as of January 2023, there may be between 10 and 30 million Americans who have, or have had, long COVID. Based on a population survey of U.S. adults conducted in mid-2022, approximately 19 million reported long COVID (Robertson et al. 2022).

A deeper mechanistic understanding of the pathophysiology of long COVID in general and neuro-COVID in particular will be required to develop effective therapies to ease the suffering of millions of people affected by the often-debilitating long-term consequences of COVID-19 (Monje and Awasaki 2022).

3.1 NEUROLOGY

Spudich and Nath (2022) consider the most likely cause of brain fog to be inflammation created by immune response. Neurological complications are often among the first symptoms of SARS-CoV-2 infection and can be the most severe and persistent. They can also affect people of all ages and with varying degrees of disease severity.

To improve understanding of the neuropathogenesis, a study of brain pathology has been undertaken in nonhuman primates (Rutkai et al. 2022). Neuroinflammation has been found in nonhuman primates with SARS-CoV-2 infection. Pathological investigation found severe brain inflammation and injury consistent with reduced blood flow or oxygen to the brain, including neuron damage and death. This research provides important insight into the mechanisms underlying central nervous system disease, observed even in the absence of severe respiratory disease, and may suggest vascular leakage and hypoxic brain injury is a common complication of COVID-19. Neuronal degeneration may indicate that nonreversible neuronal injury may be significant for those suffering from long COVID. This would suggest the need for long-term neurological follow-up of persistently symptomatic convalescent patients and underlines the importance of establishing benchmarks for long COVID prevalence.

3.2 LONG COVID PREVALENCE

In the U.K., monthly national self-reporting surveys allow regular updates of long COVID prevalence, thus providing an observational window into the evolving long COVID risk. As of January 2023, an estimated 2 million people living in private households in the U.K. (3% of the population) self-reported experiencing long COVID symptoms persisting for more than four weeks after the first suspected infection. Of these, 1.8 million were first infected at least 12 weeks before, 1.2 million at least one year before and 687,000 at least two years earlier (ONS 2023). Of those with self-reported long COVID, 612,000 (31%) first had COVID-19 before Alpha became the main variant, 251,000 (13%) in the Alpha period, 337,000 (17%) in the Delta period and 702,000 (36%) in the Omicron period. As a proportion of the U.K. population, the prevalence of self-reported long COVID was greatest in people aged 35 to 69 years, females, people living in more deprived areas, those working in social care, those aged 16 years and over who were not working and not looking for work, and those with another activity-limiting health condition or disability.

Using TriNetX electronic health records of over 236,000 COVID-19 patients, mainly American, Taquet et al. (2021) have assessed the risks of major neurological and psychiatric conditions in the six months after a COVID-19 diagnosis. They showed that both incidence and hazard ratios were greater in patients who required hospitalization or admission to intensive care, and in those who had encephalopathy during the illness, compared with those who did not. This is a robust demonstration of increased risk of neurological and psychiatric disorders in the six months after a COVID-19 diagnosis. Long COVID prevalence is socially segmented; it has been found to affect more severely older people, ethnic minorities and women.

Some specific neurological diagnoses are of special note. The risk of cerebrovascular events was elevated after COVID-19, with the incidence of ischemic stroke rising to almost one in ten in patients with encephalopathy. Furthermore, 2.66% of those aged 65 and above, and 4.72% who had encephalopathy, received a first diagnosis of dementia within six months of having COVID-19. Of the COVID-19 patients, 12.8% had developed first cases of neurological and psychiatric outcomes by six months. Such outcomes include mood, anxiety, psychotic and nerve disorders, which tend to be chronic or recurrent and could be very relevant for morbidity claims of disability insurance.

In a Chinese study for a cohort of COVID-19 survivors discharged from a Wuhan hospital, 12% had not returned to work after a year (Huang et al. 2021). This degree of long-term disability would have an impact

on disability covers. Indeed, according to Regenauer (2022), health and disability covers have the highest exposure to long COVID, followed by critical illness, long-term care and death covers.

As a mitigation of the long COVID risk, patients who are infected after full vaccination are 50% less likely to develop long COVID, according to a U.K. Health Security Agency review of evidence from 15 U.K. and international studies (Mahase 2022). Also, regarding the spread of the milder Omicron variant, scientists have reason to be cautiously optimistic and yet remain vigilant.

3.3 COGNITIVE REHABILITATION

From the prevailing global evidence, in many cases brain fog disperses on its own. Reviewing the experience of HIV, once the virus is controlled, cognitive issues resolve (Yong 2022). Without just waiting in hope for such an eventual natural resolution, cognitive rehabilitation therapy for long COVID may help speed up cognitive improvement.

As with other types of brain dysfunction, neuroplasticity offers the prospect of rehabilitation. The ability of neural networks in the brain to change, adapt and strengthen can be utilized in therapies to combat brain fog. This neuroplasticity approach has been effective with some other viral infections.

Cognitive rehabilitation is akin to physical therapy for the brain and has been successful with traumatic brain injuries, strokes and concussion. Therapists help develop metacognitive strategies aimed at making the thinking process more visible. Language training, for example, is known to help patients recover from traumatic brain injury. The process of learning a language enhances neuroplasticity and strengthens the brain. App-based language learning may provide similar benefits as brain training in improving executive function in seniors (Meltzer et al. 2021). But there is less impact on processing speed, which is an outcome of special computer brain-training exercises brought to public attention by the veteran NFL quarterback Tom Brady.

3.4 COVID-19 FATIGUE

Fatigue is one of the most reported symptoms during and after COVID-19 infection. As well as for moving around, energy is needed for mental concentration, attention, problem solving, talking and making decisions. Tiredness is common when fighting any infection and is an early symptom of COVID-19, often occurring within a week of illness, and lasting for five to eight days, but may persist up to two weeks or much longer.

In older people, but also in the context of COVID-19 infection, it is difficult to differentiate fatigue from mood disorders, depression and sleepiness. COVID-19 is characterized by increased production of pro-inflammatory cytokines, which can result in a cytokine storm. Myalgias, muscle loss and weakness are frequently observed in COVID-19 patients and might persist for several months after infection. This can partly be explained by direct virus entry into the muscle cells via the ACE2 receptor, determining local inflammation.

In every cell of the body, mitochondria are responsible for producing energy. If cells do not have enough energy, the tissues or organs may not function properly. Augmented inflammatory response might lead to mitochondrial dysfunction, further exacerbating muscle loss. Chronic low-grade inflammation and mitochondrial dysfunction are observed in some conditions that are characterized by the presence of fatigue and have been evoked as hallmarks of aging. Thus, if a significant proportion of those infected with COVID-19 suffer long-term fatigue, this may impact on longevity. The work of Glynn et al. (2022) has established that perceived physical fatigability is a robust indicator of all cause mortality in older adults.

Obesity is a recognized risk factor for increased morbidity and mortality from COVID-19. It is one of the key risk factors associated with poor COVID-19 outcomes and has been repeatedly associated with fatigue. The underlying mechanism is the release of pro-inflammatory cytokines by adipose tissue (Azzolino et al. 2022). From a cohort study in an Italian hospital, Vimercati et al. (2021) observed that being overweight and obesity could lead to prolonged symptoms after resolution of COVID-19 infection.

3.5 LONG COVID SCENARIOS FOR NONREVERSIBLE NEURONAL INJURY (NRNI)

In contrast with SARS, a high degree of asymptomatic transmission has been the crucial hidden characteristic of SARS-CoV-2, which has facilitated its global pandemic spread and hampered rigorous public health control efforts, notably with the Omicron variant, even in China. Another hidden dangerous characteristic of the coronavirus could be the latent long COVID affliction of Nonreversible Neuronal Injury (NRNI). Concern about this is already adding impetus to global COVID-19 vaccination campaigns.

Observations of neuroinflammation and neuronal injury in acute COVID-19 cases may accelerate or trigger future development of neurodegenerative diseases such as AD (Spudich and Nath 2022). Investigations including longitudinal studies with neurological and psychiatric assessments, and rigorous host-pathogen studies of nervous system interactions, have the potential ultimately to elucidate the risk over the coming years. This type of long-term risk ambiguity, with the need for clarifying longitudinal studies, is characteristic of longevity modeling in general.

Surveying the long COVID risk horizon, concern exists over the widespread prevalence of chronic fatigue and cognitive dysfunction. However, the prospect of NRNI stands out as the most significant unresolved concern, highlighted by 2022 research findings. For example, Rutkai et al. (2022) have used nonhuman primates as an animal model for understanding the neuropathogenesis and potential long-term consequences of infection. The development of animal models is critical for progressing this understanding rapidly. Neural degeneration observed in their study indicates that NRNI may be significant to individuals suffering from long COVID, and that long-term neurological follow-up is needed for persistently symptomatic convalescent patients.

Population vulnerability to NRNI is being explored by the medical research community and will vary according to a range of individual characteristic variables, as indicated in Table 1. Data to comprehend this vulnerability are progressively being gathered. Using data from Wuhan hospitals from February to April 2020, a postinfection cognitive impairment study (Liu et al. 2021) already identified the following as risk factors: older age, comorbidities, lower education level, severe COVID-19, intensive care unit admission and delirium. Higher resolution of cognitive vulnerability was achieved with the much larger study of Taquet et al. (2021) with 150 times as many patients, mainly from the U.S. For any first outcome of 14 neurological or psychiatric outcomes (intracranial hemorrhage, ischemic stroke, parkinsonism and others) within the six months after a confirmed diagnosis of COVID-19, Taquet et al. found prevalence percentages of 11.51% for patients without hospitalization, 15.29% for patients with hospitalization and 25.79% for patients with intensive care and/or therapy admission.

Existing datasets such as these still lack adequate size and statistical power for gauging the extent of NRNI vulnerability for specific population groups, and it will take a major coordinated research effort over the coming years to clarify vulnerability for diverse combinations of this sizeable 7×6 matrix. However, enough knowledge is available to develop a basic risk ranking for prioritizing actuarial and public health focus.

In particular, valuable actuarial insight can be gained from considering some specific long COVID NRNI scenarios. Already, it is apparent from existing research findings (e.g., Taquet et al. 2021) that some obvious high-risk groups, such as seniors, have significant comorbidities and spent time in intensive care.

Some other, medium risk groups, such as seniors, spent weeks in the hospital with COVID-19. These high- and medium-risk groups should continue to remain under medical surveillance for future neurological issues.

But large numbers of healthy middle-aged people contracted COVID before vaccination and had only mild symptoms, not requiring hospitalization. In the U.S., 20 million cases were reported by the beginning of 2021, when the vaccine rollout began. Already it is known that after a year a nontrivial percentage of many people with mild symptoms suffer from chronic fatigue, preventing them from living their normal lives. If even a small percentage of this group were to succumb to NRNI, it would pose an important actuarial and public health issue. Some long COVID NRNI scenarios could focus on segments of this group that would be most vulnerable, that is, those with some comorbidities as well as low cognitive reserve. The emergence of COVID-19 has highlighted the importance of cognitive resilience for longevity.

Table 1
MATRIX OF POPULATION GROUPS POTENTIALLY SUSCEPTIBLE TO NRNI

Age Range	30-40	40-50	50-60	60-70	70-80	80+
Comorbidities	None	Obesity	Diabetes	Hypertension	Cardiovascular	Cerebrovascular
Cognitive reserve	Very high	High	Good	Moderately low	Low	Very low
COVID variant	Original	Alpha	Beta	Delta	Omicron	BA.2
Hospitalization period	None	Up to one week	Two weeks	Three weeks	One month	Several months
Intensive care period	None	Few days	One week	Two weeks	Three weeks	One month
Vaccination	None	Pfizer	Pfizer + booster	Moderna	Moderna + booster	Janssen

4. COGNITIVE RESILIENCE AND LONGEVITY

Only in the 21st century has the role of positive experience and functioning in well-being and resilience been adequately appreciated. In the 20th century, psychological models focused primarily on negative aspects of human experience and functioning, along with a focus on reducing the negative rather than promoting the positive. However, positive and negative affect might be regarded as partly orthogonal dispositions, reflecting underlying neural networks of resilience. Thus, clinical depression is marked by a paucity of positive affect and associated deficits in the brain's reward circuitry. Efforts to build resilience should address pathways for both reducing distress and boosting positivity.

A neuroscientific approach to resilience building has been suggested (Tabibnia 2020). At the center of the model are three routes to resilience. The first route addresses strategies for reducing distress-related responses and down-regulating negative affect. A perceived threat can be managed through behavioral and cognitive coping responses. Behavioral coping involves active stress avoidance and stress control and is protective against distress and psychopathology. The second route to resilience addresses strategies that up-regulate positive affect, including psychological, social and physical well-being, activating neural pathways of reward and motivation. Social integration, connectedness and social support activate neural reward circuitry and can buffer stress, and have consistently been associated with lower morbidity and mortality, including lower risks of depression and PTSD. Furthermore, supporting others during times of stress is associated with adaptive outcomes, including greater longevity, psychological well-being and physical health. Resilient individuals are characterized by high positive emotionality and dispositional optimism.

A third route to resilience encompasses strategies that promote mindfulness and purpose in life. The latter is an integral part of psychological well-being and is called ikigai by the long-lived Japanese. It may be protective against physical and psychological illness and aid coping with illness (Tabibnia 2020). Having purpose in life is associated with reduced distress response in brain regions such as the amygdala. The brain's network may play a role in the salutary effects of having a sense of purpose. For retired senior citizens, further purpose in life may be gained from the presence of nature. Exposure to nature is an emerging contributor to resilience; it can improve cognitive function and have health benefits such as lower blood pressure and cortisol. In general, improving physical health can boost both physical and psychological resilience. Accordingly, a multicomponent and individualized program of exercise, diet and cognitive stimulation should be designed for older people suffering from persistent COVID-19 (Rodriguez-Sanchez, Rodriguez-Manas, and Laosa 2022).

Living to 100 depends on good cognitive functioning and a positive psychological outlook—having a reason for getting up each morning. Physical and social activity and brain training will help seniors maintain brain health. For those who succumb to AD in their 80s and 90s, they may yet reach 100, provided effective treatments are available when they need them. Even if such treatments may still be more than a decade away, younger seniors may have the benefit of such treatments in those decades and be better able to join the expanding cohort celebrating their 100th birthday in the middle of this century.

Any external stress that diminishes an individual's cognitive reserve and resilience may allow neurodegenerative processes to accelerate, which can cause symptoms of neurological disorders, such as dementia, to present earlier. Notwithstanding this negative prospect, the positive hope remains for an effective treatment for AD, which is the most common form of dementia.

The transition from a prolonged global COVID-19 shock to a renewed future of increasing longevity through medical discovery can be expedited by geroscience research into prolonging health span and alleviating chronic diseases (Gerdes et al. 2021). Deeper understanding of the processes underlying the aging of the immune system may yield targets for mitigation of immune system aging (Witkowski 2022). Inflammageing contributes to many age-related diseases, including neurodegeneration (Rea and Alexander 2022). By understanding fundamental aging mechanisms and their relationship to the COVID-19 disease process, interventions that target fundamental aging processes may turn out to be of value in treating long COVID. All the while, continuing vigilance will be needed over the lengthening shadow of uncertainty over nonreversible neuronal injury.

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