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Review

# Multifactorial Causation of Alzheimer's Disease Due to COVID-19

Paloma Monllor[a,b,1], Praktush Kumar[c,1,2], Mari-Ángeles Lloret[d], Artemis Ftara[a], Jose-Luis Leon[e], Begoña Lopez[f], Ana Cervera-Ferri[g] and Ana Lloret[a,*]
[a]*Department of Physiology, Faculty of Medicine, University of Valencia, INCLIVA, CIBERFES, Spain*
[b]*Internal Medicine Department, University Hospital of La Plana, Vila-Real, Spain*
[c]*MS4, Dr. Baba Saheb Ambedkar Medical College and Hospital, Rohini, New Delhi, India*
[d]*Department of Clinical Neurophysiology, University Clinic Hospital of Valencia, Valencia, Spain*
[e]*Ascires Biomedical Group, Department of Neuroradiology, Valencia, Spain*
[f]*Department of Neurology, University Clinic Hospital of Valencia, Valencia, Spain*
[g]*Department of Human Anatomy and Embryology, Faculty of Medicine, University of Valencia, Valencia, Spain*

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**Abstract**. There are several implications of the surge in the incidence of pandemics and epidemics in the last decades. COVID-19 being the most remarkable one, showed the vulnerability of patients with neurodegenerative diseases like Alzheimer's disease (AD). This review studies the pathological interlinks and triggering factors between the two illnesses and proposes a multifactorial pathway of AD causation due to COVID-19. The article evaluates and describes all the postulated hypotheses which explain the etiology and possible pathogenesis of the disease in four domains: Inflammation & Neurobiochemical interactions, Oxidative Stress, Genetic Factors, and Social Isolation. We believe that a probable hypothesis of an underlying cause of AD after COVID-19 infection could be the interplay of all these factors.

Keywords: Alzheimer's disease, inflammation, oxidative stress, SarsCoV-2 infection, social isolation



## INTRODUCTION

Alterations in human behavioral adaptations and environmental factors have contributed to the emergence of 30 new infectious diseases in the last three decades, 75% of which are zoonotic [1]. The most recent examples are the Nipah virus (1999), SARS Coronavirus (2002), Influenza A- H5N1 (2003), Influenza A- H1N1 (2009), Middle East Respiratory syndrome-related Coronavirus (2009), and SARS CoV-2, the Novel Coronavirus 2019 which causes the COVID-19 disease (2019) [1]. Out of all of these, the COVID-19 pandemic emerged as the latest global health crisis since the first case was detected on December 2019 from Wuhan, China. Three years later, the impact of this pandemic has been especially important in the aging population and, above all, in people with dementia [2].

[1]These authors contributed equally to this work.

*Correspondence to: Ana Lloret, Department of Physiology, Faculty of Medicine, CIBERFES, Fundación Investigación Hospital Clínico Universitario/INCLIVA, University of Valencia, Avenida Blasco Ibañez, 15, 46010 Valencia, Spain. E-mail: ana.lloret@uv.es.

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This immediate paradigm shift, which forced changes in our lives due to home isolation, has led to a deficit in the control of chronic diseases, including dementia, with Alzheimer's disease (AD) being the most common. AD is reported to represent a global burden of 57.4 million cases in 2019, forecasted to be 152.8 million in 2050 [3]. Pathologically, AD is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles, which are caused by the deposition of amyloid-β peptide (Aβ) and of hyperphosphorylated tau protein (p-tau), respectively. Both will lead to many other changes that will further increase pathology which will eventually lead to neuronal death and brain tissue damage [4].

Also, various neurological and neuropsychiatric manifestations of COVID-19 like anosmia, headache, and stroke among others, have been reported from across the world [5] given the neurotropic activity of SARS-CoV-2. Moreover, older people are more susceptible to viral infection, which is aggravated if there is cognitive impairment because of their age, coexisting morbidities, and reduced ability to adhere to preventive measures [6].

Furthermore, there is increasing evidence of a possible link between SARS-CoV-2 infection and AD, but as of today, there is no evidence of such a relationship between them despite multiple hypotheses proposing a common etiology and pathogenetic pathways among COVID-19 and AD [7]. An in-depth understanding of the association and relationship between COVID-19 and AD could be helpful for their concomitant management and prevention.

Thus, this review aims to summarize the literature with the latest evidence linking AD with COVID-19 infection. To fulfil this purpose, we will approach the common factors between COVID-19 and AD that can be grouped in different fields, ranging from the molecular level to the social sphere. We will discuss the neuro-biochemical common pathways between AD pathological cascade and SARS CoV-2 infection, with particular attention to the possible route of entry of the virus into the brain, and the induction of inflammation and oxidative stress. We will also consider genetic factors modified by COVID-19 that may exacerbate AD. Finally, we will discuss some social factors associated with the pandemic that have had a clear impact on AD patients. Figure 1 aims to reflect all the multiple causes that could have a role in AD development due to COVID-19.

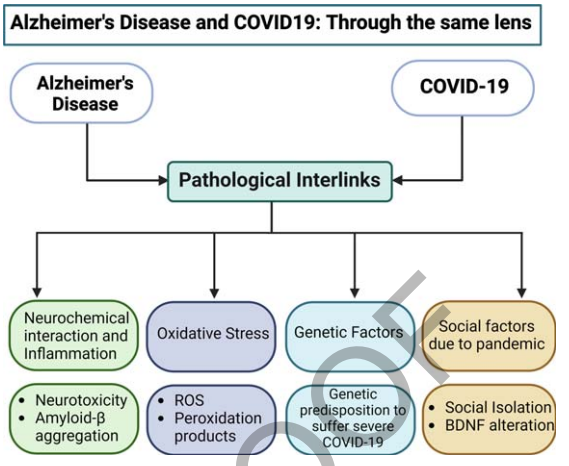


Fig. 1. Interplay of common pathogenetic factors in Alzheimer's disease and COVID-19. ROS, reactive oxygen species; BDNF, brain derived neurotrophic factor. Image created on BioRender.com.

## METHODOLOGY

### *Search strategy*

To select the articles used for this review, we used Medline (via PubMed), Cochrane Library and Embase as the databases. As COVID-19 is a recent disease, there was no need to limit the search to recent years. Terms associated with Boolean operators were included to make the results as specific as possible for the initial search: [COVID-19] OR [Coronavirus] OR [SARS CoV2] AND [Alzheimer's disease] OR [AD] OR [neurodegenerative disease] OR [Cognitive decline] OR [Dementia] AND [Common]. Additional records were searched via the references of included articles. Finally, a search with the keywords [COVID-19] OR [Coronavirus] OR [SARS CoV2] AND [Alzheimer's disease] limited to observational studies/meta-analysis were made.

### *Study selection*

Regarding the study types, the search strategy was not limited by study type. As this was not a meta-analysis, all studies, ranging from a letter to the editor to a cohort study, were selected, reviewed and information was extracted to conduct the literature review. We excluded articles not written in English, and when the title does not show either of COVID-19 or AD.

## NEURO-BIOCHEMICAL INTERACTIONS: ACE2 OVEREXPRESSION AND RENIN-ANGIOTENSIN-SYSTEM ACTIVATION

The novel coronavirus SARS-CoV-2, responsible for the COVID-19 pandemic, is composed of a lipid envelope derived from the host cell membrane, which encloses the viral genetic material and various structural proteins. Its molecular structure plays a crucial role in the virus's ability to infect and replicate within the human body, especially the spike protein (S) that facilitates the viral entry in the cell. This protein specifically binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell [8].

In humans, the ACE2 receptor is found in the airway epithelia and is highly expressed in the nasal epithelium, especially in ciliated cells, lessening the rate of expression as the respiratory epithelium became much thinner [9] being circumstantial in the lung parenchyma. Despite the dominant clinical feature of COVID-19 being respiratory, ACE2 receptors are also found in other tissues such as the small intestine, vascular endothelium, and kidney, and curiously, is also expressed in the brain [10, 11]. As revealed by a study [12], astrocytes, pericytes, and cells composing the blood-brain barrier (BBB) express ACE2 providing a target where SARS-CoV-2 could infect the Central Nervous System (CNS). Furthermore, we have to consider that the integrity of BBB is lost in AD subjects but also elderly people, although to a lesser degree [13, 14].

Nevertheless, there is also evidence that the SARS-CoV-2 virus could reach the CNS directly, bypassing the BBB, using the olfactory bulb (for a review, see [15]). This theory is sustained on the evidence that the ACE2 receptor has been described in the olfactory bulb in both mice [16] and humans [17–19], providing an entrance gate with neuroinvasive features. In this line, it has been proposed that ACE2 could be overexpressed in AD brains as shown in a genome-wide association study (GWAS) [20], suggesting that AD patients are at a high risk of COVID-19 comorbidity.

The neuroinvasive features are relevant to AD brains since it has been described that Aβ precursor protein (AβPP) is overexpressed in the olfactory bulb and the olfactory nerve layer in rats [21]. Moreover, in humans, there is also evidence suggesting that Aβ deposition occurs in the olfactory bulb very early in the disease, before AD symptoms onset [22]. Furthermore, a recent study has described that olfactory network regions measured by MRI were significantly reduced in subjects with dementia compared with controls [23]. Therefore, we believe that since the olfactory bulb is a functionally affected area in AD, may be even more vulnerable to SARS-CoV-2 entry.

Once the SARS-CoV-2 S protein binds to the ACE2 receptor its expression is downregulated [24] increasing the level of Angiotensin II. In the brain, ACE-2 depletion and Angiotensin II would cause cerebral vasoconstriction, resulting in hypoperfusion and hypoxia [25] and related to this, a very recent study has reported cerebral hypoperfusion in post-COVID cognitively impaired subjects [26].

On a cellular level, it has been described that Angiotensin II could activate NADPH oxidase, which generates reactive oxygen species (ROS) [27, 28]. This could increase oxidative stress and inflammatory response in the brain and, together with brain hypoperfusion, both actions could synergically lead to neurodegeneration, as we will discuss in further parts of this work. Interestingly, a recent meta-analysis has revealed that the downregulation of ACE2 by SARS-CoV-2 results in AβPP upregulation and could exacerbate the onset and progression of AD [29].

Figure 2 summarizes all these ideas.

## INFLAMMATION

In this section, we start with the idea that both AD and COVID-19 are diseases with a concomitant inflammatory process, so the convergence of the two could therefore greatly aggravate neurodegeneration.

In AD, damaged neurons, extraneuronal Aβ deposits and neurofibrillary tangles are stimuli for brain inflammation leading to a localized rise in inflammatory molecules [30]. Accumulated over years, this microfoci of inflammation cause direct and bystander damage to neurons. Given that AD begins decades before clinical symptoms, it is not surprising that inflammation has been proposed to be an early phenomenon, even more so than neurofibrillary tangles and senile plaques [30].

There are two inflammation-related receptors associated with a higher risk of AD, the triggering receptor expressed on myeloid cells 2 protein (TREM2) and the CD33 receptor. TREM2 receptor is involved in the activation of immune cells such as microglia, macrophages, and dendritic cells [31], being the variant R47 H (Arg47His) associated with a higher risk of AD [32]. Moreover, despite the variant, an increased expression of TREM2 in the peripheral blood of AD patients is shown [33]. Interestingly, TREM-2 is

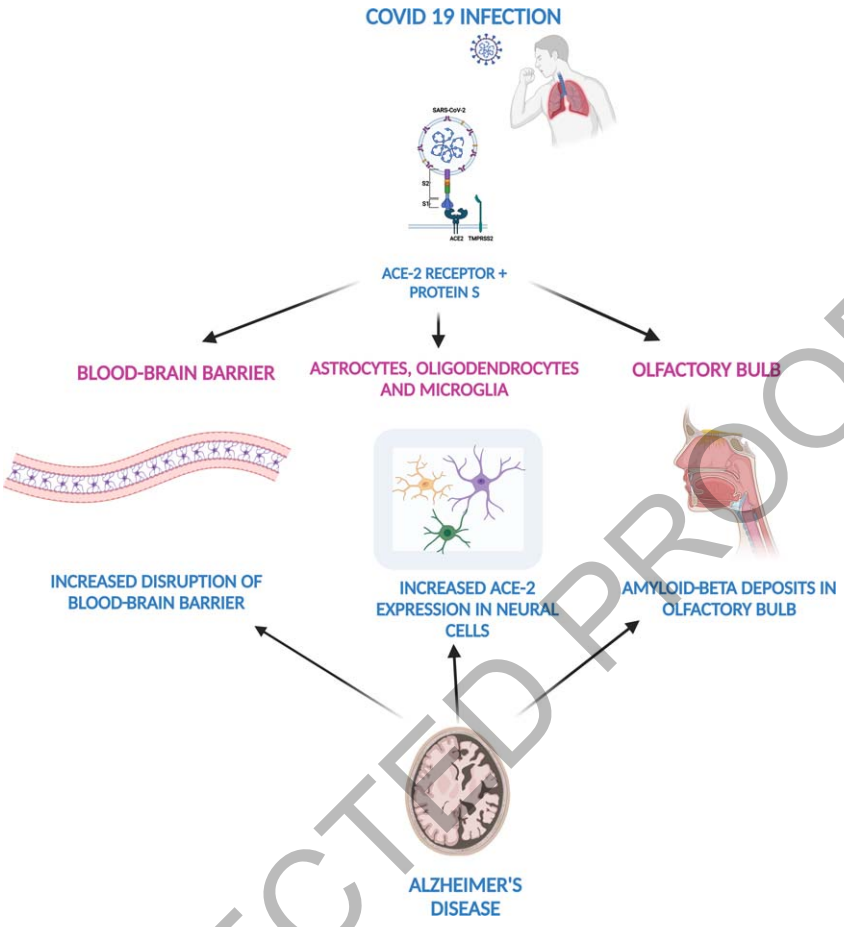


Fig. 2. Common pathways related to ACE-2 receptor between COVID-19 and AD. Image created on BioRender.com.



also upregulated in the periphery and lung-infiltrating T cells from patients with COVID-19 [34].

On the other hand, the CD33 receptor is expressed in immune cells and its role is to attenuate the immune response by cell-to-cell interactions, and it has been associated with higher susceptibility to suffer AD [35]. CD33 is also overexpressed in microglia in AD human brains compared to age-matched controls [36]. And recently, a GWAS study has shown that elevated peripheral expression of CD33 is causal to the development of AD [37]. Curiously, the spike glycoprotein secreted by SARS-CoV-2 (SGP) is a valid ligand for CD33 increasing the response by myeloid-derived suppressor cells and monocytes and aggravating the severity of infection [38]. Therefore, AD patients, and in particular those with the CD33 SNPs (single nucleotide polymorphism) or with the TREM2 variants discussed above, could have a genetic predisposition to severe COVID-19 disease.

Besides, there is a theory that supports that inflammation mediators may be a common factor that could worsen the long-term complications of COVID-19 in terms of the dementia process [39]. In this line, it has been shown that SARS-CoV-2 causes microglial activation in the brain that ultimately modulates the expression of TNF-α, IL-6 and IL-1β, which are hallmarks of neuroinflammation and could affect dysfunctional neurons in a way that aggravates the neurodegenerative process [40].

Furthermore, elevated IL-6 in plasma has been long associated with poor cognitive performance in humans [41, 42]. Note that TNFα, IL-10, and IL6 levels have been suggested to correlate with the amount of brain Aβ in AD [43, 44] in humans, so it is not surprising that the cytokine storm given in SARS-CoV-2 infection is implicated in the worsening of the dementia process.

Another agent involved in the inflammatory cross-talk between COVID-19 and AD is the inflam-

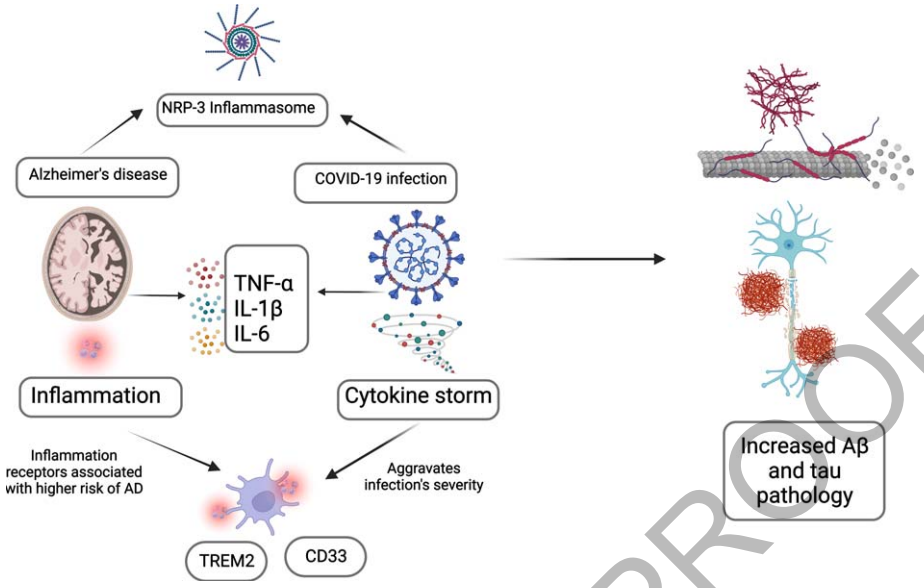


Fig. 3. Inflammation is a convergence factor between AD and COVID-19. Aβ, amyloid-β peptide. Image created on BioRender.com.

masome, a specialized structure coupling pathogen and stress-sensing pathways into complex signaling. Inflammasomes are members of the NOD innate immune system family of receptors that consist of 3 closely related subfamilies: nucleotide-binding oligomerization domain (NOD), NOD-like receptor CARD domain containing (NLRC), and NOD-like receptor Pyrin domain containing (NLRP). Out of them, NLRP3 inflammasome has been related to COVID-19 hyperinflammation [45].

NLRP3 inflammasome impairs Aβ clearance by impairing the phagocytic capacity of microglia in mice as proven by a study [46]. Furthermore, the activation of the NLRP3 inflammasome also could promote tau pathology, which may encourage the occurrence and progression of AD [47].

Figure 3 contains a summary of the above-mentioned aspects.

## OXIDATIVE STRESS

Oxidative stress has been defined as an imbalance among oxidants and antioxidant compounds in favor of the firsts [48]. ROS levels vary according to many events, both physiological and pathological. For example, exposure to pollutants, radiation, toxins, as well as viral infections in airways, is associated with oxidative stress causing damage [49, 50].

Several respiratory viruses induce an exacerbation of ROS formation, mainly as a result of increased inflammatory cell recruitment at the site of infection, as is the case of SARS-CoV-2 [51]. For instance, a study [52] reports that patients with COVID-19 pneumonia show increased levels of oxidative stress parameters compared to healthy individuals. Another study [53] describes increased lipid peroxidation along with deficits in some antioxidants (vitamin C, glutathione, thiol proteins) in critically ill COVID-19 patients. All these studies agree with the idea that the rates of COVID-19 severe illness and death could increase by oxidative stress [54]. Inflammation and oxidative stress are intimately related in the pathogenic substrate of neurodegenerative disease, being, therefore, a possible new synergistic pathway between COVID-19 and AD [55]. On the other hand, the relationship between oxidative stress and AD has been broadly studied where oxidative stress is an early event associated with AD's pathophysiology [56, 57]. According to this, peroxidation products could have the capacity to bind to amino acid residues on proteins, altering their structure and function and causing oxidative dysfunction of key enzymes and products of cellular energetics in the mitochondria [58, 59]. In general, oxidation products have been demonstrated in all macromolecules in the brains of AD patients [60].

With this evidence, authors such as Wang et al. [2021] defend that the continuous accumulation

of ROS-mediated oxidative lesions could have the potential mechanisms for COVID-19 to induce AD [61].

Another study concludes that SARS-CoV-2 infection could worsen pre-existing AD conditions and is also related to a worst patient outcome since it triggers higher levels of oxidative stress and inflammation, causing neurotoxicity [62].

The two ideas we have presented are two sides of the same coin, on one side individuals with AD experience greater comorbidity when they have COVID-19 due to their altered redox state. On the other side, individuals who contract COVID-19 face a rapid increase in oxidative stress that can affect their antioxidant reserves and pave the way for a faster clinical decline of AD.

## GENETIC FACTORS

AD is a multifactorial disease probably with a variable genetic component. In the last 20 years, our understanding of this genetic component has increased with the identification of the familial AD genes that trigger an early-onset disease (mutations in *APP*, *PSEN1*, or *PSEN2* genes) and the sporadic genes, which increase the risk of suffering AD [63, 64]. From these, *APOE4* is the first AD susceptibility gene [65], followed by the Bridger integrator gene (BIN1) [66, 67]. Interestingly, both of them have been associated with severe COVID-19. Using the UK Biobank Community Cohort, Kuo et al. have described that carrying an *APOE* ε4 allele increases the risk of severe COVID-19 infection, independent of pre-existing dementia [68].

*APOE4* has also been linked to the severity of COVID-19 [69]. This study shows a higher vulnerability of *APOE* ε4/ε4 neurons to infection with SARS-CoV-2 and an increased rate of neuronal degeneration following infection. Moreover, when comparing the length and quantity of neurites to evaluate neuronal harm post-infection, APOEε4/ε4 experienced considerably more negative impact compared to APOEε3/ε3.

Another study carried out with the UK Biobank cohort, compared mortality rates in subjects infected with the virus. They found that those individuals carrying BIN1's SNP which is also present in AD suffered a higher mortality rate compared to those subjects carrying the major (non-AD) BIN1 allele [70].

Considering the cytokine storm triggered by COVID-19 and the role of inflammation described in AD, we were not surprised when we found evidence that an interferon-induced gene, the oligoadenylate synthetase 1 was involved with both diseases. Oligoadenylate synthetase 1 has a significant antiviral function in the immune response and very recently a genetic variant (rs1131454) was related to an increased risk of AD by its enrichment in transcriptional networks expressed by microglia [71]. In this same study the authors point out that this same locus has been associated with severe outcomes in COVID-19.

Ahmed et al. found in the available repository data another pathway that could link COVID-19 and AD from a genetic point of view [72]. They hypothesize that SARS-CoV-2 infection causes the overexpression of some genes involved in neurodegeneration. The authors relate exosome-derived transport of some transcription factors from COVID-19-infected lungs to neurodegeneration-related brain regions. Of all these transcription factors identified, the signal transducer and activator of transcription-1 (STAT1) stands out as it has been linked to AD. Increased STAT1 expression in cell nuclei is implicated in inflammatory activation in the AD brain [73].

## THE IMPACT OF SOCIAL ISOLATION

We do not want to end this paper without talking about one of the main collateral damages of the pandemic which is social isolation. Loneliness is a reality for many elderly individuals around the world and it was exacerbated by the need for isolation to avoid COVID-19 infection.

A meta-analysis has shown that social isolation is associated with poorer cognitive function in later life [74]. Social isolation has also been associated with Aβ-related cognitive decline in people with dementia and increased risk of dementia diagnosis in people with previously normal cognitive function, assessed by longitudinal studies [75, 76]. Likewise, the risk of developing AD is increased in lonely persons compared with persons who were not lonely [77].

The same has been confirmed by experimental studies in animal models where socially isolated mice increased plaque deposition and worsened memory [78]. In this line, a recent study with rats shows that acute social isolation causes social memory loss that is partially reverted upon regrouping [79].

From a more molecular view, it is hypothesized that neurodegeneration of the entorhinal cortex, which is affected early in AD, leads to decreased ability to engage in social activities [80]. Besides, social isolation can itself trigger neuroinflammation, oxidative stress, and synaptic dysfunction, due to reduced α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) expression and declined neurogenesis via decreased brain-derived neurotrophic factor (BDNF) [79, 81, 82].

The BDNF is a protein that has many important roles in the brain. For example, it plays a crucial part in the neurite growth, development, and survival of glutamatergic and GABAergic synapses. Its many other functions, make the BDNF to be considered an instructive mediator of functional and structural plasticity [83–85]. For an extended review, please see [86].

Concerning our topic, low levels of BDNF could be another link between social isolation, COVID-19, and AD. In AD, there is a decreased brain BDNF expression [87], probably caused by Aβ toxicity in its oligomeric form [87, 88], but also in the patient's serum [89, 90]. Interestingly, COVID-19 patients also show lower BDNF levels than healthy controls [91, 92].

On the other hand, as we know, confinement has led to a decrease in physical exercise in the population. Although the literature compiles a variety of results, there seems to be a consensus that physical exercise increases BDNF levels in the brain [93, 94]. Therefore, if extrapolated, we could hypothesize that BDNF levels may have decreased in the absence of necessary physical activity [95].

With COVID-19 forcing lockdown measures, a cascade of events occurs starting with limited social contact and physical activity coupled with anxiety, stress, uncertainty, and fear of the pandemic. This ultimately led to the psychological outcomes deterioration especially of the already vulnerable AD patients.

Figure 4 represents the plausible connection between both disease and confinement.

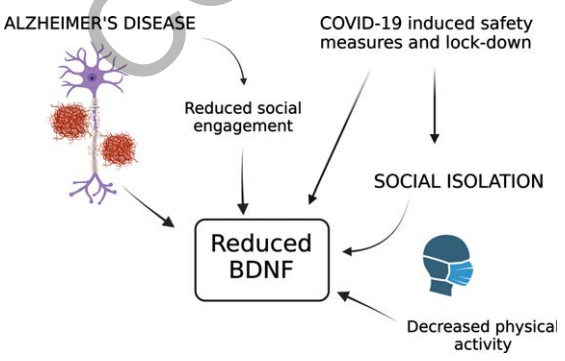


Fig. 4. The impact of Social Isolation. BDNF, brain derived neurotrophic peptide. Image created on BioRender.com.

## CO-MORBIDITY AND MORTALITY

To finish this review, after discussing the pathological pathways common to the two diseases, we would like to analyze observational studies that deepen from a clinical point of view into the impact of different comorbidities in subjects with COVID-19 and AD and their relationship with each other.

Wang et al. carried [96] a study involving 360 US hospitals and nearly 62 million patients and conclude that patients with AD were at higher risk of COVID-19 infection (AOR: 1.86 [IC 95%, 1.77–1.96], $p < 0.001$). In addition, both the risk of hospitalization at 6 months (59.26%) and the risk of death (20.99%) were higher in patients with COVID-19 and dementia. In the same line, Zhang et al. selected from the TriNetX research network 387,841 patients with COVID-19, of whom 4,174 were diagnosed with AD. The authors present a logistic regression with age, sex, race, ethnicity, and 30 comorbidities; one of the analyses revealed that COVID-19 mortality rates were significantly elevated in the AD group (OR: 1.20, CI 95%: 1.09–1.32, $p < 0.001$) [97].

Zhou et al. include 389,620 participants from the UK Biobank and conclude that the most significant risk factor for COVID-19 includes AD (OR: 2.29, 95% CI: 1.25–4.16) [98]. Yu et al. extending this study, show that patients with AD showed the highest susceptibility to SARS-CoV-2 infectivity, being 4.15 times higher compared to individuals without AD (OR: 4.15, 95% CI 3.22–5.34, $p < 0.05$). In addition, patients with AD showed higher mortality compared to individuals without AD (OR: 4.17 95% CI: 2.87–6.05, $p < 0.05$) [99].

Moreover, Fathi et al. conduct a cohort study comparing the prognosis of individuals admitted to hospitals with AD diagnosis who also contracted COVID-19, in contrast to other hospitalized COVID-19 patients without dementia. Out of a total of 67,871 patients with confirmed COVID-19 diagnosis through PCR and chest CT, a subset of 3,732 individuals was chosen, with 363 of them having AD. The researchers deduce that patients hospitalized

with AD exhibited a heightened 28-day mortality risk due to COVID-19 infection. However, the presence of Parkinson's disease did not significantly correlate with an increased COVID-19 mortality prediction [100].

In another study, Chung et al retrospectively selected 22,763 COVID-19-positive, aged-matched subjects (5,725 with AD) and showed that there was a connection between AD and a higher likelihood of experiencing severe complications from COVID-19 (OR 2.25). Further analysis of secondary outcomes revealed that individuals with AD faced an elevated risk of mortality (OR 3.09) compared to non-demented subjects [101].

## CONCLUSIONS

AD could be one of the common CNS comorbidities of the COVID-19 infection. The two diseases are interlinked with an interplay of a variety of neurochemical, biological, physical, and also social factors in a bidirectional manner. Evidence suggests that AD influences the risk of getting infected by SARS-CoV-2 and the risk of severe COVID-19 outcome, but also, that SARS-CoV-2 itself and the severity of COVID-19 influence on cognitive function in people with previously diagnosed AD. Therefore, the concomitant presence of the two diseases shall create a vicious cycle leading to a poor prognosis, as observational studies show.

To the best of our knowledge, current therapies involving both diseases are not implemented in clinical practice. As COVID-19 restricted mass gatherings, virtual interactions with family and friends became a possible option for a good social engagement which are protective against dementia. Engaging in indoor physical and psychological activities can be a good aid for patients. Although meta-analyses have not been reported yet, a randomized controlled trials on older adults during COVID-19 confirmed improved executive functions and physical activity from the baseline, which can be hypothesized to have protective effects on AD patients [102].

Finally, we believe that the greatest limitation of our work is the number of studies carried out in this area. Due to the difficulties of conducting studies in a health system dominated by emergency care, the conditions have not been ideal for prospective observational studies; however, the evidence to date does seem to indicate a relationship of comorbidity and mortality between COVID-19 and AD based on molecular and cellular common pathways.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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