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## Review

# Can healthy lifestyle reduce disease progression of Alzheimer's during a global pandemic of COVID-19?

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## ABSTRACT

The novel coronavirus disease 2019 (COVID-19) has pushed the medical system to its breaking point. While the virus does not discriminate, the elderly and those with comorbidities, including hypertension severe obesity, diabetes mellitus, coronary disease, pneumonia and dementia, are at a greater risk for adverse outcomes due to COVID-19. While many people navigate their new normal, the question of what the long-lasting effects of the pandemic may be, lingers. To investigate how vulnerable populations are affected by the pandemic, we focused on Alzheimer's disease, a vector to understanding how the virus has impacted AD progression and risk via aging. By assessing the effect of COVID-19 on AD patients, we explore genetics, metabolism, and lifestyle factors in both COVID-19 and Alzheimer's disease that can work synergistically to precipitate adverse outcomes. This article also discusses how age-related conditions and/or age-related comorbidities susceptible to COVID-19. We also discuss possible healthy lifestyle factors reduce and/or combat COVID-19 now and in the future.

## 1. Introduction

The novel coronavirus disease 2019 (COVID-19) is a virus that has severe adverse effects on the elderly and those with comorbidities including hypertension, severe obesity, diabetes mellitus, coronary disease, pneumonia, and dementia. Furthermore, these patients are at an increased risk of contracting the virus due to their impaired immune systems. While many people navigate their new normal life, the question of what the long-lasting effects of the pandemic may be, lingers. This article focuses on Alzheimer's disease (AD) to understand how the virus may impact AD risk and progression in the future. This article explores how genetics, metabolism, and lifestyle factors in both COVID-19 and AD can work synergistically to precipitate adverse outcomes. The article

also discusses factors that may reduce and/or combat COVID-19. The content presented and discussed will be useful to the general public, elderly individuals with comorbidities, students, scholars, and researchers of ageing and Alzheimer's disease.

### 1.1. Alzheimer's disease

First studied in 1906 by the German neuropathologist, Alois Alzheimer, Alzheimer's Disease is a neurodegenerative disease that affects both declarative and non-declarative memory especially in the elderly. With more than 50 million people affected by AD globally, Alzheimer's disease has becoming increasingly prevalent with numbers expecting to quadruple by 2050 (Oliver and Reddy, 2019). It is the 6<sup>th</sup> leading cause

**Abbreviations:** ACE2, angiotensin converting enzyme 2; AD, Alzheimer's disease; APOE4, apolipoprotein E4 genotype; APP, amyloid beta precursor protein; Aβ, amyloid beta; BMI, body metabolic index; CNS, central nervous system; COVID-19, coronavirus disease 2019; COX, cytochrome c oxidase activity; CypD, cyclophilin D; DMV, double membrane vesicles; HIF-α, hypoxia inducible factor-1α; IFN, interferon; MCI, mild cognitive impairment; MFRTA, mitochondrial free radical theory of aging; MHV, mouse hepatitis virus; MitomiRs, mitochondrial microRNAs; MtDNA, mitochondrial DNA; NO, nitric oxide; NPIQ, neuropsychiatric Inventory-Questionnaire; ORF, open-reading frames; PARP, poly-ADP-ribose polymerase; PS1, presenilin 1; PS2, presenilin 2; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxidative species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCD, sickle cell disease; T2D, type 2 diabetes; TMPPSS2, transmembrane protease serine 2; TNF-α, tumor necrosis factor α; TyG, triglyceride and glucose index; WD, Western diet.

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of death in the United States (Koffie et al., 2011). There are two forms of AD: early-onset familial and late-onset sporadic. AD is characterized molecularly by the accumulation of amyloid- $\beta$  protein ( $A\beta$ ) that form plaques when aggregated (Bhatti et al., 2019). A postmortem specimen of an AD affected brain demonstrated accumulation of  $A\beta$  in plaques and vessel walls, especially in regions involved in memory and learning such as the hippocampus and temporal cortex (Reddy and Beal, 2008). AD is also characterized by neurofibrillary tangles as well as hyperphosphorylation and polyubiquitination of tau protein. Tau protein stabilizes and arranges microtubules. As AD progresses, there is brain atrophy, impaired energy metabolism, chronic oxidative stress, and DNA damage (Daulatzai, 2017). These changes further amplify the AD progression thus acting as both an antecedent and consequence. Progressing over decades, AD first manifests as subtle memory failure that then progresses to significant memory loss.

Many researchers have been investigating the underlying risk factors and possible therapeutic mechanisms to identify preventative measures and promising cures. Recent research efforts have been made to identify lifestyle modifications for people prone to AD in hope of preventing the rapid progression of AD. Such efforts include exercise, a healthy/balanced diet rich in vitamins and antioxidants, maintaining cardiac health, avoiding obesity, smoking cessation, controlling diabetes, and avoiding depression. Kivipelto and colleagues, in 2018, noted that multiple trials, such as the FINGER trial, have shown that preventative lifestyle interventions are particularly effective for at-risk patients (Kivipelto et al., 2018). However, the coronavirus pandemic that started in late 2019 has greatly affected the lifestyles of everyone, especially those with AD.

### 1.2. Coronavirus 2019 and Alzheimer's disease

From the RNA virus family, Coronavirus, named for its crown shaped halo due to the spike protein projections on their surface, is a family of viruses that can infect both humans and animals (Vallamkondu et al., 2020). The novel Coronavirus, named SARS-CoV-2, is a highly infectious virus from this family with a long incubation period. The most common risk factors for those hospitalized with COVID-19 include old age (>65), obesity, and hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease (Butler and Barrientos, 2020; Finer et al., 2020; Finucane and Davenport, 2020; Martinez-Ferran et al., 2020) (Fig. 1). As the virus spread through communities, a new policy of social distancing and isolation has been growingly adopted to protect the vulnerable populations. As a result of these measures, many lifestyle modifications had to be made by AD patients.

In a Wall Street Journal article, Kamp and Overberg, recorded the devastation in nursing homes caused by COVID-19 noting that there has been an 18 % increase in fatalities in AD patients. While they do not draw a direct link to coronavirus infection as the cause of death, they

attribute much of the spike of deaths to the SARS-CoV-2's impact on healthcare and management (Kamp and Overberg, 2020). As researchers' study COVID-19 further, they have noted that patients with dementia are 40 % more likely to experience adverse outcomes if infected with SARS-CoV-2. Further investigation into the correlation between COVID-19 and neurologic vulnerability led to the discover of many ACE2 receptors in the brain that could pose as sites of entry for the virus (Ferini-Strambi and Salsone, 2020). This finding may shed greater light onto how SARS-CoV-2 can produce neurologic symptoms such as anosmia and dysgeusia. Furthermore, the cytokine storm brought on by SARS-CoV-2 may increase amyloid deposition via amyloid-stimulated Type 1 interferon pathways and this deposition may lead to AD or an acceleration of AD symptoms (Ferini-Strambi and Salsone, 2020) (Fig. 3). These amyloid depositions can aggregate as fibrils and further trap the viral particles and activate microglia. Complement cascade activation can further destroy synapses (Ferini-Strambi and Salsone, 2020).

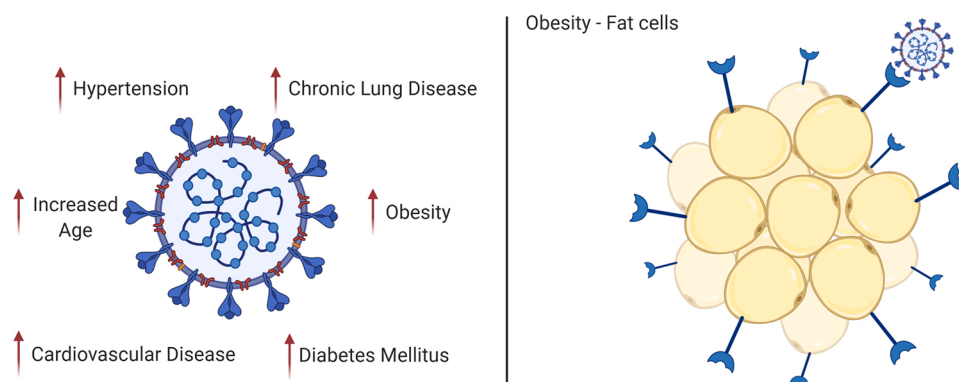
Isaia and colleagues presented a case study of an 83-year-old Alzheimer's patient in Italy who was affected by COVID-19. While the patient survived the infection, the doctors noted that patients with dementia and COVID-19 may present with mild symptoms but are highly vulnerable due to their deteriorating health. The researchers noted these patients require early supportive measures for better prognosis (Isaia et al., 2020).

Currently, elderly individuals have taken extreme measures such as living in total isolation and even grocery shopping at allotted hours to avoid exposure. These measures are necessary because there is a known phenomenon of immune-senescence in the elderly that leads to less production of new T-cells and B-cells to fight infections. Furthermore, there is a glycoprotein impairment on T-cells. As a result, there is a great inflammatory response but a delayed and weak adaptive response. Therefore, the elderly take more time to clear a virus and have a decreased ability to mount a coordinated B-cell driven defense against pathogens (Albin et al., 2020).

### 1.3. COVID-19 and neurologic damage

In 30–40 % of COVID-19 cases, especially amongst the elderly, there are neurological symptoms alongside the constitutional symptoms and dyspnea (Lee, 2020). The loss of smell and taste has been a widely reported neurological symptom of COVID-19. In a research study of 417 patients, researchers found that 85.6 % of those with mild COVID-19 had loss of smell and 88.0 % had loss of taste (Giacomelli et al., 2020). Similar research done by Lennon and colleagues also corroborate olfactory dysfunction as an early symptom (Lennon, 2020).

Researchers at the Beijing Ditan Hospital have found SARS-CoV-2 in the cerebrospinal fluid of patients infected with the virus. The presence of this virus in the CNS, along with its resulting cytokine storm, could



**Fig. 1.** Comorbidities can significantly increase the likelihood of adverse outcomes with SARS-Co-2. For example, patients with excess fat are more susceptible to SARS-Co-2 as a result of increased ACE2 receptors on fat cells.

lead to toxic encephalopathy (Wu et al., 2020). While the mechanism of how SARS-CoV-2 enters the brain is unclear, researchers have noted that SARS-CoV-2 can enter cells through the ACE2 protease and there are many ACE2 proteases in the brain (Abate et al., 2020; Fotuhi et al., 2020). Some researchers propose that the virus can reach the brain through the olfactory nerves especially given the large percentage of patients who experience anosmia prior to other COVID-19 related symptoms. SARS-CoV-2 may migrate through the sensory nerve using motor proteins such as dyneins or kinesins. Furthermore, the connection between the nasal cavity and the forebrain makes SARS-CoV-2's attachment to the olfactory neurons particularly effective for CNS penetration (Fig. 2). Some researchers note that the virus can infect nasal cells and spread to the brain in under 7 days. Recent research has uncovered that the nasal goblet cells express high amounts of ACE2, thus providing an avenue for the virus to enter the olfactory neurons. ACE2 was also found in the motor cortex, substantia nigra, astrocytes, oligodendrocytes and microglial cells. There are fewer ACE2 expressing cells in the hippocampus (Abate et al., 2020).

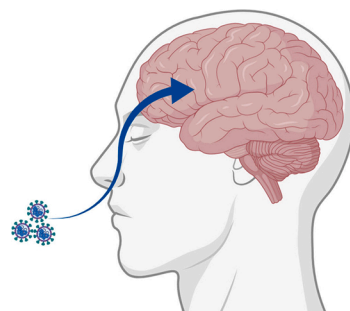
If the SARS-CoV-2 virus makes it into the brain, it is very difficult to remove especially as nerve cells do not have major histocompatibility complex antigens (Fig. 2). Furthermore, the hypoxia caused by the severe pneumonia that the virus causes can lead to CNS damage. The accumulation of acid as a result of the impaired gas exchange can lead to cerebral edema and ischemia (Wu et al., 2020). From a study of 125 COVID-19 cases in the United Kingdom selected for a study on the neurologic effects of COVID-19, researchers noted that 77 patients had cerebrovascular events, of whom 57 had a stroke and 9 had intracerebral hemorrhages (Varatharaj et al., 2020). Furthermore, 5–6 % of COVID-19 patients may have a missed CVA diagnosis during their course of treatment (Lee, 2020). Researchers noted that while cerebrovascular events were particularly prevalent in this study, encephalopathy or encephalitis also presented in a majority of patients with altered mental status. This study also noted that younger populations suffered more severely from altered mental status because of COVID-19 while the older population had a higher prevalence of cerebrovascular events. The finding of increased altered mental status in younger populations is particularly interesting as this is a finding most often associated in infections of the elderly. Researchers attributed the increased cerebrovascular events in the elderly to the declining vasculature health as a result of aging (Varatharaj et al., 2020). However, the sample sizes of these studies are small and offer an interesting opportunity for future research with larger sample sizes.

From strokes, to seizures and encephalopathy, COVID-19 is linked to severe neurologic damage (Fig. 2). Many of these patients had confusion and agitation following their neurovascular events. Fotuhi and colleagues have grouped COVID-19 effects on the brain as following:

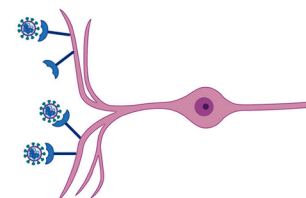
**Stage 1:** Limited to smell and taste dysfunction with controllable cytokine storm. Dysfunction resolves on its own (Fotuhi et al., 2020).

**Stage 2:** High cytokine storm that leads to strokes, vasculitis, and thrombosis

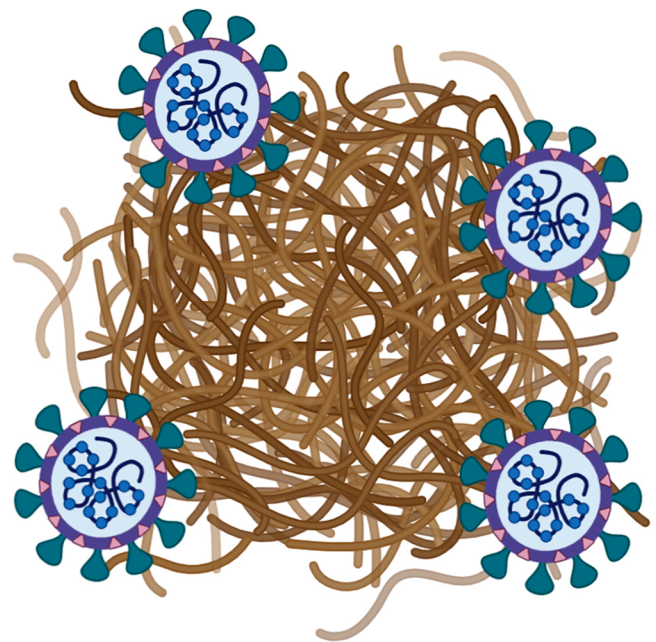
(Fotuhi et al., 2020).



Anosmia  
Dysgeusia  
Delirium/Dementia  
CVA  
Seizures  
Encephalopathy



**Fig. 2.** SARS-CoV-2 may enter the CNS via the olfactory neurons that have abundant ACE2 receptors. Once inside the neurons, they may travel via axonal transport mechanisms to the motor cortex.



**Fig. 3.** Both a protective and a damaging process, amyloid deposition traps SARS-CoV-2 for clearance, but may lead to further AD pathology.

**Stage 3:** High cytokine storm that damages blood-brain barrier. Edema and brain injury that leads to delirium, seizures, and encephalopathy. Hypertension and increased vascular resistance (Fotuhi et al., 2020).

Researchers have also noted that infections can exacerbate the AD pathology. Using 3xTg-AD mice and mouse hepatitis virus (MHV), researchers noted that the immune response triggered by the viral infection of the CNS resulted in increased infiltration of macrophages, microglial activation, and T cell activation. This inflammatory response, if activated for a long period of time, can increase levels of phosphorylated tau and negatively affect learning and memory (Sy et al., 2011). While nitric oxide (NO), produced as a result of infection can have a protective effect against AD, when its levels are too high, NO can exacerbate AD risk. In COVID-19, the persistent infection can stimulate the glial cells to generate a cytokine storm that can increase both NO production and IL-6. The increased activity of these glial cells can increase neurodegenerative disease risks (Abate et al., 2020).

The amyloid fibrils, characteristic in Alzheimer's disease, can trap viral particles. Researchers have hypothesized that creation of amyloid fibrils may be a host response to infection to both trap the infection and to activate microglia for further destruction of foreign matter. This further raises concerns of an increased Alzheimer's spike in future populations as a result of COVID-19 CNS injury that may have led to increased amyloid beta accumulation in the brain (Naughton et al.,



2020). Furthermore, there is evidence of abnormal folding and aggregations of protein in the neurons of COVID-19 survivors (Fotuhi et al., 2020).

Even though some patients can recover from the virus in 20 days, the neurologic damage may be more extensive. Alterations in the Blood-CSF barrier also has been recorded in COVID-19 and may increase risk of future neurodegenerative diseases. The psychological stress on people as a result of the virus can also exacerbate AD progression. Furthermore, COVID-19 muscular injuries recruit neutrophils to maintain homeostasis which may lead to further tissue damage and deposition of toxins that can increase AD risk (Lennon, 2020). Therefore, a longitudinal study on whether the injury events caused by COVID-19 as well as the abnormal folding of proteins may lead to AD in the future is recommended. Furthermore, these studies should include a larger sample size.

#### 1.4. Genetics and COVID-19

The disproportional effects of COVID-19 on racial minorities, as seen by the difference between population makeup and COVID mortalities in Table 1, show that there may be a different effect of COVID-19 on different races. ACE2 is found on the X chromosome and seems to more expressed in Asians than in Caucasians and in African Americans (Shi et al., 2020; Verdecchia et al., 2020). ACE2 and transmembrane protease serine 2 (TMPRSS2) are expressed variably in different populations and are affected by comorbidities such as diabetes mellitus. From a 3-year longitudinal study of 330 asthmatic patients and 79 healthy patients, researchers noted that African Americans had higher amounts of ACE2 and TMPRSS2 than Caucasians. With reference to the Caucasian population, African Americans had 1.28 times the amount of TMPRSS2 ( $p < .001$ ). Since Coronavirus uses ACE2 to enter cells, these populations may be more susceptible to the coronavirus (Peters et al., 2020).

Patients with chronic underlying conditions such as hypertension and diabetes, are greatly affected by the novel coronavirus as it taxes an already overactive renin-angiotensin system (Vallamkondu et al., 2020). The dysregulation of the RAAS system leads to an extreme inflammatory response that has systemic effects (Albin et al., 2020; Bhatti et al., 2019; Vallamkondu et al., 2020). The RAAS system affects vascular tone and the sympathetic nervous system. By doing so, it maintains blood pressure (Cohall et al., 2020). With an increasingly likelihood of an overactive RAAS system due to higher risks of hypertension, African Americans are also at a higher risk for poor outcomes from the novel coronavirus as it exacerbates the RAAS system. Many genes, such as CYP11B2 and SCNN1B, may have variations in African Americans that can lead to primary aldosteronism and even Liddle Syndrome (Cohall et al., 2020).

Sickle cell disease (SCD) patients have compromised immune systems thus are susceptible to COVID-19. The instance of SCD is higher in African Americans than in other groups. Concomitant respiratory illnesses can further elevate the risk of COVID-19. Interestingly, while more susceptible, these patients are also able to fight off the infection and have mild symptoms. Researchers postulate that the chronically activated immune system, along with the anemia, may protect the patients from the more severe cases of Covid-19 (Hussain et al., 2020).

Different races also have different susceptibilities to comorbidities that affect their response to COVID-19. Of patients who have a

comorbidities, 45.4 % of patients who contract COVID-19 are at risk for serious complications (Adams et al., 2020). For example, Native American populations have a high risk of complications from COVID-19 due to many underlying conditions such as heart disease and diabetes (Dorn et al., 2020; Kakol et al., 2020).

#### 1.5. Genetics and Alzheimer's disease (AD)

Genetics are a non-modifiable risk factor for AD, therefore, are not greatly affected by the coronavirus pandemic. Genetic researchers have found genes associated with familial AD such as amyloid precursor protein (APP), presenilin 1, and presenilin 2. Of these, presenilin 1 is the most common mutation for familial AD and accounts for 30–70 % of familial AD. Amyloid precursor protein accounts for 2–5 % of familial AD while presenilin 2 accounts for about 5% of cases (Amakiri et al., 2019; Bird, 1993). There is currently ongoing research to identify genetic risk factors of AD.

#### 1.6. Genetics of AD with ApoE4 and increase COVID-19 risk

A study done in the UK noted that amongst 16,749 patients who were hospitalized for COVID-19, many of them had dementia as a comorbidity. Furthermore, they noted an association between dementia and a higher mortality rate. To further assess whether the ApoE4 gene found in AD had any increased risk for COVID-19 mortality, researchers looked at a sample size of 322,948 patients. They noted that ApoE e4e4 homozygotes had a statistically significant higher risk for COVID-19 (Kuo et al., 2020). Some researchers noted this correlation remained strong even after excluding comorbidities such as hypertension, coronary artery disease, and type 2 diabetes. Even within the ApoE family, Finch and colleagues noted that ApoE4 homozygotes have a 2.2-fold increased risk for COVID-19 contraction and 4.3-fold increased fatality in comparison to other ApoE variants such as ApoE3 (Finch and Kulminski, 2020). ApoE4 plays a role in inflammatory and anti-inflammatory responses (Kuo et al., 2020). ApoE4 increases the risk for both AD and severe COVID-19. Researchers, using markers of activation such as CD68, noted that ApoE4 carriers had increased gliosis. Given that increased microglial activity can damage the brain, this is an area for further study (Abate et al., 2020). ACE2, an entry site for the virus into cells, is highly expressed in the brain and is a marker for worse outcomes in AD patients (Kuo et al., 2020; Lim et al., 2020). As a result, along with the common symptoms of delirium and dementia in COVID-19 patients, it stands to reason that the virus can enter and greatly affect the brains of COVID-19 patients especially in severe AD patients (Lim et al., 2020).

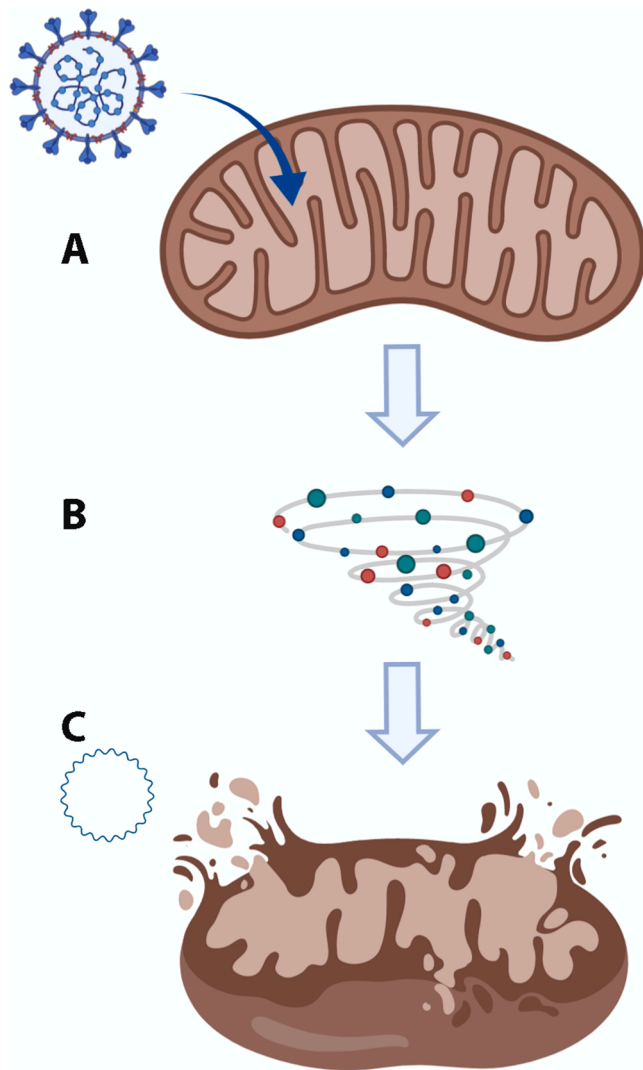
#### 1.7. Mitochondrial dysfunction and COVID-19

Researchers hypothesize that SARS-CoV-2, through its cytokine storm, can increase mitochondrial oxidative damage (Fig. 4). Furthermore, this mitochondrial dysfunction can lead to thrombosis, ferroptosis and mortality (Polidori et al. 2021). As inflammation increases, there is an increase in oxidative stress. Inflammatory cytokines produced by the cytokine storm, such as TNF-alpha, can increase the mitochondria's production of reactive oxidative species (ROS) that result in the increased oxidative stress. The cytokines, through a cascade of events that include reduced ATP production by the mitochondria, can also lead to mitochondrial membrane permeabilization and cell death. The destruction of mitochondria can further exacerbate the inflammatory response as mitochondrial contents spill into the extracellular environment (Saleh et al., 2020).

Hyper-ferritinemia can lead to increased severity of illnesses. The mitochondria take up iron for heme synthesis and storage. Increased levels of iron or impairments in iron metabolism can lead to cellular stress. Increased iron can affect the oxygen consumption in the mitochondria. A dysfunctional mitochondrion will lead to iron accumulation and increased ROS production through reactions such as the Fenton

**Table 1**  
Racial disparities in COVID-19 mortality.

Race	% of US Population	% of COVID deaths	Source
White (non-Hispanic)	75.1 %	49.9 %	
Black	14.1 %	22.2 %	(Bureau, 2018) (CDC, 2020)
Hispanic/Latino	18.1 %	17.2 %	
Asians	6.8 %	5.2 %	
Native American	1.7 %	.7%	



**Fig. 4.** Molecular links between SARS-CoV-2 and mitochondria in relation to cytokine storms. **A.** Represents the location of SARS-CoV-2 to mitochondria. **B.** Shows cytokine storm leads to increased free radical production and **C.** Represents reduced mitochondrial ATP, leading to reduced mitochondrial membrane potential.

reaction. Eventually, this dysregulation can lead to ferroptosis or programmed cell death. Mitochondria in the platelets are also affected. Since platelet life is determined by the mitochondria, mitochondrial dysfunction can reduce platelet life that can lead to reactive clotting or thrombosis (Saleh et al., 2020).

To affect the mitochondria, SARS-CoV-2 enters the cell via ACE2 and TMPRSS2. ACE2 can regulate mitochondrial function and ROS production via its regulation of the NADPH oxidase 4. TMPRSS2, the transmembrane serine protease, can regulate mitochondria via the estrogen-related receptor- $\alpha$ . Once inside the cell, SARS-CoV-2 can localize to the mitochondria using open-reading frames (ORFs) such as SARS-CoV-1 does. These ORFs, in particular ORF-9, can affect the outer mitochondrial membrane and are involved in suppression of anti-viral signaling systems such as MAVS (Shenoy, 2020) (Fig. 4).

SARS-CoV-2 needs double membrane vesicles (DMV) for replication. These DMVs can help protect the virus from host cell defense as well. The mitochondria and endoplasmic reticulum, through cross talk as a result of mitochondrial stress, can induce the formation of these DMVs. Therefore, the mitochondrial dysfunction caused by SARS-CoV-2 may also help with its entry and replication within cells (Singh et al., 2020).

Mitochondrial dysfunction can also play a role in COVID-19 sepsis.

Organs typically affected by sepsis, a life threatening condition characterized by wide spread organ dysfunction, include the lungs, heart, liver, and the brain. SARS-CoV-2 increases mitochondrial inflammatory cascades, while impairing mitochondrial function, structure, and autophagy genes. Reactive oxidative species that are not cleared by the mitochondria damage the lipid membrane of the mitochondria, resulting in leakage of mtDNA or danger-associated molecular patterns. These DAMPs activate pathogen recognition receptors on immune cells to activate an inflammatory response. Further activation of NF- $\kappa$ B pathway can lead to tissue dysfunction and multi-organ failure (Shenoy, 2020).

Hypoxia, as a result of deficient aerobic respiration, presents in sepsis. Hypoxia inducible factor-1 $\alpha$  (HIF- $\alpha$ ) / Sirtuins signaling pathway are upregulated during hypoxia and inflammation. Sirtuins, the NAD<sup>+</sup> energy sensors that maintain homeostasis are particularly affected by the depressed levels of NAD<sup>+</sup>. SARS-CoV-2 upregulates poly-ADP-ribose polymerase (PARP) that depress levels of NAD<sup>+</sup>. Furthermore, lower Sirtuins result in increased ROS production and further downregulation of Sirtuins and inactivation of HIF- $\alpha$ . The reduced HIF- $\alpha$  and Sirtuins trigger an anti-inflammatory state that hampers the clearance of the virus (Shenoy, 2020).

Mitochondria dysfunction in COVID-19 may also have a sex bias as there is a higher prevalence of worse outcomes in males than in females. Some attribute this discrepancy to the immunocompetence handicap model whereby males use their sex hormones for development of sex traits thus divert resources from mounting a strong immune response. Another theory of poor immune response relates to poor mitochondria that were inherited from the mother as well as the impaired mitochondria in males. These poor quality mitochondria exist because of the quality control step is female-based and do not select against deleterious effects on males [40].

#### 1.8. Mitochondrial dysfunction and Alzheimer's disease

During AD, there is great mitochondrial dysfunction that leads to impaired ATP generation and substrate metabolism. Mitochondrial microRNAs, or mitomiRs, lead to impaired oxidative abilities, decreased mitochondrial volume, reduced mitochondrial membrane potential, and impaired electron transport chain activity. As a disease of the elderly, ageing also contributes to impairments of the mitochondria, especially in the mitochondrial free radical theory of aging (MFRTA). The imbalance between the reactive oxygen species and the ability to combat these free radicals leads to oxidative stress that is characteristic of mitochondrial dysfunction (John et al., 2020). When mitochondria are damaged, they further exacerbate the oxidative stress by producing increasing amounts of free radicals that can lead to protein and nucleic acid damage especially since the mitochondrial DNA is not protected. This can also lead to impaired mitochondrial trafficking due to the sheer amount of inactive and nonfunctioning mitochondria. Poor mitochondrial availability leads to neurodegeneration due to a lack of synaptic transmission (Bhatti et al., 2019). Oxidative damage is seen in AD patient neurons in the form of altered mitochondrial DNA and a surge of cytochrome oxidase (COX) levels. Oxidative stress is increased further due to inhibition of the electron transport chain. There is an increase in cyclophilin D which affects mitochondrial calcium levels at the synapses. By opening pores, Cyclophilin D destroys the membrane potential and can cause neuronal death (Jan et al., 2017).

#### 1.9. Mitochondrial dysfunction and increase COVID-19 risk

With impaired reductive abilities and increased mitochondrial dysfunction, AD compromises the host such that fighting off the virus is made even harder. Since the mitochondria in the AD patients are 'poor quality' mitochondria, the virus can take advantage lead to further damage. While further study needs to be done on AD mitochondria in COVID-19, the literature demonstrates an increased vulnerability to viruses, especially those that can localize to the mitochondria, block

anti-viral mechanisms of the mitochondria, and generate inflammatory cascades that overwhelm the cell.

#### 1.10. Insulin resistance and COVID-19

Insulin allows cells to absorb and utilize glucose in order to generate the energy needed to expend on cellular processes. Insulin resistance, on the other hand, compromises the cell and can lead to increased vulnerability to insults. The triglyceride and glucose index (TyG), a marker of insulin resistance, nonalcoholic fatty liver disease, and hypertension. Researchers, in a study of 151 patients in Wuhan, noted that TyG was significantly associated with increased risk of mortality in COVID-19 and could be used as a marker for poor outcomes of the disease (Ren et al., 2020). Yan and colleagues also noted a similar correlation between diabetes and severity of COVID-19 when they studied 193 COVID-19 patients. The median survival rate for COVID-19 hospitalized patients with severe diabetes was 10 days compared to those without diabetes (18 days) (Yan et al., 2020).

#### 1.11. Insulin resistance and Alzheimer's disease

The brain uses glucose as its major energy source as it can easily cross the blood brain barrier. In AD animal models and patients, insulin signaling decreases while the total amount of insulin needed increases. The feedback loop of increased insulin secretion due to resistance is well understood and can lead to elevated blood glucose levels. Insulin resistance can lead to decreased hippocampal function, as the hippocampus is sensitive to insulin deficits and requires spikes of glucose to maintain its role as the memory center of the brain. The decrease in hippocampal function correlates with the progression of AD and is noted in patients in memory deficits. Evidence of this decreased hippocampal function is quantified via the synapse to neuron ratio in cortical neurons of AD patients. In normal aging, there is a 20–30 % decrease in the synapse to neuron ratio. However, in AD hippocampal samples, there is an almost 50 % decrease in synapse to neuron ratio (Reddy, 2009). Since AD is heavily influenced by insulin resistance, some scientists call AD a type three diabetes or an insulin resistance of the brain. Furthermore, the hypometabolism of glucose is an early marker of AD that can precede diagnosis by decades (Daulatzai, 2017). Glucose metabolism promotes further pathologies such as neuroinflammation which can decrease nitric oxide (NO), increase endothelin, and increase A $\beta$  deposits (Daulatzai, 2017).

#### 1.12. Insulin dysfunction and increased COVID-19 risk

Insulin resistance in Type 2 diabetes, for example, is a major risk factor for severe COVID-19 infections as well as Alzheimer's disease. African Americans and Hispanics are 2 times more affected by Alzheimers and diabetes in comparison to white populations. Type 2 diabetes plays a role in increasing the effects of COVID-19 and Alzheimers via the Interferon regulatory factor 5 pathway that leads to a cytokine storm. While it can exacerbate the inflammatory response in COVID-19, it can also lead to increased amyloid stimulated Type 1 Interferon (IFN) response that can lead to Alzheimer's disease. Especially in the hippocampus, there is an increased expression of genes that are triggered by IFN. These IFNs can also exacerbate the reactive inflammatory response in COVID-19 (Naughton et al., 2020).

#### 1.13. Obesity and COVID-19

Obesity may increase patient susceptibility to COVID-19 due to a higher expression of ACE2 in adipose tissue (Kassir, 2020). Obesity decreases expiratory reserve volume and functional capacity that can result in compromised ventilation (Dietz and Santos-Burgoa, 2020). Obesity can cause a worse prognosis in patients hospitalized with COVID-19 due to obesity induced atelectasis and raised pleural

pressures that can increase the risk of alveolar capillary collapse. A study in France showed a higher incidence of mechanical ventilation for patients hospitalized with COVID-19 who have a BMI > 35 (Finucane and Davenport, 2020). Foldi and colleagues conducted a meta-analysis of 24 studies to examine whether obesity is a risk factor for critical conditions of COVID-19 also confirmed that obesity poses a significant risk factor for ICU admission and invasive mechanical ventilation. Invasive mechanical ventilation incidence increased at a BMI greater than or equal to 25 (Foldi et al., 2020). Dietz and colleagues associate the increased fatality in Italian compared to Chinese older adults to the increased prevalence of obesity in Italians. Likewise, there is a high prevalence of obesity in the United States that could count for the high mortality due to COVID-19. This pattern was previously noted with the impact of obesity on mortality in the United States due to the H1N1 influenza, where obesity increased prevalence of hospitalization and mechanical ventilation (Dietz and Santos-Burgoa, 2020). When studying the H1N1 influenza, scientists noticed that obese patients shed the virus 42 % longer than non-obese adults. A similar increased duration of shedding in the obese is seen in the case of SARS-CoV-2 (Kassir, 2020).

#### 1.14. Obesity and Alzheimer's disease

Although obesity is already a well-known risk factor for chronic disease such as Type 2 diabetes and heart disease, researchers have noted that it may affect AD and vascular dementia development. Recent studies have demonstrated an "obesity paradox" in AD. Obesity during the mid-life stage pose a higher risk for AD development than obesity during the later stages of life. In a study done with 405 middle aged subjects, obesity was correlated with longitudinal cortical thinning in the entorhinal cortex, hippocampus, and posterior cingulate in obese participants in comparison to a control (Pegueroles et al., 2018). However, it is difficult to draw generalizations from this study because another study done by Franz and colleagues with 373 men, showed no relationship between obesity and white matter abnormalities (Franz et al., 2019). Additionally, a study by Fitzpatrick and colleagues that used waist circumference to measure adiposity in the elderly, found that increased circumference was related to increased risk of dementia (Fitzpatrick et al., 2009). The conflicting findings demonstrate that obesity and its link to AD is an area for further study. Furthermore, a sudden lower BMI in later life can be used cautiously as a biomarker for early dementia as patients may be forgetting to eat as well. It is important to note that BMI is not an accurate measure of body composition in the elderly due to aging related loss of body mass.

#### 1.15. Obesity of AD and increased COVID-19 risk

While obesity is slightly correlated with AD, it requires further study to elucidate the correlation. Therefore, conclusions on obesity in AD and COVID-19 are difficult to draw. However, the literature does state that obesity is a high-risk factor for adverse outcomes in COVID-19 and obesity does play a role in increased risk for dementia.

#### 1.16. Nutrition and COVID-19

Martinez and colleagues explored the outcomes of decreased physical exercise (step count) and modified eating habits (overeating) especially during COVID-19. Furthermore, an international online survey launched in April 2020 by Ammar and colleagues noted that there was a negative impact on physical exercise intensity levels and an increase in daily sitting time from 5–8 h (Ammar et al., 2020). A decrease in physical exercise has been noted as a risk factor for metabolic syndrome. Metabolic consequences include increased abdominal fat, inflammatory cytokines, and increased insulin resistance. Sedentary activities lead to a positive energy balance that could worsen the metabolic consequences of quarantine-like sedentary lifestyles. They also noted that confinement can likely lead to a decrease in muscle mass



(Martinez-Ferran et al., 2020).

Ammar and colleagues also noted that there was an increase in unhealthy food consumption, eating frequency, and alcohol binging (Ammar et al., 2020). Butler further notes that diet, especially during COVID-19, may affect outcomes. A Western Diet (WD) comprises of a diet high in saturated fats, refined carbohydrates, sugars, and low levels of antioxidants. A diet in high saturated fats induces an increase in B cell apoptosis and decreases both B and T cell maturation and proliferation. WD impairs the adaptive immune system, which causes chronic inflammation and defense against viruses such as COVID19. As a result, COVID-19 infection may lead to long term health consequences such as dementia due to its resulting increase in inflammation. It could also lead to long term lung damage (Butler and Barrientos, 2020).

### 1.17. Nutrition and Alzheimer's disease

Diet may have a role in AD progression and severity. It was found that a Mediterranean diet (including legumes, fish, grains, fruits, and vegetables) increased Vitamin D and decreased cognitive decline. On the other hand, food groups such as meats and high dairy products full of saturated fats, promote cognitive decline (Solfrizzi et al., 2017). Although a ketogenic diet is an effective therapy for neurodegenerative disease, it is difficult to implement in many AD patients who are elderly. A ketogenic diet in the elderly can result in malnutrition due to decreased food intake and appetite (Wlodarek, 2019).

The Mediterranean diet consists of olive oil, grains, fresh fruits and vegetables, legumes, and fish. The Mediterranean diet has been extensively studied in AD. For example, unsaturated fatty acid consumption such as in fish, antioxidants in fruits, and vitamin B is related to a decreased rate of AD (Cao et al., 2016). In a study done on adherence to the Mediterranean diet, researchers noted that maintaining the diet can improve cognitive function and increase performance on processing speed and memory tests such as backwards digit span and clock drawing test. Low diet adherence, on the other hand, demonstrated delayed recall (Pettersson and Philippou, 2016).

It is important to note that looking at diet as a modifiable factor for Alzheimer's inherently carries some difficulty because no one race's data explains the varieties and unique diets of those that make up a racial category. One such example is the Latinx paradox in that research often groups Hispanics and Latinos together, often inconsistently (Siega-Riz et al., 2014). Furthermore, within these racial categories, as seen in Table 2, there are stark differences that are not captured with broad

comments on diet. Asians also encounter a similar paradox as Hispanics/Latinos. For example, Asians can include Chinese, Japanese, Korean, Indian, Pakistani, and Bengali subgroups, each of which have different cultural diets. Many of these diets vary greatly due to factors such as climate (different spices are available in different regions) and religion (some countries do not eat pig, whereas others do not eat cow, still others do not eat any meat) (Jiwani et al., 2017). Therefore, more focused study of diets may yield more info on their similarity to the Mediterranean diet as well as how it may affect AD risk.

### 1.18. Nutrition in AD that is affected by COVID-19

Access to food may affect general health of older populations (Schrack et al., 2020). For AD patients who do not live at a care facility, the ability to receive food from meal delivery services may be affected due to overall increase demand and decreased in-restaurant dining options. Furthermore, surveillance of food intake by AD patients by an outside party may be decreased due to an increased exposure risk.

AD patients may also develop vitamin D deficiency as they are forced to stay indoors. Reduction in vitamin D may further compromise an already fragile immune system thus increasing risk of infection (Palmer et al., 2020). Vitamin D deficiency exacerbates existing autoimmune diseases and researchers have noted a relationship between low levels of vitamin D and increased disease activity and severity (Aranow, 2011). Furthermore, vitamin D modulates production of the antimicrobial peptide cathelicidin that is involved in the innate and adaptive response to infections. Researchers also note that low levels of vitamin D can gear the immune system to be pro-inflammatory (Gunville et al., 2013). This may exacerbate effects of COVID-19 as it will stress an already taxed and fragile immune system.

In both AD and COVID-19, diet can affect outcomes by impairing the immune system and increasing inflammation. As a result, many researchers are suggesting a Mediterranean diet rich in carbohydrates with a low glycemic index (fruits, legumes, vegetables), high protein with a low-fat percentage (fish, turkey), and dairy products, especially for older adults, during the COVID-19 isolation period (Butler and Barrientos, 2020; Martinez-Ferran et al., 2020).

### 1.19. Stress and COVID-19

The pandemic has resulted in breaks in routine both in interaction with others as well as day-to-day activities. This may increase fear,

**Table 2**  
Diets of various races in comparison to the Mediterranean diet.

Race	Incidence of AD	Diet	Resources
Caucasian	10 %	Fresh fruits, vegetables, cereal grains, vitamins. <b>Similar to Mediterranean diet.</b>	(CDC, 2014) (Li et al., 2017)
African American	14 %	More trans-fat and protein. Lower intake of micronutrients such as calcium, magnesium, potassium, vitamin B, vitamin D, fiber. Lower healthy eating index. <b>Not similar to Mediterranean diet.</b>	(CDC, 2014) (Li et al., 2017)
Hispanic / Latino	12 %	Fat intake: Cubans > Mexicans > Dominicans. Puerto Ricans have high saturated fat intake, low total fruit, low vegetable intake. Low fiber intake. Dominicans have high carbohydrate intake and low vegetable intake. Cubans have low carbohydrate intake and high vegetable intake Mexicans have high intake of vitamin A & C, potassium, folate, calcium, and iron. Cubans had low intake of the mentioned micronutrients <b>Not similar to Mediterranean diet</b>	(CDC, 2014)
Native American	0.5 % for Cree Indians in 1993. Current data not available	Squash, beans, salmon, corn, tortillas Low saturated fats High whole grains, fruits, and vegetables <b>Similar to Mediterranean diet</b>	(Anderson et al., 2004)
Asians	< 10 %	Increased consumption of fried and calorie dense foods. Increased rice and fish intake. Variety of meats, vegetables, grains, and spices. <b>Mildly similar to Mediterranean diet</b>	(Jiwani et al., 2017)



anxiety, and anger. From losing jobs and businesses, to losing loved ones, the pandemic has increased the stress on the world. Many countries around the world established strict social isolation policies in order to contain the virus. In France, visitation to nursing homes, unless it is an end-of-life situation, was restricted since March of 2020. Furthermore, nursing homes had to restrict activities such as group activities and communal dining (El Haj et al., 2020). Some researchers attribute a similar stress level (high) in social isolation to physical immobilization (Fotuhi et al., 2020; Palmer et al., 2020). There is also a great amount of fear in the community due to the virus that affects all ages and races. Especially in the elderly, there is growing fear of contracting a virus that their bodies may not be able to fight off is another factor for stress and anxiety in the elderly (Palmer et al., 2020).

### 1.20. Stress and Alzheimer's disease

Environmental factors such as occupation, diet, stress, depression, and hypoxia can also play a role on AD progression. Stress is known to cause severe inflammation of the brain. As a result, people with depression have a higher risk for Alzheimer's. According to a research study done at the University of Wisconsin, African Americans who reported more stressful events in their lives, such as living in a disadvantaged neighborhood, bankruptcy, alcoholism, and educational complications, were linked with low cognitive function (Zuelsdorff et al., 2020). Another study done at UCSF found a higher rate of dementia in African American participants living in states with high infant mortality. African American participants had a 92 % increased dementia risk in states with high infant mortality and even demonstrated a 36 % increased risk in states without high infant mortality rates. Populations that were not exposed to such high levels of stress did not show a correlation between state of residence and dementia risk (Gilsanz et al., 2019).

While most people associate AD with its characteristic memory decline, there are a number of neuropsychiatric symptoms that also emerge in patients with AD. Furthermore, early presentation of these neuropsychiatric symptoms are strong predictors of progression from MCI to AD. These neuropsychiatric symptoms can be split into three phases such that patients may present with depression and irritability (phase 1) that can exacerbate towards anxiety and agitation (phase 2) that finally progresses into delusions and hallucinations (phase 3). These neuropsychiatric symptoms, regardless of the methods of classification, can be recorded using the neuropsychiatric Inventory-Questionnaire (NPIQ) (Boutoleau-Bretonnière et al., 2020).

### 1.21. Stress in AD that is exacerbated by COVID-19

Delirium is a response to changes in stimuli that the brain is routinely exposed to. Therefore, the disruption caused by COVID-19 social distancing can exacerbate delirium especially in AD patients (Lee, 2020). Strong social distancing measures that reduce exposure risk may also negatively affect those with AD (Fig. 5).

AD patients have established routines to off-set their memory lapses. Breaks in their routines brings them great stress. Lara and colleagues

demonstrated the effects of routine disruption in 20 MCI and 20 mild AD patients in Spain during 2020 due to government mandate. As patients who have existing memory problems, this change in routine generated anxiety for these patients. Using the Neuropsychiatric Inventory and EuroQol-5D, the researchers assessed the cognitive state of the patients prior to the isolation and how it changed as a result of the isolation. After 5 weeks of confinement, patients scores increased from 33.75 to 39.05 and demonstrated increased agitation and apathy. In both populations, MCI and AD, patient's neuropsychiatric symptoms worsened with statistical significance. While quality of life showed no statistically significant worsening, patient anecdotes noted that they felt as if their health condition had worsened (Lara et al., 2020). Haj and colleagues corroborated this trend in their study of AD patients. 50 % of AD patients experience depression and 25–71 % of AD patients experience anxiety. Using the Hospital Anxiety and Depression Scale, the researchers noted that participants (58 AD patients) reported an increase in depression ( $p = .005$ ) and anxiety ( $p = 0.004$ ). As a result, the researchers concluded that depression was exacerbated by the social distancing measures that reduce physical contact (El Haj et al., 2020). Similarly, Boutoleau-Bretonnière and team, through telephone interviews of caregivers and patients with AD, used the NPIQ to understand neurologic changes in AD patients as a result of COVID-19 lockdown measures. They also demonstrated similar results as they too found a significant relationship in 10 of their 38 patients between duration of confinement and increased neuropsychiatric. However, these patients already had poor cognition prior to confinement. This may show that confinement may not exacerbate in patients with normal cognition. However, patients with poor cognition at the onset of the isolation may experience even greater cognitive decline that correlates with the length of time that they were confined (Boutoleau-Bretonnière et al., 2020). Ferini-Strambi and colleagues also noted that the duration of social distancing and social disruption correlated significantly with the increased severity of neuropsychiatric symptoms in AD patients especially in those who already had low cognitive function. Furthermore, a concomitant COVID-19 infection exacerbated these neuropsychiatric dysfunctions (Ferini-Strambi and Salsone, 2020).

Other stressors can negatively impair the elderly and those with AD. The grief of lost ones can exacerbate depression in AD patients (Brown et al., 2020). If an AD patient falls or if they have a sudden health deterioration, the lack of assistance due to social isolation may contribute to increased adverse outcomes (Brown et al., 2020). The combination of the socioeconomic and genetic risk factors across races further amplifies the AD risk factors especially during the COVID-19 pandemic.

## 2. Limitations

Validation for the SARS-CoV-2 increasing Alzheimer's disease statistics hypothesis requires a longitudinal study with a large sample pool. One large effort that has been announced is the Alzheimer's Association International Cohort Study of Chronic Neurological Sequelae of SARS-CoV-2. This study was announced in July of 2020 and will include patients from more than 50 centers across more than 30 countries. Using

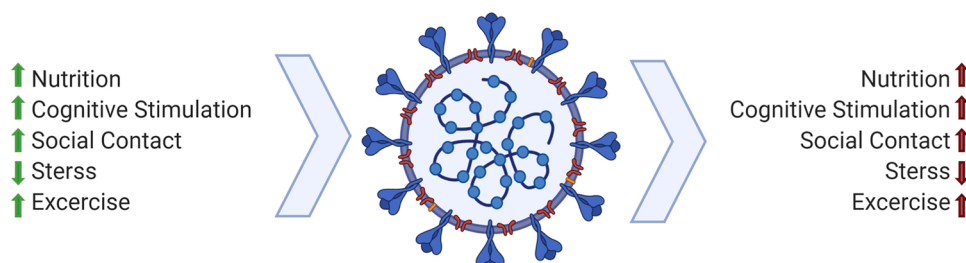


Fig. 5. As a result of COVID-19 lockdown measures, there has been stark changes in people's lifestyle.

health registries, hospital discharge records, and pre-existing data, the researchers hope to investigate the effects of COVID-19 on the brain after 6 months and 12 months of recovery. Details from this study will be announced in May 2021 and may add great value to the hypothesis presented in this article (Lempriere, 2020).

### 3. Conclusions and future directions

The coronavirus pandemic has shaped the way the world functions. From the strict social isolation measures, to increased stress and fear, the effects of coronavirus may have a lasting mark on the health and well-being of the general public. This review investigated factors that increase the risk of Alzheimer's disease and how they were affected by the COVID-19 pandemic. By assessing how SARS-CoV-2 affects different risk factors, we propose that Alzheimer's disease prevalence and progression may be affected far beyond the current SAR-CoV-2 pandemic. Further larger sample longitudinal studies must be done to check how the insults brought on by COVID-19, as well as how the lifestyle that communities are forced into during the COVID-19 pandemic, affects current and future AD development. These studies of COVID-19 patients with neurological damages can be further stratified into those with prior increased risk for dementia and those without. These studies can also be stratified based on income level, reported nutrition, and physical exercise.

This article also touched on the impact of COVID-19 on lifestyle habits. Quarantine could result in an increased sedentary lifestyle, poor eating habits, and social isolation. Daily routines have been disrupted and therefore it is necessary to develop positive coping mechanisms to combat this stressful time. Despite COVID-19's impact on normalcy, people should still strive for healthy lifestyles by exercising at home, cooking healthy meals, and staying in touch with loved ones. These preventative measures can reduce the risk of obesity, diabetes, anxiety, and depression. Reducing the risk for these illnesses is important in AD prevention and reducing overall AD risk. Furthermore, these tactics prove essential even for those who have been infected with COVID-19 because there is no concrete knowledge of long-term immunity or future long-term health implications of prior infection.

### Declaration of Competing Interest

The authors report no declarations of interest.

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