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The impact of the COVID-19 pandemic on dementia risk: Potential pathways to cognitive decline

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Abstract

Background: Coronavirus Disease 2019 (COVID-19), the far-reaching pandemic, has infected approximately 185 million of the world's population to date. After infection, certain groups, including older adults, men, and people of color, are more likely to have adverse medical outcomes. COVID-19 can affect multiple organ systems, even among asymptomatic/mild severity individuals, with progressively worse damage for those with higher severity infections.

Summary: The COVID-19 virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily attaches to cells through the angiotensin-converting enzyme 2 (ACE2) receptor, a universal receptor present in most major organ systems. As SARS-CoV-2 binds to the ACE2 receptor, its bioavailability becomes limited, thus disrupting homeostatic organ function and inducing an injury cascade. Organ damage can then arise from multiple sources including direct cellular infection, overactive detrimental systemic immune response, and ischemia/hypoxia through thromboembolisms or disruption of perfusion. In the brain, SARS-CoV-2 has neuroinvasive and neurotropic characteristics with acute and chronic neurovirulent potential. In the cardiovascular system, COVID-19 can induce myocardial and systemic vascular damage along with thrombosis. Other organ systems such as the lungs, kidney, and liver are all at risk for infection damage.

Key Messages: Our hypothesis is that each injury consequence has the independent potential to contribute to long-term cognitive deficits with the possibility of progressing to or worsening pre-existing dementia. Already, reports from recovered COVID-19 patients indicate that cognitive alterations and long-term symptoms are prevalent. This critical review highlights the injury pathways possible through SARS-CoV-2 infection that have the potential to increase and contribute to cognitive impairment and dementia.

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Author Contributions

J.D.P. drafted the manuscript. A.M.B. and J.D.P. worked together to craft the hypothesis, critique the manuscript, tables, and figure, and approve the final manuscript.

Conflict of Interest Statement

In the past three years, Dr. Brickman has received paid compensation for consultation or advisory activities to Regeneron Pharmaceuticals, F. Hoffmann-La Roche Ltd, Cognition Therapeutics, Inc, and Albert Einstein College of Medicine. He owns stock in Venus Medtech via Mars Holding Company. Dr. Brickman has a US patent (US9867566B2), patent pending (US20180228422A1), and has a copyrighted neuropsychological test instrument. His work has been supported by the US National Institutes of Health and Mars Symbioscience.

Keywords

COVID-19; SARS-CoV-2; dementia risk; cognitive decline; neurological symptoms

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected every aspect of global society, including alarming alterations to public health, medical care access, and the global economy. To date, approximately 185 million of the global population has been infected with significant risk for more infections in the future [1]. Mutations to the SARS-CoV-2 virus have the potential to amplify the number of future COVID-19 cases through higher infectivity rates and vaccine-resistant strains [2]. While recent vaccination efforts are effective and have the potential to curtail the wide-spread SARS-CoV-2 infections as well as decrease infection severity, those already affected and those with infections to come will experience the brunt of the long-term health consequences. Our proposition is that the long-term health consequences of COVID-19 could manifest as cognitive decline in some people.

Below, we first outline the mechanism by which SARS-CoV-2 infects cells, how infection utilization can compound organ damage, and provide possible routes for the virus to infect the brain directly. Then, we review the neurological symptoms and neuroimaging findings in COVID-19 patients, neuropathology seen from autopsy studies, and subsequent cognitive alterations and long-term symptoms exhibited in recovered COVID-19 patients. The processes by which COVID-19 affects the brain are interdependent and happen through multiple independent pathways. A critical subset of pathways to brain injury, covered next, include cardiovascular interactions and organ damage to the lungs, kidney, and liver. Understanding the mechanism by which COVID-19 affects the body then allows us to speculate why some groups of people, including those with cardiovascular risk factors, those of older age, people of color in the United States, and men, experience disproportionate impact from SARS-CoV-2 infection with poorer medical outcomes relative to other groups [3]. Notably, most of these groups are at particularly elevated risk for dementia [4], with COVID-19 potentially acting additively or synergistically with pre-existing comorbidities to contribute to the onset or progression of cognitive impairment and dementia.

Overall, this critical review synthesis examines possible viral infection pathways to the brain, interactions between the SARS-CoV-2 virus infection and multiple critical organ systems, and the implications of COVID-19 for short-term neurological consequences and long-term dementia risk. Our hypothesis is that SARS-CoV-2 infection, due to plausible COVID-19 cognitive decline pathways, evidence of prevalent neurological symptoms in patients, and relevant long-term symptoms in recovered individuals, promotes risk for cognitive decline and has the potential to exacerbate pre-existing dementia.

SARS-CoV-2 General Infection Characteristics

To understand why COVID-19 can increase dementia risk, we must start with how SARS-CoV-2 is exposed to, enters, and damages the body. The primary mode of SARS-CoV-2 infection is through respiratory droplets that spread from an infected person. Infection occurs when these droplets are introduced directly to the lungs/mouth/nose of a non-infected individual through breathing inhalation and/or surface transfer (fomite transmission) [5]. After this introduction, the virus travels to organs throughout the body, where it directly or indirectly influences each organ's respective functions. According to biopsy and autopsy findings from SARS-CoV-2 positive individuals, direct SARS-CoV-2 infections can be found in the lungs [6,7], brain [8], heart [9], kidney [10], liver [11], cerebral spinal fluid (CSF) [12,13], lymph nodes [7,14], spleen [7,14], intestines [7], and testes [7]. Additionally, wide-spread viral organ damage has been observed in the lungs, brain, heart, kidney, liver, and gut, highlighting the potential systemic influence of the virus throughout the body [15]. While more extensive autopsy findings are still needed to understand the full extent of the direct SARS-CoV-2 infection, it is clear that organ damage also occurs from indirect immune responses. This wide-spread propensity of SARS-CoV-2 is due to the mechanism of the viral pathway, specifically the cellular attachment points that are found in most organ systems and their relationship with cardiovascular and immune systems. This mechanism underlies the injury cascade from COVID-19 and provides important context for our conclusions regarding how COVID-19 can affect long-term cognitive function.

SARS-CoV-2 Viral Entry (ACE2, host proteases, and NRP1):

To initiate viral replication, SARS-CoV-2 attaches to healthy cell membranes primarily through the angiotensin-converting enzyme 2 (ACE2) receptor present within many organs systems [16]. ACE2 receptors are found in the lungs [17,18], brain [18,19], kidneys [17,18], intestines [17,18], female organs [20], male organs [17,18], heart [17-19], colon [17], liver [17,19], adipose tissue [16,19], vasculature [18,19], stomach [19], central nervous system [16], thyroid [20], adrenal gland [20], muscle [20], bone marrow [20], blood [20], nasal and oral mucosa [19]. The highest ACE2 expression is in the gastrointestinal tract, male reproductive system, kidney, gallbladder, heart, and thyroid [20,21].

Notably, the presence of ACE2 alone is not sufficient for SARS-CoV-2 cellular infection. A host cell protease, such as transmembrane protease serine 2 (TMPRSS2), cathepsin L, or furin, is also required for SARS-CoV-2 Spike (S) protein priming [22-24]. Other important host cell entry factors, such as the protein Neuropilin-1 (NRP1), can enhance the infectivity of SARS-CoV-2 after furin cleaves the viral S protein into the subsequent S1 and S2 proteins [25,26]. All of these proteases can be found throughout the body with TMPRSS2, for example, being found in the cardiovascular system, heart, kidney, and lungs with medium confidence, and found in the brain and central nervous system with low confidence [27]. For neurological considerations, both ACE2 and TMPRSS2 receptors have been discovered in the head and neck regions, specifically within sustentacular, stem neuronal, epithelial, goblet, and oligodendrocytes cell types [28,29]. Additionally, furin may play an important role in the central nervous system due to its high protein prevalence in the cerebral cortex, hippocampus, and cerebellum [22]. NRP1 is expressed in endothelial cells,

olfactory epithelium, vascular smooth muscle cells, vascular macrophages, and neurons with evidence NRP1 could be implicated in the neurological disruption of COVID-19 [30]. While the absolute amount of ACE2 receptors and various proteases are related to a tissue's direct infection risk [29] (dependent on the SARS-CoV-2 virus reaching that tissue), these factors do not fully represent the degree of subsequent injury risk.

Organ Injury Through SARS-CoV-2 Induced ACE2 Deficiencies:

The importance and function of ACE2 should be highlighted to understand how organ injury is initiated after SARS-CoV-2 infection. ACE2 is a component of the renin-angiotensin-aldosterone system, which partially regulates cardiovascular function such as arterial blood pressure, total blood volume, and vascular remodeling [31,32]. In particular, ACE2 acts as negative regulation component by promoting vasodilation and hypotension [33]. Thus, ACE2 is typically considered to be cardioprotective, renoprotective, hepatoprotective, and protective against fibrosis [17,34].

As SARS-CoV-2 infects healthy cells, it decreases the bioavailability of ACE2 receptors within the renin-angiotensin-aldosterone system. ACE2 deficiency can result in organ injury through uncontrolled non-specific inflammation (cytokine storm [35]) as well as increased coagulation, increased fibrinolysis, myocardial injury [36], increased vascular permeability [27], and acute lung injury [37]. For those with pre-existing ACE2 deficiencies before SARS-CoV-2 infection, such as individuals with hypertension, diabetes mellitus, and those of older age, the risk of more severe symptoms is increased due to the lack of ACE2 bioavailability as the infection spreads [18,38]. Additionally, the degree of induced inflammation and risk of detrimental cytokine storm, through ACE2 deficiency due to SARS-CoV-2 infection, is dependent on sex and age [20,39,40].

In the brain, the loss of ACE2 bioavailability impairs blood pressure control and autoregulation ability in the form of altered baroreflex sensitivity and endothelial cell function [19,41,42]. Mechanistically, endothelial cells, smooth muscle cells, glial cells, and neurons all utilize ACE2 for proper function [41] in many brain regions [43]. Consequently, brain levels of ACE2 are relevant for degree of ischemic injury and its subsequent potential impact on neurodegeneration, Alzheimer's disease (AD), and dementia risk [43-45]. ACE2 levels are accordingly inversely correlated with parenchymal amyloid beta(A β) and tau in AD [46]. For cases of COVID-19, where cardiovascular and cerebral ACE2 receptors are taken up by the SARS-CoV-2 virus, acute exasperation of these ACE2 limited effects could contribute to neurological symptoms. Another potential contributor to neurological symptoms, and a pathway to cognitive decline, is the direct cerebral infection risk posed by SARS-CoV-2. Below, we will discuss these direct pathways to the brain, the neurological symptoms present in COVID-19 patients, the implications of direct brain infection, types of neuropathology observed, and cognitive alterations and long-term symptoms reported from recovered COVID-19 patients.

SARS-CoV-2 Neurological Infection Characteristics

Cerebral Viral Pathway - Neuroinvasive and Neurotropic:

From a neurological perspective, it is important to understand how SARS-CoV-2 potentially infects the cerebrum and the consequential clinical implications. The SARS-CoV-2 virus is classified as a human betacoronavirus, joining the ranks of other epidemic-causing viruses such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome-related coronavirus (MERS-CoV) [47]. Human coronaviruses, including at least human coronavirus 229E (HCoV-229E, common cold), human coronavirus OC43 (HCoV-OC43, common cold), and SARS-CoV-1 (SARS), have both neuroinvasive and neurotropic properties [47-49], which refer, respectively, to the ability to invade the central nervous system from the periphery and the ability to directly infect neurons and glial cells [48]. Potentially due to being structurally/genetically similar to SARS-CoV-1 [50], SARS-CoV-2 also appears to exhibit neuroinvasive [12] and neurotropic [8] properties.

There are multiple possibilities for SARS-CoV-2 neuroinvasive pathways, including neural and hematogenous routes [49,51,52]. One possibility for the neural route is through the olfactory nerves, where SARS-CoV-2 potentially utilizes axonal and transneuronal transport to enter the central nervous system [51]. This pathway is directly supported by findings of SARS-CoV-2 infection of neurons in the olfactory mucosa [53] and low levels of SARS-CoV-2 RNA in the olfactory bulb [54]. This possibility was also demonstrated with the SARS-CoV-1 virus in intranasally inoculated mice [51,52]. Of note, NRPI could play a role in the neural pathway by enhancing the infectivity of SARS-CoV-2 into olfactory neurons [30]. While the neural route is a slow transport mechanism, considering the proximity of the olfactory nerve to the brain, it could be a cause of early cerebral infection as well as induce olfactory symptoms [52]. In one patient with SARS-CoV-2 infection and anosmia, magnetic resonance imaging (MRI) revealed abnormalities within the right gyrus rectus and olfactory bulbs early in the infection timeline [55]. Overall, up to 64% of clinical COVID-19 patients have olfactory dysfunction, which could be partially caused by this infection route, though changes significant enough to be visualized in MRI may only occur in the earliest phase of the infection or in subsets of the population [55,56]. The axonal transport through the olfactory bulb could have specific consequences for the hippocampus and entorhinal cortex. These brain regions are positioned in close proximity to the olfactory bulb and contain direct neuron projections connecting these territories [57]. Both the hippocampus and entorhinal cortex are regions involved in early Alzheimer's disease progression [58] and injury by SARS-CoV-2 could have implications for cognitive decline.

The hematogenous route, shown to be possible in SARS-CoV-1 infected mice, would take the form of SARS-CoV-2 passing through the blood brain barrier (BBB) and appears possible in humans [8,52]. This hematogenous pathway, while not mutually exclusive from the neural pathway, could exploit increased blood brain barrier (BBB) permeability from systemic inflammation (from cytokine and/or bradykinin storms) or could exploit direct endothelial cell infection to enter the brain [52,59,60]. If infectious SARS-CoV-2 virions were to pass through a leaky BBB, they would travel in blood unaided or could exploit transport through an infected cell. While infectious SARS-CoV-2 virions have not

been confirmed in blood, non-infectious SARS-CoV-2 ribonucleic acid (RNA) has been confirmed, highlighting the potential for this pathway [61]. The exact mechanism for SARS-CoV-2 to infect blood is currently unknown, but one possibility is for SARS-CoV-2 to infect lymphoid tissue directly, shown possible in humans [7,14], and then transfer to blood via lymph fluid [52]. The direct infection through CSF appears to be rare with only 6% of patients with central nervous symptoms testing positive for SARS-CoV-2 in the CSF, suggesting that indirect inflammatory damage may play a larger role in COVID-19 [62]. Alternatively, infected leukocytes could act as a carrier of viral particles to aid viral entry across the BBB [59]. As this hematogenous pathway may be dependent on BBB permeability (driven from neuroinflammation or cerebral hypoxia [63]), it is possibly a later-stage neuroinfection route. Individuals with pre-existing BBB dysfunction, such as those with hypertension, diabetes, older age, cerebrovascular disease [64], and neurodegenerative disease (Alzheimer's disease, Parkinson's disease, and multiple sclerosis [65]), could be particularly vulnerable. It is worth noting that these same groups with pre-existing BBB dysfunction, those with cardiovascular risk factors, those of older age [3], and those with neurodegenerative diseases [66,67] are all at elevated risk for a more severe COVID-19 course, including death. While there may be multiple explanations for poorer outcomes among older adults and those with cardiovascular risk factors, detailed below, poorer outcomes among those with neurodegenerative diseases could be explained by ACE2 disruption, BBB dysfunction, or higher rates of NRP1 expression [68]. Additionally, elevated COVID-19 severity and death risk is correlated with the presence of neurological symptoms [69] indicating a connection between neurological involvement and COVID-19 disease course.

SARS-CoV-2 Neurological Symptoms/Manifestations:

Regardless of viral pathway, reports of COVID-19 commonly show a diverse set of neurological symptoms that can be classified as central nervous system, peripheral nervous system, and skeletal muscular injury involvement [70]. Neurological clinical symptoms, split into severe and non-severe COVID-19 cases along with unspecified or case studies, are represented in Table 1. Overall, at least one neurological symptom is present within 46-93% of severe and 30-79% of non-severe COVID-19 clinical patients [71-73]. Typically, patients will experience between one to three neurological symptoms throughout the course of COVID-19 [73]. Of note, the major differences between severe and non-severe cases can include encephalopathy, altered state of consciousness, cerebral ischemic stroke, rhabdomyolysis, taste and smell impairment [72,73]. The more rare symptoms include cerebral hemorrhage, encephalitis, meningitis/myelitis, ataxia, seizures, polyneuropathy, and Guillain-Barré syndrome [74]. Typically, more severe COVID-19 cases are associated with increased likelihood of neurological symptoms [51,71], which have the potential to occur anytime over the duration of the infection [73]. While disentanglement of infection root causes of neurological symptoms is difficult, in any case there are potential long-term consequences for the individual [70].

SARS-CoV-2 Neurovirulent Potential:

With the establishment of neuroinvasive and neurotropic characteristics for SARS-CoV-2 as well as clinical neurological symptoms, it remains to be seen if the virus has neurovirulence

or will induce neurological diseases in humans. These possible neurological diseases range from acute forms such as encephalitis, to postinfectious encephalomyelitis, to the induction of neurodegeneration [48,90]. Viral acute encephalitis, direct neuroinflammation of gray matter, is typically characterized by neuronal death (either directly from viral replication or immune response), perivascular inflammation, and tissue necrosis [91]. Postinfectious encephalomyelitis is more typically associated with white matter damage through demyelination and perivascular inflammation, and occurs days to weeks after the infection seemingly is cleared [90,91]. The initiation of viral acute encephalitis has been documented in humans across multiple viruses including herpes simplex virus (HSV), rabies virus, Japanese B encephalitis, measles, mumps, and rubella [48,90]. For cases of chronic viral-induced neurodegeneration, viruses such as herpes simplex virus type 1 (HSV-1) and human herpes virus 6 (HHV-6) have been hypothesized to promote or exacerbate Alzheimer's disease while human immunodeficiency virus (HIV) has been causally linked to neurodegeneration [48]. Congruent with the neurological impact of HSV-1, HHV-6, and HIV, a proposed underlying theory for neurovirulence states that neuroinflammation consequences from any viruses, bacteria, and/or fungal infection source could contribute to Alzheimer's disease pathogenesis [92]. For neurotropic and neuroinvasive human coronaviruses, the connection with chronic neurovirulent properties is not yet established. That said, in animal models, several respiratory coronaviruses have neurovirulent properties including the mouse hepatitis virus (MHV), porcine hemagglutinating encephalitis virus (PHEV), and feline coronavirus (FCoV) [48]. Therefore, it is important to investigate the neurovirulence potential of SARS-CoV-2 in both acute and chronic possibilities.

The most extreme forms of SARS-CoV-2 acute neurovirulence would include meningitis or encephalitis. While there have been reported cases of meningitis/encephalitis in human patients with SARS-CoV-2 [12,13,93], the total extent and chronic hazard are less clear. To explore the source of this encephalitis/neuroinflammation, neurovirulent viruses can directly produce proinflammatory signaling in the brain [94]. The primary cells responsible for immune system signaling in the brain, astrocytes and microglia, produce higher signaling levels specifically with neurotropic viral infection [94]. Patients with moderate and severe COVID-19 have evidence of astrocytic activation and injury, [95] suggesting neurotropic properties of SARS-CoV-2 that possibly induces this proinflammatory signaling. Additionally, there are increased concentrations of plasma neurofilament light protein in severe COVID-19 patients, suggesting neuronal injury as the disease progresses [95]. In murine models, SARS-CoV-2 infection causes direct astrocyte, microglia, and neuronal infection [96]. These observations have implications for neurotropic viruses, as the activation of neuroinflammation presents a potential pathway to acute neurovirulence and/or chronic neurodegeneration [97,98]. While these human and animal findings provide evidence that part of the neuroinflammation could be directly occurring from SARS-CoV-2 neurotropism, systemic inflammation may also influence the immune signaling of astrocytes and microglia. In particular, mere exposure to pro-inflammatory cytokines, expressed from the periphery, could increase the permeability of the BBB (increasing likelihood of direct viral infection) as well as influence astrocytes in such a way to induce neurodegeneration and further neuroinflammation [99]. Therefore, the generation, quantity, and type of periphery pro-inflammatory cytokines plays an important role in neurodegeneration [97].

Regardless of whether SARS-CoV-2 directly uses astrocytes as viral hosts or influences them from indirect periphery signals, there are multiple pathways to acute neurovirulence that need to be further researched to understand exactly how the brain is affected [99].

Establishing the chronic neurovirulence potential of SARS-CoV-2 is difficult early in the timeline of the COVID-19 pandemic, especially among individuals with mild COVID-19 symptoms, but certain essential traits such as persistence of virus within the central nervous system can establish the risk potential for chronic pathogenesis. Similar to how HSV-1 can persist in human brains throughout a lifetime [100], some human coronaviruses could have this capability. For example, HCoV-229E and HCoV-OC43 have the ability to infect neural cells persistently (for at least 130 days) as well as produce infectious virions throughout the infection duration [101,102]. These particular human coronaviruses are not known to express any chronic neurovirulent properties, but other neurovirulent viruses such as HSV-1, HHV-6, and HIV can act as a template for determining the warning signs of potential long-term SARS-CoV-2 risk [48]. Additionally, chronic neuroinflammation is present across many neurodegenerative diseases and plays a role in the disease progression for Parkinson's disease and Alzheimer's disease as well as psychiatric diseases such as schizophrenia, bipolar disorders, and substance abuse [103,104]. Chronic neuroinflammation has the potential to initiate or worsen pre-existing neurodegeneration; understanding the role of SARS-CoV-2 infection on chronic neuroinflammation will be critical for long-term treatment [103,105]. Especially important for younger individuals and those with mild/asymptomatic cases of COVID-19 will be determining if chronic neuroinflammation is present and if so, the extent [104]. While neurovirulent characteristics can be difficult to substantiate, neuropathology and neuroimaging can provide insight into potential risk.

Neuropathology and Neuroimaging:

Damage to the central nervous system from viral infection can occur through three separate pathways. The first pathway is direct damage to cells through viral replication, termed virus-induced neuropathology [48]. The second pathway is indirect cell damage originating from an overactive immune response, designated virus-induced neuroimmunopathology [48]. The third pathway is through systemic/cerebrovascular disorder that includes cellular hypoxia (driven by hypoperfusion, arterial thromboembolism, and/or acute respiratory distress), sepsis, hyperpyrexia, and hypercoagulability [106]. Together, these pathways comprise the neuropathological possibilities of COVID-19 and can exist independently of each other. Seemingly consistent with the neurovirulence hypothesis of SARS-CoV-2, autopsy and MRI studies confirm aspects of expected acute damage. Since categorizing the root causes of downstream cerebral damage is not always possible without more in-depth analysis, along with the challenge of untangling pathology from pre-existing comorbidities, all the following MRI and neuropathology findings will not be binned into pathways except for some specific cases. Observed neuropathology includes focal hemorrhagic white matter lesions [106,107], discrete foci of acute axonal injury (with myelin loss) [107], florid leukocytoclastic reaction within infarcts, lymphohistiocytic inflammation [108], and neuronal cell loss [109]. Overall, neuropathology of these types are more consistent with immune-mediated damage or hypoxia than direct virus-induced neuropathology [54,107], especially since SARS-CoV-2 virus is not always found in the injured brain

[110] or is found at very low levels [54]. For example, demyelination is consistent with immune-mediated damage such as in cases of Guillain-Barré syndrome or acute disseminated encephalomyelitis [106], though demyelination may not be a common feature of COVID-19 [54]. The leukocytoclastic and lymphohistiocytic reactions are interesting because they could hint at neuroimmunopathological roots or may be a typical reaction to reperfusion injury within infarct regions [108]. Other neuropathology, potentially indicative of systemic/cerebrovascular disorder, has cerebral manifestations of neocortical infarcts [54,107], scattered shrunken/necrotic neurons [54,107,109], microhemorrhage [106], and acute hypoxic ischemic damage [54,111]. The degree of stroke, clot and hypoxic/ischemic damage seen across clinical COVID-19 cases means that a portion of this damage can be attributed to thrombotic origins. While this establishes the neuropathological possibilities within patients who have died from fatal COVID-19 complications, the neurological implications for moderate, mild, and asymptomatic COVID-19 patients are less clear.

To explore the domain of COVID-19 patients who survive the initial infection, clinical brain imaging can offer insights into potential damage. In general, clinical imaging supports neuropathological findings with acute/chronic infarcts [76,112-114], white matter microhemorrhages [112-114], microangiopathy [76], parenchymal hematomas [113], olfactory bulb abnormalities [113], and lymphohistiocytic inflammation [108]. Insights from imaging showcases perfusion abnormalities in cases of posterior reversible encephalopathy syndrome (PRES) will be discussed in more detail within the cardiovascular interactions section. Additionally, cerebrospinal fluid (CSF) and plasma biomarker evidence supports potential astrocytic injury and neuronal injury from COVID-19, but this evidence is non-specific and only highlights that damage is indeed occurring [95]. Of those with neurological symptoms and subsequent CSF testing, 40% had hyperproteinorrhachia supporting inflammation or axonal injury [62]. Of clinical COVID-19 patients who received an MRI from altered mental status or focal weakness, neuroimaging studies showed that 22% of these patients have microbleeds and 26% have leukoencephalopathy [115]. Most of the microbleeds were found in subcortical white matter and the corpus callosum [115,116] consistent with microbleed patterns observed in cases of hypoxemia and critical illness [117,118]. Although, endotheliitis, kidney failure (through uremic toxins increasing BBB permeability) and thrombosis, have also been theorized to be independent or compounding factors in COVID-19 microbleed formation [116,117,119]. In a group of three-month recovered COVID-19 patients, neuroimaging demonstrated changes in both gray and white matter with few differences dependent on severity level other than a decrease in global gray matter volume correlated with inflammation (lactate dehydrogenase levels) [120]. Gray matter increases across multiple regions occurred in these recovered COVID-19 patients including the olfactory cortices and hippocampus [120]. White matter changes, in general, were characterized by lower diffusivity and higher fractional anisotropy (with no differences in total white matter volume), indicating a potential remyelination [120]. Additionally, resting-state fMRI findings in individuals recovered from mild COVID-19 showed states of hyperconnectivity [121]. These neuroimaging findings demonstrate that structural brain changes are possible, even spanning across non-severe cases, but regardless, more imaging studies are necessary, including in recovered COVID-19 patients, to better quantify risk and potential long-term consequences.

Cognitive Alterations and Long-Term Symptoms from Clinical COVID-19 Survivors:

Ultimately, one of the major concerns with a neurological viral influence is its subsequent impact on cognition. Overall, plausible cerebral injury from SARS-CoV-2 may induce or worsen cognitive impairment and dementia [46]. In particular, damage from hypoxia/ischemia, thromboemboli/stroke, and neuroinflammation, all possible from SARS-CoV-2 infection, are associated with cognitive decline and dementia [46]. While existing studies are currently limited, immediate cognitive alterations were observed in patients recovered from COVID-19. Of note, the reported long-term cognitive decline spans several domains, including concentration, memory, executive function, psychomotor coordination, information processing, and language [122-127]. During the recovery phase of COVID-19, a middle-aged population, of various severity levels, experienced loss of sustained attention [128]. The degree of sustained attention alterations correlates with post-infection blood-based inflammatory levels [128]. Even within asymptomatic COVID-19 patients, cognitive deficits were observed in language and visuoperception, though there was no difference in overall cognitive ability from the control group [129]. The severity of COVID-19 disease state, from asymptomatic to requiring hospitalization, correlates with degree of cognitive changes [130]. The degree of cognitive changes can be consequential with hospitalized patients having between .45-.57 standard deviations of global cognitive performance loss compared with control populations [130]. Mostly relevant for higher severity COVID-19 patients, other aspects of COVID-19 such as development/duration of delirium and ventilator treatment due to hypoxia can all contribute to long-term cognitive risk. Of clinical COVID-19 patients, 11-33% develop delirium [79-81]. Of those admitted to the intensive care unit (ICU) from COVID-19 infection, up to 80% develop delirium at least once during their treatment [131]. Establishment of delirium and systemic inflammation, both present in severe and critically ill COVID-19 patients, are associated with future risk of dementia [98,132,133]. As supported in a recent meta-analysis, delirium development in clinical patients is an independent risk factor for long-term cognitive decline (up to 2.3x higher risk) [134]. Shown in populations initially free of cognitive impairment and across age, longer duration of delirium can induce novel cognitive impairment at levels comparable to mild Alzheimer's disease [135]. Patients who require ventilator treatment still often experience hypoxia; persistent dysfunction in attention, memory, language, processing speed, and executive functioning can occur in these patients for years after recovery [49]. Additionally, for those with pre-existing cognitive impairment there is a greater risk for precipitous cognitive decline due to interactions between delirium and dementia [132,136].

Other long-term effects of COVID-19, such as insomnia [137], chronic fatigue [138], social isolation [139] and development of psychological disorders such as post-traumatic stress disorder (PTSD) [140] and depression [141] can contribute to cognitive decline. As seen in Table 2, clinical COVID-19 survivors can experience long-term symptoms that may have primary or secondary effects on cognitive function. Long-term symptoms such as fatigue, cognitive alterations, myocardial inflammation, PTSD, insomnia, depression, pulmonary function abnormalities, resting heart rate increase, hematuria, proteinuria, and abnormal liver enzyme levels have all been reported in COVID-19 survivors. Of note, when compared with influenza or other respiratory tract infections, diagnosis rates of psychiatric illnesses, mood disorders, or anxiety disorders are higher after COVID-19 [142]. Often,

recovered COVID-19 patients can have several of these long-term symptoms lasting at least 70 days with an unknown final duration [123,124]. Additionally, as is the case for symptoms of fatigue, COVID-19 severity does not always correspond with likelihood of developing long-term symptoms [124]. This observation is inconsistent with other post-viral fatigue syndromes, such as those attributed to brucellosis, glandular fever, and Lyme disease, where disease severity correlates with the extent to which patients experience fatigue [143]. Even among ambulatory care COVID-19 patients, 35% have post-acute symptoms 16 days after COVID-19 testing, suggesting prolonged symptoms in non-severe cases [144]. In a sample of health care professionals with mild COVID-19 severity and seropositive testing, 26% reported 1 long-term symptom after 2 months of recovery and 15% reported 1 long-term symptom after 8 months of recovery [145]. For those with persistent long-term COVID-19 symptoms, termed “long-COVID”, 13.3% of these individuals experience symptoms longer than 28 days, 4.5% longer than 56 days, and 2.3% longer than 84 days [146] with neurological manifestations and fatigue being the most prominent in non-hospitalized individuals [147]. In general though, findings from other similar viral diseases suggest that cognitive alterations, psychological disorders, and long-term symptoms are all possible in COVID-19 patients. For example, recovered severe acute respiratory syndrome (SARS) patients reported long-term depression, insomnia, memory impairment, fatigue, and PTSD [148-150]. Other conditions such as sepsis, pneumonia, and acute respiratory distress syndrome can similarly increase risk for cognitive impairment and dementia in survivors [74,149]. These conditions speak to the overall contribution of the body’s organs in maintaining brain health, and, in the context of COVID-19, the health of the cardiovascular system likewise has implications for cognitive decline.

Cardiovascular Interactions with COVID-19

The cardiovascular system is intimately intertwined with neurological function and dementia risk. For example, heart disease, diabetes mellitus, hypertension/hypotension, hypercholesterolemia, obesity, lack of aerobic exercise, smoking [161, 162], stroke [163], and vascular damage [164] are well-documented risk factors for dementia. Of particular relevance to SARS-CoV-2, heart disease, risk for stroke, and vascular damage worsen in patients with moderate to severe cases of COVID-19. Additionally, SARS-CoV-2 disproportionately targets those with pre-existing cardiovascular risk factors, typically making cases more severe, and has the potential to compound pre-existing cardiovascular damage [165,166]. Injury to the cardiovascular system, from COVID-19, including myocardial, thromboemboli, and vascular damage could synergistically increase future dementia risk or exacerbate existing dementia.

In the case of heart disease, clinical COVID-19 can induce myocardial injury (7-25% [77,167]), myocardial infarction/shock (7-14% [77,82]), and arrhythmias (17% [77]). Fifty-five percent of clinical patients, both with and without pre-existing cardiac disease, have an abnormal echocardiography feature in the left, right, or both ventricles to varying degrees of severity [168]. Even in asymptomatic and symptomatic college athletes, COVID-19 can induce subclinical pericardial (27%), myocardial (17%), and myopericardial (13%) abnormalities, though appropriate control groups are needed to rule out athletic cardiac adaptation [169]. Similar to the viral pathway in the brain, the heart can have both direct

myocardial infection [9,170], indirect damage from immune response, and/or ischemic damage [171]. Clinically, these pathways are difficult to disentangle, but non-specific cardiac biomarkers such as elevated troponin levels and ECG abnormalities are used to demonstrate cardiac damage [167,171]. Damage to the heart can take many forms including myocardial infarction, microinfarcts, ventricular fibrosis, and/or atrial fibrosis [171]. This damage can progress to cardiomyopathy, systolic/diastolic abnormalities, ventricular tachycardia, and atrial fibrillation [171]. Transthoracic echocardiography findings demonstrate that 35% of clinical COVID-19 patients have abnormal left ventricle wall motion and reduced ejection fraction (< 50%), 15% have increased right ventricle size, and 40% have decreased right ventricle systolic function [172]. In seemingly recovered COVID-19 patients, independent of infection severity level and comorbidities, 30-60% still have myocardial inflammation around 3 months after diagnosis [154,155]. In total, heart damage induced by COVID-19, both acute and chronic, can impair blood flow to the rest of the body including the flow-sensitive brain and in general is associated with risk for future cognitive impairment [161,162].

In the case of stroke, clinical COVID-19 can induce macro/micro arterial/venous thromboemboli (4-7% non-severe, 8-31% severe [82,173-176]) with acute cerebrovascular attack (0.5-1.4% non-severe, 1.2-5.7% severe [71-73,82]) occurring as a subset. Additionally, in autopsy studies, it appears that deep vein thrombosis and pulmonary emboli can occur silently in clinical COVID-19 patients, [177,178] indicating that rates of thrombosis may be under-reported [173]. Importantly, abnormal coagulation parameters associated with thrombosis are highly linked with mortality in COVID-19 [179]. Coagulopathy manifests in a hypercoagulability/prothrombotic state to generate thrombi [176]. Typically, coagulopathy is defined as lower levels of platelets and increased D-dimer levels, prothrombin time, fibrinogen, factor VIII, and von Willebrand factor with D-dimer levels often used for disease prediction [176]. States of coagulopathy are documented in 19% of clinical COVID-19 patients [180] and elevated rates of D-dimer are documented in 46% of patients [181]. From a causal standpoint, coagulopathy could be the result of infected cells generating proinflammatory cytokines or hypoxic conditions [177,182]. While the dangers of macro thromboemboli are clear and present, the rates of micro thromboemboli would be more difficult to detect clinically and may have long-term consequences. In further autopsy studies, microscopic thrombi are found in 80-100% of lungs [182], opening the possibility that micro thromboemboli are traveling to other organs, including the brain, in severe COVID-19 patients. From MRI scans of COVID-19 patients, non-confluent multifocal white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) have been found [114]. Similar patterns were observed following transcatheter aortic valve implantation that may result in long-term suboptimal cognitive outcomes [183]. Additionally, if present, micro thromboemboli may contribute to coronary dysfunction [171] as well as damage to other organs. More studies are needed to determine if micro thromboemboli or subclinical thromboemboli are present in milder cases of COVID-19.

In the case of vascular damage, the potential for COVID-19 to do lasting damage derives from endothelial cell injury after direct viral infection (shown systemically in SARS-CoV-2 infected organs [184]) or immune-mediated inflammation. Endothelial cell injury

can contribute to the dysregulation of the renin-angiotensin-aldosterone system, which partially controls arterial blood pressure fluctuations and cerebral blood flow. With impaired endothelial cells, the regulation of vascular tone (autoregulation) is disrupted and thus higher fluctuations of blood pressure and cerebral blood flow occur. With SARS-CoV-2 decreasing the bioavailability of ACE2 receptors, vasoconstriction and hypertension tend to increase. Posterior reversible encephalopathy syndrome (PRES) is a possible consequence of endothelial cell dysfunction and/or hypertension where autoregulation compensation abilities cannot control cerebral blood flow adequately [185]. Thus, symptoms of PRES can manifest either as cerebral hypoperfusion or hyperperfusion [185]. The reason why these seemingly opposite flow manifestations can occur is potentially explained by the timeline of disease progression [186]. As uncontrolled hypertension increases, possible in COVID-19 as the renin-angiotensin-aldosterone system is disrupted, autoregulatory mechanisms compensate with vasoconstriction that results in cerebral hypoperfusion. Then, as endothelial cell dysfunction continuously weakens autoregulation abilities and hypertension increases, autoregulatory mechanisms eventually reach their maximum vasoconstriction abilities, resulting in cerebral hyperperfusion. In a pre-print publication, PRES is listed as a possible COVID-19 manifestation shown by 25 patients clinically presenting with PRES in both the hypoperfusion and hyperperfusion progression stages [187]. PRES has also been observed in other COVID-19 patient populations to varying degrees [112,188]. Hypoperfusion and flow disruptions are especially damaging to cerebral white matter; notably, a majority of Alzheimer's disease patients manifest with white matter hyperintensities, suggestive of similar ischemic damage [46]. Perfusion abnormalities within small cerebral blood vessels, in the context of COVID-19, are primarily attributed to a decrease in endothelial cells due to a loss of vascular wall adhesion [189]. Endothelial cell dysfunction, similar to the effects of hypoperfusion, could lead to decreased clearance of cerebral metabolites such as amyloid beta (A β) and have been implicated in tau formation [46]. Disruptions to endothelial cells, in the form of endotheliitis, could also be implicated in the origins of cerebral microbleeds, especially in COVID-19 patients diagnosed with encephalopathy [190]. In addition to endothelial dysfunction, vascular damage could take the form of impaired baroreflex that would risk the ability of the body to respond to dynamic blood pressure needs [191] as well as chronic atherosclerosis [192]. Evidence from young adults 3-4 weeks after mild COVID-19 recovery indicate systemic vascular alterations in the form of increased vascular stiffness, measured through pulse wave velocity, and decreased flow-mediated dilation in the arm [193]. This vascular evidence across mild to severe COVID-19 patients indicates that perfusion abnormalities and endothelial/vascular dysfunction can occur in both the systemic and cerebral cardiovascular system with risk for cognitive decline.

Pulmonary, Renal, and Liver Interactions with COVID-19

In addition to the cardiovascular system, damage to other organ systems by COVID-19 can potentially increase risk for future cognitive decline. For example, damage to the pulmonary system, renal dysfunction [162,194], and liver dysfunction [195,196] can increase dementia risk or affect dementia progression. For the pulmonary, renal, and hepatic systems, SARS-CoV-2 can directly infect these organs, indirectly damage them from systemic inflammatory

response, and/or induce thromboembolic damage [197,198]. Analogous to the brain and cardiovascular system, downregulation of ACE2 due to the SARS-CoV-2 attachment plays a critical role in COVID-19 pathogenesis. ACE2 levels are a critically important aspect of pulmonary protection against damage [17,199]. This also holds true for the kidneys, where decreases in ACE2 expression can compound renal damage [200]. Across COVID-19 severity, damage to these organ systems have been observed to varying degrees ultimately presenting as increased risk for future cognitive decline.

One of the most consistent clinical signs of COVID-19 include a cough that could be indicative of pneumonia, diagnosed through chest computed tomography (CT) evaluation. Ground glass opacity areas can be seen broadly in the lungs, from CT imaging, in up to 98% of patients throughout infection [201]. Many other virus-associated changes are commonly observed in the lungs, including consolidation, reticulation, air bronchogram, and vascular enlargement [201]. Physical pulmonary abnormalities occur even in patients presenting with asymptomatic and mild COVID-19 cases, including young children [202,203]. While asymptomatic cases have a lower presentation of pulmonary abnormalities than symptomatic COVID-19 patients, the percentage is still high at 49% [202]. At the extreme, one of the most serious forms of pulmonary dysfunction is acute respiratory distress syndrome (ARDS). This syndrome is diagnosed when arterial blood oxygen levels are low enough to induce hypoxia. About 33% of hospitalized COVID-19 patients experience ARDS, with many needing ICU or ventilator treatment [204]. Additionally, 30% of clinical patients experience COVID-19 induced acute pulmonary embolism [205]. In autopsy results, the type of pulmonary damage present primarily takes the form of diffuse alveolar damage across a large majority of cases [206,207]. Additionally, macrovascular (42%), but especially microvascular (84%) thromboemboli were present in autopsied lungs [206]. This type of damage to the lungs is consistent with systemic hypoxia, known to be associated with a wide range of outcomes such as an increase in inflammatory factors as well as increased blood coagulation [208,209]. For the brain, hypoxia can induce neuronal injury/loss through disruption of cerebral homeostasis. As oxygen levels decrease in the brain, rising carbon dioxide levels result in an acidosis that, at extreme levels, will induce vasospasm and vascular permeability. Ultimately, this cascade could result in neuronal and astroglial injury/death that will present as cognitive decline [208]. As worsening pulmonary health is correlated with neurological symptoms in COVID-19 patients, the hypoxia cascade is a plausible component of detrimental neurological alterations [210]. Fibrosis is a possible long-term pulmonary consequences from COVID-19, especially after long duration severe disease, that can reduce overall lung capacity and reduce the efficiency of gas exchange [211]. In recovered clinical COVID-19 patients with no pre-existing pulmonary comorbidities, long-term pulmonary alterations have been observed after three months [152]. Of the recovered patients, who mostly comprised of moderate COVID-19 severity, 71% had abnormalities on chest CT scans with 31% of those with CT abnormalities manifesting as noticeable pulmonary abnormalities [152]. Even within the group without CT abnormalities, some individuals experienced pulmonary abnormalities suggesting that sub-imaging damage can occur [152]. In cases of similar pulmonary damage from SARS-CoV-1 and Influenza A, full recovery could take years [212]. Ultimately, chronic pulmonary damage from COVID-19 may increase risk of future cognitive impairment as similar to

chronic hypoxemia, chronic obstructive pulmonary disease, and obstructive sleep apnea [213]. In severe COVID-19 cases, the possibility of future cognitive impairment is even higher based on reports of patients with ARDS who develop cerebral atrophy, ventricular enlargement, and cognitive alterations [49,214].

Kidney damage is also common in COVID-19 and pre-existing kidney damage represents a mortality risk factor. Across the broad-spectrum of clinical COVID-19 patients, 44-75% presented with abnormal kidney function [215], which could be signs of kidney damage, both in the form of blood in urine (hematuria: 42%) and high levels of protein in urine (proteinuria: 66%) [159]. Of note, these COVID-19 rates of hematuria and proteinuria are similar to rates present from other critical illness [159]. In non-severe patients, acute kidney injury (AKI) was observed in about 2% of clinical patients, but severe patients had much higher rates at 19-37% [215,216]. For those with more serious AKI, about 20% of the severe patients, renal replacement therapy such as dialysis is required [217]. Autopsy studies showed kidney damage, with the primary form being acute tubular injury/necrosis [159,197,218]. While long-term data regarding kidney damage are still necessary, information from hospital discharge can give some insight into expected recovery rates. For example, of the discharged clinical COVID-19 patients who experienced renal dysfunction, 69% had proteinuria recovery and 43% had hematuria recovery [159]. Of patients with AKI, only 18% fully recovered by hospital discharge [159]. For those who required renal replacement therapy (associated with severe AKI) and survived COVID-19, 33% remain dependent on renal replacement therapy at discharge with 17% remaining dependent after 60 days [217]. As in other diseases cases of AKI, the progression to chronic kidney disease could be as high as 25%, demonstrating long-term damage potential [219]. Renal damage, beyond the direct dysfunctional effect, could interact synergistically with cardiovascular abnormalities resulting in further myocardial dysfunction [191]. Acute kidney injury has the potential to accumulate nitrogenous waste in the brain, disrupt cerebral osmolality, and promote cerebral inflammation [220]. These alterations can disrupt the permeability of the BBB [220]. The renal injury effects can influence multiple brain regions, but the hippocampus appears to be particularly susceptible [220]. Ultimately, the culmination of long-term renal damage, due to COVID-19, presents a cognitive impairment risk to survivors [162,194].

For COVID-19, liver abnormalities in the form of elevated enzyme levels occur across the spectrum of disease severity. For example, 18-21% and 21-22% of clinical COVID-19 patients have elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), respectively [181,221]. Other potential markers of injury include γ -glutamyltransferase (GGT, 11-21%), total bilirubin (TB, 6-35%), and alkaline phosphatase (ALP, 4-6%) with 16-53% of total hospitalized COVID-19 patients experiencing abnormal liver function [181,221-223]. Overall, worse COVID-19 severity correlates with higher levels of liver abnormalities [224,225]. With severe COVID-19 cases, liver abnormalities can progress to acute liver injury in 5-6% of clinical COVID-19 patients [224,225]. In terms of pathological damage, injury can take the form of micro- and macrovesicular steatosis as well as dysfunction of intrahepatic portal vein branches, mild lobular and portal inflammation, ductular proliferation, and cellular necrosis [222]. As mentioned, organ damage can have a number of plausible origins, but for the liver

specifically, hepatotoxic drug-induced injury from various treatment options is an additional possibility [197]. Within 14 days of hospital discharge, ALT, ALP, AST/ALT, GGT, and other liver enzyme levels remained abnormal in recovered COVID-19 patients, compared with controls [160]. While overall liver enzymes trended towards recovery over 40 days in these patients, not all enzymes fully normalized making the complete recovery timeline unknown [160]. These enzyme trends are supported by abnormal plasma metabolic profiles, after three months of recovery time, that could indicate prolonged liver injury [226]. While the complete long-term implications of abnormal liver function are not yet known and additional follow-up data are needed, warning signs of liver injury exist in recovered COVID-19 patients that could contribute to dementia risk [195,196].

Aging Complications

With the viral mechanisms and major damage pathways to COVID-19 induced cognitive decline risk delineated, certain groups, such as older adults, are at greater risk for severe COVID-19 and subsequent cognitive decline. Advancing age is the strongest independent risk factor for COVID-19-related severe illness and death, with extreme risk for those above 80 years old [3,227]. This disproportional mortality is extreme; 94-99% of patients who died from COVID-19 were older than 50 years old [228,229]. While pre-existing comorbidities for the elderly, relevant for 35-66% of those above 65 years of age [230], can increase the severity and mortality risk of COVID-19, age alone still exists as an independent risk factor for heightened COVID-19 severity. On the other end of the age spectrum, children, though not free of COVID-19 symptoms or mortality [231], most often experience asymptomatic or mild symptoms from COVID-19 [232]. It is those of older age who are at greatest risk for dementia [233], thus it is important to examine how COVID-19 might modulate this risk. There are multiple contributing factors that could explain this steep gradient in age-related COVID-19 response, including changes in ACE2 expression, immune response, and systemic frailty.

Starting with ACE2 levels, the attachment point for SARS-CoV-2, the mechanism of limited ACE2 bioavailability could influence response severity to the virus [18]. Similar to those with pre-existing ACE2 deficiencies such as individuals with hypertension and diabetes mellitus, those of older age experience a decrease in ACE2 bioavailability leading to increased risk of organ injury. Overall, adults can have lower systemic ACE2 expression than children [234] as well as lower circulating ACE2 levels [235]. For vascular considerations, based on mice experiments, ACE2 expression steadily decreases with age [236]. In the brain specifically, where ACE2 levels influence blood pressure control and autoregulation [41,42], there is an age-dependent component where ACE2 levels are more critical for older adults. For example, in mouse models with ischemic injury, higher ACE2 levels are considered to be protective against damage with those of older age experiencing the most benefit [44]. For cases of COVID-19, where ACE2 receptors are being taken up by the SARS-CoV-2 virus in a lower bioavailability state due to aging, acute exasperation of these negative vascular effects could affect neurological symptoms.

To effectively battle SARS-CoV-2, the body's immune system must recognize the viral threat, signal the proper immune cells, destroy the virus, and clear the debris [237]. As

the body ages, the immune system undergoes alterations in the form of immunosenescence and inflammaging [237]. Immunosenescence, the decline of recognition, signaling, and clearance abilities of both the innate and adaptive immune systems, has implications for viral defense [237-239]. Likewise, inflammaging (chronic, systemic, and low-grade inflammation) occurs as part of the aging process through a disrupted inflammation balance that increases an individual's viral susceptibility [240]. Overall, these age-related changes in the immune system allow for greater viral replication due to delayed alerting and an over-active immune response that could result in a detrimental cytokine storm [237]. Observations in differing antibody profiles between adults and children with COVID-19 shows that children have the ability to clear the SARS-CoV-2 infection faster with a less powerful immune response protecting them from an excessive immune reaction [241]. Overall, while there are multiple aspects to the aged immune system interaction with SARS-CoV-2 [237,242], immune response and development to cytokine storm are among the most important factors in an individual's outcome to COVID-19 and neurological symptoms [35].

As a common part of aging, systemic frailty influences multiple aspects of the body that play an essential role in fighting off SARS-CoV-2 infection. While the definition of frailty is not always robustly defined in the elderly, it is considered distinct from comorbidities and disability, though there can be significant overlap [230,243]. Frailty stems primarily from the culmination of multiple non-optimally operating organ systems and lack of robustness in maintaining homeostasis [230,244] derived from both biological and pathophysiologic sources [245]. Ultimately, with relevance for COVID-19 illness, frailty leads to reduced mechanical advantage, atypical presentation, and the comorbidity of pulmonary disease in the elderly [239]. For reduced mechanical advantage, weakening of thorax muscles paired with increased stiffness of lung structures can diminish oxygen uptake through limited gas exchange across a reduced pulmonary reserve, as well as impair cough strength, thus reducing possible clearance of viral particles [239,246]. Those who are frail, independent of age and comorbidities, are at greater risk for severe COVID-19 and mortality [243,247-249]. In fact, frailty status can be a better predictor of COVID-19 response than age or comorbidity alone, depending on the scale utilized [248].

Disparities

While advancing age is the biggest predictor of COVID-19 severity, disparities in COVID-19 severity and outcome have been observed across both sex and race/ethnicity in the United States. Independent of age and with similar infection rates, men are more likely to have severe COVID-19 that requires admissions to intensive care units [227,250,251] and a higher fatality rate than women, with men making up approximately 70-75% of COVID-19 deaths [166,228,250]. In the United States, Black Americans, Hispanic/Latinx, and American Indian populations have been disproportionately affected by COVID-19 compared with non-Hispanic White populations. For Black Americans, the risk of SARS-CoV-2 infection is three times higher than non-Hispanic White populations [252]. This stark disproportion leads to Black Americans comprising 34% of the COVID-19 mortality rate while only representing 13% of the United States population [253]. Hispanic/Latinx populations, within the United States, make up 28% of the COVID-19 cases while only comprising 18% of the general population [254]. Ultimately, based on New York

City estimations, Hispanic/Latinx populations have twice the risk of COVID-19 mortality compared to non-Hispanic White populations [254]. Pooled across 23 states, American Indians and Alaskan Native persons experience 3.5 times more SARS-CoV-2 infections than non-Hispanic White populations [255]. While overall mortality across these states is not fully documented [255], using Arizona as an example, 18% of the COVID-19 deaths are of American Indians while only comprising 5.3% of the state's population [256]. Importantly, sex differences in COVID-19 response appear to stem from biological causes while, in our opinion, racial/ethnic differences are primarily the result of systemic racism.

Parsing through sex disparities in COVID-19 response includes the main factors of ACE2 expression and immune system differences. Regarding ACE2 expression, women generally have higher levels of ACE2 expression overall [234], though this has been contested [20]. Additionally, women have a less dramatic decrease in ACE2 expression with age compared with men [234]. The higher ACE2 expression in women could be the result of increased estrogen levels, which may reduce COVID-19-related organ damage via relatively higher levels of systemic ACE2 availability [234,235]. In general, women and men have sexual dimorphism in immune response that could interact with ACE2 expression [257,258]. Typically, women mount stronger immune responses to pathogens [258], but higher ACE2 levels can dampen this immune response in the context of COVID-19 [20]. For example, in the lungs, higher ACE2 levels in SARS-CoV-2 infected women correlated with a lower immune response whereas lower ACE2 levels in men correlated with stronger immune response and increased risk of cytokine storm [20]. Lastly, COVID-19 interactions with pre-existing comorbidities stratified by sex may influence outcome, but more data are needed [259].

With respect to racial/ethnic differences in SARS-CoV-2 infection response, there is little supporting evidence of biological differences between groups that influence outcomes. When controlling for comorbidities, no differences in ACE2 levels exist across race [20]. Once including cardiovascular and pulmonary comorbidities, differences in ACE2 polymorphisms could account for aspects of increased COVID-19 susceptibility [260]. Additionally, differences in nasal TMPRSS2 levels could be influential in COVID-19 infection risk [261]. Notably, cardiovascular disease and gene expression (ACE2 and TMPRSS2) differences across race are influenced by social and environmental factors (also known as social determinants of health) [262,263]. In the United States, Black, Hispanic/Latinx, and American Indian populations have higher rates of vascular risk factors such as hypertension, diabetes, and obesity [264] compared with non-Hispanic White populations. These differences are mediated by reduced medical access, limited resources, discrimination, and other social determinants of health across the lifetime, and may interact to increase dementia risk in certain groups [265]. Higher rates of COVID-19 exposure due to in-person work and household exposure increase infection potential [253,256]. In the context of COVID-19, Black Americans, Hispanic/Latinx, and American Indian populations have a greater pre-existing risk of cognitive decline that is now potentially compounded with disproportionate rates and more severe cases of COVID-19. This occurrence of higher rates and more severe cases within marginalized populations is consistent with previous disease outbreaks, such as in the H1N1 Influenza A pandemic and seasonal influenza [266]. Ultimately, more access to medical care, health insurance options, societal support, and

vaccine access need to be distributed to Black Americans, Hispanic/Latinx, and American Indian populations disproportionately battling the COVID-19 pandemic.

Implications for Dementia

Overall, SARS-CoV-2 infection, moderated in severity by age-, sex-, and race/ethnicity-dependent factors, initiates a disease progression that has the potential to promote cognitive decline and exacerbate pre-existing dementia (see Figure 1). The damage cascade of COVID-19 is multifaceted and interdependent, with multiple pathways that could lead to cognitive hazard mechanisms. One such cognitive hazard mechanism, cerebral direct infection, is possible with the SARS-CoV-2 virus exhibiting neuroinvasive and neurotropic characteristics with neurovirulent potential. The greatest cognitive risk though may be from immune-mediated damage originating as cytokine storms that have far reaching consequences for multiple organ systems, including the brain. Damage to organ systems and detrimental immune response, across the disease progression of COVID-19, may affect cognition via cerebral ischemia, hypoxia/acidosis, and neuroinflammation. The initiation of a coagulation cascade, from excessive immune response, that can generate micro/macro thromboemboli also poses significant risk. While long-term cognitive outcomes have not been fully evaluated, emerging reports indicate high rates of long-term symptoms and cognitive alterations in recovered COVID-19 patients. Due to these plausible COVID-19 cognitive decline pathways, evidence of prevalent neurological symptoms in patients, and long-term symptoms in recovered individuals, our conclusion is that COVID-19 represents a credible risk for cognitive decline and has the potential to exacerbate pre-existing dementia. For those at higher baseline dementia risk, older adults, those with cardiovascular risk factors, and people of color, COVID-19 may not only increase the risk of cognitive decline, but also interact in a synergistic way with pre-existing dementia risk factors to disproportionately increase this dementia risk.

For those with severe COVID-19 or cases of long-term symptoms, there are limited evidence-based interventions that address cognitive decline or risk of future decline. While long-term studies on the effectiveness of recovery therapies have not yet been evaluated, strategies based on the medical needs of recovered critically ill COVID-19 patients and past recovery experience from patients with sepsis may provide some guidance [149,267]. For example, recovering COVID-19 patients may benefit from adhering to structured exercise programs, attending physical/occupational therapy, optimizing nutrition, reducing existing cardiovascular risk factors, practicing proper sleep hygiene, seeking out peer support [268], attending cognitive therapy/training and seeking mental health support [149,267]. Clinicians should be aware of the possibility of risk for cognitive decline or persistence of cognitive symptoms and monitor cognitive health closely, seeking formal neuropsychological evaluation when indicated [267]. Additionally, patient reports indicate the need for follow-up appointments, the review/optimization of medication on a regular basis, facilitation of referrals to specialists, education on respiratory treatments, and coordination across health services and between providers [149,267]. When possible, early rehabilitation after complete recovery, or especially during hospitalization, is shown to be more beneficial in COVID-19 patients than later [267]. Together, these suggestions may help mitigate the effect of COVID-19 on long-term symptom outcomes.

There is an essential need for longitudinal studies that include recovered COVID-19 patients to evaluate long-term symptoms, measure organ damage where possible, and perform cognitive outcome measures [49]. To quantify the viral effects properly, populations of interest should include all ranges of COVID-19 severity from asymptomatic to severe patients as well as broad age ranges. Of critical importance is the inclusion of underrepresented populations as well as non-hospitalized individuals who had COVID-19. Cases of multiple infection and long-COVID will also be important for understanding mechanisms potentially linking COVID-19 to cognitive decline [269]. Longitudinal studies should ideally include neuroimaging to track potential cerebral structural, functional, and cerebrovascular consequences of infection. For existing studies about cognitive aging and dementia, it will be important to collect participant information related to COVID-19 [49]. Other critical topics include quantifying the persistence of SARS-CoV-2 in the brain to understand potential neurovirulence effects and fully identifying its role in potential neuropathogenesis [47].

In the United States, the COVID-19 pandemic has disproportionately affected minoritized communities. With both higher infection rates and more severe outcomes, these populations have endured the brunt effects of COVID-19 in a multifaceted way. The amplified influence of COVID-19 in these population could be mitigated through improved medical access, food security, job-based personal protective equipment, housing availability, financial assistance, and better public health initiatives to increase trust [266,270]. COVID-19 is unlikely to be the world's last coronavirus outbreak, so creating robust systems for health equality to prevent this type of damage to our communities is essential moving forward [49].

Based on the availability of current data, we can make predictions about how many individuals are at risk for dementia progression. To establish a baseline percentage of COVID-19 severity across cases, the largest recorded population of 44,000 COVID-19 cases from the Chinese Center for Disease Control and Prevention indicates that $\approx 80\%$ of COVID-19 cases are asymptomatic/mild, $\approx 14\%$ severe, and $\approx 5\%$ critically ill [271]. If all severe COVID-19 cases are considered to be at risk for cognitive decline from infection, then to date, an additional 4.7 million individuals within the United States and 26 million people worldwide would be at risk [1]. While the death rate of COVID-19 is high, the long-term health consequences of those recovering from COVID-19 should not be understated or ignored [272]. These numbers represent an alarming clinical case load for extended COVID-19 monitoring, a significant challenge, but essential for full population recovery.

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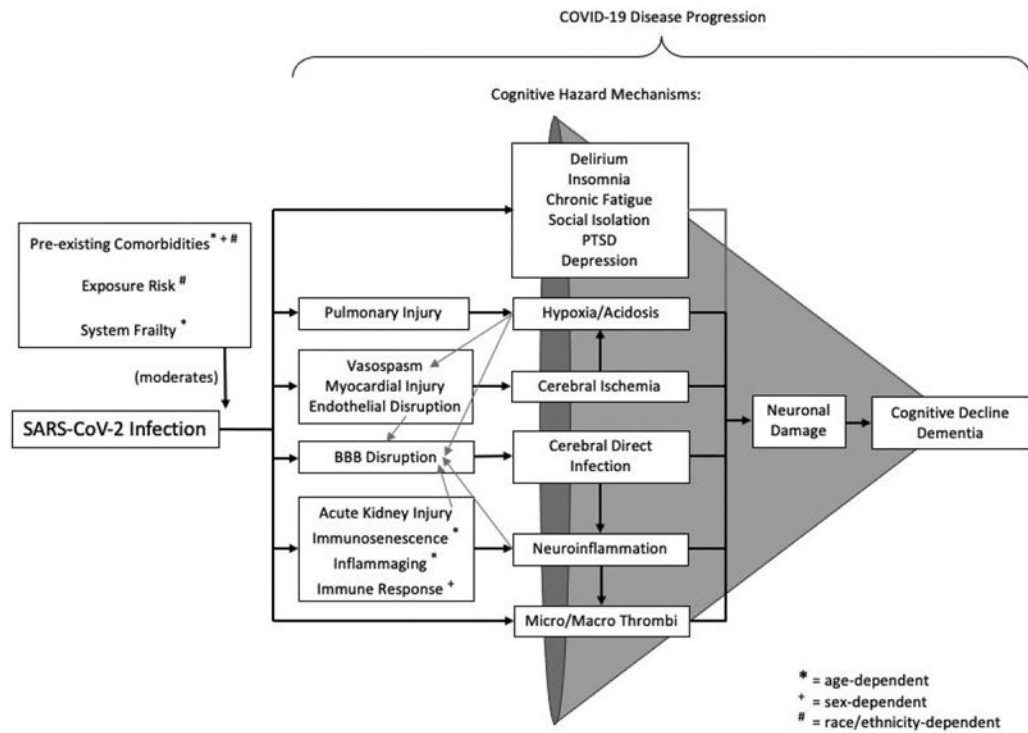


Fig. 1. SARS-CoV-2 infection, with age-, sex- and race/ethnicity-dependent moderators that influence severity, initiates interdependent damage pathways that have the potential to cascade towards the outcome consequence of long-term cognitive decline and/or dementia. Lighter gray arrows represent conditional influences.

Table 1.

Rate estimations of neurological symptoms, loosely organized by frequency, are broken down into central nervous system, peripheral nervous system, and skeletal muscular injury categories, among clinical COVID-19 patients. Severe vs non-severe COVID-19 cases were distinguished based on respiratory/pneumonia metrics with severe cases passing the criterion for mechanical ventilation [71,73].

	Neurological manifestation	Severe case	Non-severe case	Unspecified severity or case studies
Central nervous system	Encephalopathy	65-84% [73,75]	13% [73]	42% [76]
	Dysexecutive syndrome	36% [75]	-	-
	Dizziness	5-30% [71-73,77]	7-30% [71-73,77]	-
	Headache	8-32% [71-73,77]	6-40% [72,73,77,78]	-
	Altered state of consciousness	5-39% [71-73]	2-7% [71-73]	33% [76]
	Delirium	11-33% [79-81]	-	-
	Nausea / vomiting	8-11% [77]	2-10% [77,78]	-
	Ischemic stroke	1.2-5.7% [71-73,82]	0.5-1.4% [71-73,82]	1.6-5.4% [76,83]
	Acute hemorrhage	0.7-0.9% [72,73]	0% [72,73]	4.5% [76]
	Acute encephalitis	0% [72,73]	0.2-0.3% [72,73]	- [12]
	Meningitis / myelitis	0% [73]	0% [73]	- [12,84]
	Ataxia	1.1% [71]	0% [71]	-
	Seizures	0-1.2% [71-73]	0-1% [71-73]	-
Peripheral nervous system	Taste impairment (ageusia/dysgeusia)	3-4% [71,72]	7-55% [71,72,78]	-
	Smell impairment (anosmia/dysosmia)	3-13% [71-73]	6-86% [71-73,85]	-
	Nerve pain (neuralgia)	4.5% [71]	0.8% [71]	-
	Vision impairment	2.3% [71]	0.8% [71]	-
	Polyneuropathy	0-1.5% [72,73]	0-0.2% [72,73]	-
	Guillain-Barré syndrome + variants	0% [73]	0% [73]	0.004-0.005% [86-89]
Skeletal muscular injury	Myalgias	42-65% [72,73]	10-53% [72,73,78]	-
	Rhabdomyolysis	2.2-13% [72,73]	0.3-0.4% [72,73]	-
Overall		46-93% [71-73]	30-79% [71-73]	-

Table 2.

Rate estimations of long-term symptoms, loosely organized by frequency, from clinical patients recovered from acute features of COVID-19. A similar reference population is compared with to disentangle the effects of the COVID-19 pandemic from SARS-CoV-2 infection. Only symptoms that could have a primary or secondary effect on cognition are included.

	Clinical COVID-19 survivor	Comparison population
1 Symptom	50% [†] [122], 76% [‡] [151]	-
Chest CT abnormalities	71% [†] [152], 53% [‡] [151]	-
Fatigue	53% ^{**} [123], 28-53% [†] [122,124], 63% [‡] [151]	9-22% [122,153]
Myocardial inflammation	30-60% [†] [154,155]	-
Psychomotor coordination impairment	57% [†] [127]	-
Executive function impairment	50% [†] [127]	-
PTSD	28% ^{**} [126]	3-17% [156,157]
Loss of concentration	26% ^{**} [125], 33% [†] [127]	-
Verbal fluency loss	32% [†] [127]	-
Insomnia/sleep disturbance	8-40% ^{**} [125,126], 18% [†] [122], 26% [‡] [151]	5-32% [122,156]
Depression	21-31% ^{**} [125,126], 4.3% [†] [122], 23% [‡] [151]	1-28% [122,156,157]
Memory loss	18% ^{**} [125], 24% [†] [127]	-
Pulmonary function abnormalities	21-58% [†] [122,158], 22-56% [‡] [151]	5% [122]
Resting heart rate increase	11% [†] [122]	0% [122]
Hematuria (kidney)	57% [*] [159]	-
Proteinuria (kidney)	31% [*] [159]	-
Liver ALT, AST/ALT, GGT & ALP Levels	[*] [160]	-

* = Measurements at Hospital Discharge.

** = Measurements at 1 month.

[†] = Measurements at 3 months.

[‡] = Measurement at 6 months.