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Shared Neurological and Cognitive Factors in COVID-19 and Alzheimer's Disease: A Literature Review

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Abstract

Introduction: The neuropathological etiology of COVID-19 suggests infection may increase the risk of neurodegenerative disorders, most notably Alzheimer's disease (AD). Despite some overlap between COVID-19 and AD, the current research on this relationship is developing and evidence has been mixed. This review aims to assess the literature on how the neurological and cognitive sequalae associated with COVID-19 infection affect risk for AD and its associated symptoms, and vice versa.

Methods: Articles were found by searching through the PubMed database with the terms (sensory OR cognitive OR neurological OR neuroimaging) AND (Alzheimer's disease OR Alzheimer's OR dementia) AND (COVID-19 OR SARS-CoV-2 OR COVID). Search inclusion criteria required the papers be written in English, be published in 2020 or later, and pertain to COVID-19 and/or AD specifically. This process was supplemented by manual searching. The articles used for this review include meta-analyses, literature reviews, and prospective and retrospective empirical studies.

Results: Various well-known AD risk factors and outcomes may be observed in COVID-19 patients, and vice versa. These include amyloid precursor protein (APP) buildup, tau hyperphosphorylation, the apolipoprotein E (APOE) e4e4 genotype, angiotensin converting enzyme 2 (ACE2) gene expression, cholinergic functioning, delirium, cognitive decline, and deleterious effects on brain structure and function.

Discussion: COVID-19 may increase AD risk and development by increasing protein build-up and damaging AD-related brain regions, which may underlie sensory and cognitive deficits. Furthermore, COVID-19 and AD may interact in positive feedback loops to worsen the development of both. These interactions may be mediated by demyelination, inflammation, APOE e4e4 genotype, and ACE2 expression. Clinical implications for those with COVID-19 and/or AD include the possibility of treatments aimed at cholinergic functioning, as well as high flow oxygen therapy.

Conclusion: COVID-19 may increase the risk for and development of AD. AD, in turn, may also increase risk for COVID-19 infection, acting in a positive feedback loop. Future directives include further research on tau pathology, delirium, and amyloid precursor protein processing. Additionally, studies could benefit from telemedicine. Lastly, assessment of AD risk due to COVID-19 could integrate delirium and subjective reports of "brain fog" as measures for underlying risk factors.

Keywords: SARS-CoV-2; Alzheimer's disease; beta-amyloid peptide; tau; demyelination; APOE gene; ACE2; cognitive decline

Introduction

Since its first confirmed case in 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, also known as COVID-19) has caused over 6.5 million deaths worldwide as of 2022 [1]. The symptoms and effects of COVID-19 infection vary individually, but infection tends to impair sensory, cognitive, and neural functioning. Effects include olfactory and gustatory dysfunction, long-term "brain fog" (i.e., subjective reports of fatigue long after COVID-19 infection), and delirium [2-4]. Research on the neuropathological etiology of COVID-19 in the central nervous system (CNS) suggests the COVID-19 spike protein binds to angiotensin converting enzyme 2 (ACE2) receptors of neurons and glial cells, and on the capillary endothelium of the cerebrum [5]. This leads to a systemic inflammatory response, as seen in ensuing cytokine storms [6], which are severe immune system reactions involving elevated cytokine levels and immune cell hyperactivation. Inflammation from COVID-19 infection can then compromise the blood-brain barrier (BBB) [6]. Ensuing brainstem infection can then impair cardiovascular and respiratory function, resulting in hypoxia, or low levels of oxygen in body tissues [6,7]. Hypoxia and neuroinflammation may damage the cerebral cortex including the hippocampus, which may influence the presentation of clinical symptoms resembling those of neurodegenerative of disorders [7].

Alzheimer's disease (AD) is part of the group of neurodegenerative disorders that can cause the clinical syndrome of dementia. Dementia due to AD is associated with loss of independent function and cognitive decline in memory, executive function, and language; as well as neuropsychiatric symptoms (NPS) such as depression, psychosis, and sleep disorders [8,9]. AD is usually preceded by mild cognitive impairment (MCI), a prodromal stage of dementia involving memory loss that does not affect a person's ability to complete daily activities. It has been proposed that in AD, amyloid precursor protein (APP) in the brain is broken down into beta-amyloid (Aβ) proteins, which clump together into plaques that result in cell death [10]. Although Aβ is implicated in AD progression, it should be note that its exact role is uncertain [11]. Hyperphosphorylated tau proteins also clump together, forming neurofibrillary tangles (NFTs) that further disrupt neural functioning [8]. The abnormal protein build-up results in brain atrophy in critical areas for memory functioning, such as the hippocampus [8]. AD may also be a demyelination disorder, where the loss of myelin may increase Aβ plaque deposition, which in turn worsens myelination [12].

Some research has implied a potential overlap between symptoms and risk factors in COVID-19 and in AD. For instance, those who experience persistent symptoms after COVID-19 infection (i.e., "long COVID") may exhibit long-term "brain fog" [3], a symptom that shows similarities to deficits in processing speed and memory that are apparent in individuals with AD. Although COVID-19 may play a role in people with AD or AD risk (and vice versa), this lacks robust empirical evidence. The literature on the specific neurological and cognitive interplay of COVID-19 and AD is a relatively new and still developing field of research.

It has been proposed that AD weakens the peripheral immune system in a way that allows it to predict COVID-19 mortality [13]. Furthermore, hospitalized COVID-19 patients were found to have similar or higher levels of neurodegenerative biomarkers than levels observed in the blood plasma of those with AD who were not COVID-19 positive [14]. Although such findings seem promising, evidence for a relationship between COVID-19 and AD is mixed. One study found no significant differences for the prevalence of dementia between non-severe and severe COVID-19 patients [15]. Contrarily, other meta-analyses have found a relationship between dementia and COVID-19 infection severity and mortality [16,17]. Such conflicting evidence suggests the need for a deeper investigation of shared factors and pathology between COVID-19 and AD. Given this limited research, this paper aims to review and evaluate the strength of the literature on how the neurological and cognitive sequelae associated with COVID-19 affect the risk for AD and its associated symptoms, and vice versa.

Methods

Articles for this review were found by searching the PubMed database with the terms (sensory OR cognitive OR neurological OR neuroimaging) AND (Alzheimer's disease OR Alzheimer's OR dementia) AND (COVID-19 OR SARS-CoV-2 OR COVID). Additionally, search inclusion criteria required that the papers be written in English, be published in 2020 or later, and pertain to COVID-19 and/or AD specifically. This search process was supplemented with manual searching, including information from reference lists of relevant articles. As this paper investigated a relatively new phenomenon, there was a lack of primary research; therefore, the search results mostly yielded review articles and meta-analyses. Preprints, conference proceedings, and graduate student theses were excluded. In total, 19 articles were used in this literature review. These included summary articles, literature reviews and meta-analyses, meta-analyses with bioinformatics tools, retrospective studies on pre-existing data, prospective studies, longitudinal studies, cross-sectional studies, a letter to the editor, and cell culture studies. These sources included cognitive measures, as well as neuroimaging measures such as magnetic resonance imaging (MRI) scans.

Results

Biological/Biochemical/Immunological Outcomes

APP and Tau

A meta-analysis using bioinformatic methods found that the increase in cytokine activity in later stages of COVID-19 infection increased the expression of APP, which could then be transformed into the Aβ plaques associated with AD [18]. Although immune system activation plays a role in removing Aβ plaques, its hyperactivation can lead to neuronal damage and increase neurodegenerative risk [18]. Contrarily, a meta-analysis of brain lysates from individuals with COVID-19 infection and controls noted that infection had no effect on APP processing in the cortex and cerebellum [3].

COVID-19 and AD displayed an additional overlap in tau pathology [3]. Calcium release channels, specifically ryanodine receptor 2 (RyR2) in the cortex and cerebellum of COVID-19 patients, demonstrated a "leaky" phenotype compared to controls, which could hinder cognitive and behavioural functioning [3]. These defective channels could lead to tau hyperphosphorylation, which is associated with AD [3]. This was supported by the finding that levels of phosphorylated tau-181 (p-tau181), a neurodegenerative biomarker, were associated with the severity of COVID-19 infection [14].

Gene Expression: ACE2 and Apolipoprotein E (APOE)

The e4 allele of the APOE gene plays a role in COVID-19 risk [19]. Compared to e3e4 and e3e3 genotypes, e4e4 genotypes are associated with increased risk of test positivity and mortality following a positive test [19]. Furthermore, the e4e4 genotype heightens the risk of AD

progression by influencing BBB leakage and cerebral amyloid angiopathy, i.e., the accumulation of Aβ peptide deposits in cerebral arteries [20]. Additionally, post-mortem brain tissue analyses of individuals with AD revealed elevated ACE2 gene expression, which may increase risk of COVID-19 transmission [21]. Contrarily, another study of AD brain tissue found reduced ACE2 activity, which was also related to tau hyperphosphorylation and Aβ pathology [22].

Cholinergic Functioning

A hallmark of AD pathology is deteriorated CNS cholinergic activity [23]. Acetylcholine (ACh) mediates the lowered production of pro-inflammatory cytokines, including the ones produced in COVID-19 cytokine storms [24]. Therefore, both individuals with COVID-19 infection and those with AD may benefit from interventions aimed at the cholinergic system [7]. Though they may have adverse side effects, acetylcholinesterase inhibitors (aChEIs) may ameliorate AD symptoms [25] and pro-inflammatory cytokine production [26].

Neurologic, Sensory, and Cognitive Effects

In one study of hospitalized COVID-19 patients, the most common neurologic manifestation was delirium (confusion and lack of awareness of surroundings and orientation), which also often occurs in people with dementia [4]. These patients who developed neurologic events were more likely to experience greater COVID-19 symptom severity [4]. Such cases of delirium were enriched in individuals with APOE e4 genotypes [27]. Tau pathology may also contribute to COVID-19-related neurological manifestations, specifically subjective reports of "brain fog" in long-COVID syndrome [3].

A cross-sectional study examined longitudinal cognitive decline in formerly hospitalized COVID-19 inpatients over 60 years old [28]. At the time of assessment, the current cognitive impairment and longitudinal cognitive decline were associated with symptom severity. COVID-19 severity and delirium were associated with concurrent cognitive impairment, and COVID-19 patients exhibited greater longitudinal cognitive decline at 6 months compared to controls. Similarly, cognitive decline was associated with greater infection severity. Notably, high flow oxygen therapy was found to be a successful preventative measure against this decline [28].

Neuroimaging

MRI scans of participants before and after COVID-19 infection indicated greater reduction in global brain volumes and greater cognitive decline [29]. With regards to specific brain regions, there was greater reduction of grey matter thickness and intensity contrast in the orbitofrontal cortex and parahippocampal gyrus [29]. Regions functionally connected to the primary olfactory cortex, including the hippocampus, exhibited greater changes in markers of tissue damage [29].

Review Articles

As this literature review investigated a relatively new phenomenon, the limited primary empirical research in this field was supplemented with other pre-existing commentaries—especially regarding future research—from other related literature reviews. For example, one review article suggested conducting a longitudinal follow-up of COVID-19 patients, specifically by looking at shared biomarkers between COVID-19 and AD [30]. Other suggestions included determining how COVID-19 invades the CNS and investigating increased COVID-19 mortality in those with AD [31]. Furthermore, future research could also explore the effects of COVID-19 on AD-related pathological and behavioural changes [31]. Possible systemic changes included a greater focus on psychological evaluation; it was also found that telemedicine will play a greater role in future clinical trials [32].

Discussion

To summarize, this paper reviewed the literature on the links between COVID-19 infection and AD. The reviewed studies examined biological, neuropathological, and immunological outcomes including APP buildup, hyperphosphorylation of tau, the e4 allele of the APOE4 gene, ACE2 gene expression, and cholinergic functioning. Neurologic, sensory, and cognitive similarities included delirium and cognitive decline [4,28]. Lastly, COVID-19 was shown to have deleterious effects on brain structure and function [29].

Theoretical Implications

Effects of COVID-19 on AD

COVID-19 infection may significantly impact the development of Aβ plaques as it might increase their precursor, APP [18], though evidence for this view is mixed. The meta-analysis supporting this relationship used a bioinformatics tool that analyzed data from a repository [18], whereas opposing evidence came from a study of brain lysates [3]. While further research is needed to determine the validity of this relationship, it is worth noting that a meta-analysis incorporates more data than a single study. This is important in the case of COVID-19 and AD research as the field is not well-explored and findings are heterogeneous. However, considering the increasing uncertainty over the relationship between Aβ and AD [11], this link between COVID-19 and AD is highly speculatory.

COVID-19 can also contribute to tau hyperphosphorylation, although it is unclear whether tau hyperphosphorylation from AD could contribute to COVID-19 infection [3]. Nevertheless, it is important to note that since tau may contribute to "brain fog" in COVID-19 patients [3], COVID-19-positive people with

AD may be more likely to experience this symptom, which could further compound AD-associated cognitive decline.

The finding of tissue damage in regions essential to olfaction and memory in COVID-19 may also play a role in AD pathology. As well as exhibiting memory deficits, individuals with AD experience sensory deficits. A review article found that compared to healthy controls, those with MCI exhibit worsened odour identification, which, alongside worsened odour memory performance, is also present in AD [33]. Through white matter neurodegeneration in olfactory and memory regions of the brain, such as the hippocampus and parahippocampal gyrus [29], COVID-19 infection in those with AD could worsen pre-existing odour and memory deficits.

As MCI is often characterized as a prodromal stage of AD, it is important to consider the effect of COVID-19 on cognition. The outcomes of some studies [28] could suggest cognitive decline associated with COVID-19 infection may worsen memory or executive functioning deficits in MCI, and thus possibly further increase risk for AD–although this is speculatory and lacks empirical evidence.

Shared Factors and Interactions Between AD and COVID-19

The myelin sheath's integrity decreases with age and cognitive decline, which may account for COVID-19 and AD becoming more apparent in older age, as both are associated with demyelination [12,34]. Demyelination may result in a cyclical interaction between COVID-19 and AD. Prior research indicates cognitive decline long after COVID-19 infection [28], as well as demyelination due to infection [34], which may act in a positive feedback loop with Aβ plaque formation in AD [12]. Furthermore, myelin damage from AD likely leads to the activation of the immune system, specifically T and B cells, which are linked to the inflammatory response induced by COVID-19 infection [12]. This supports the proposal that AD predicts COVID-19 mortality because it alters the peripheral immune system response [13]. Moreover, as the inflammatory response increases APP expression in COVID-19 patients [18], immune activation from either AD or COVID-19 could increase risk of the other.

The APOE e4 genotype is a possible shared risk factor for COVID-19 and AD [19,27], and, like demyelination, may mediate the interaction between the two. The APOE e4 genotype increases BBB leakage [20], and therefore could heighten the neurological effects of COVID-19, which then may go on to increase AD risk and act in a positive feedback loop. Similarly, ACE2 gene expression, which may increase the risk of COVID-19 infection, is increased in AD [21], potentially causing another feedback loop in the opposing direction. This is opposed by the finding that ACE2 expression is associated with decreased tau phosphorylation and Aβ plaques [22], which could then counteract related effects of COVID-19 on AD. As such, greater evidence is needed to confirm or disconfirm an ACE2-mediated feedback loop.

Both COVID-19 patients and those with AD may experience delirium [4], although it is unclear whether delirium influences the development of COVID-19 and AD. While this evidence alone only draws associations between symptoms rather than explaining shared neuropathological mechanisms, the finding of APOE e4 as a possible mediator [27] enriches this link. As with many findings in this paper, this does not indicate certainty or causality, but instead guides future research down a specific path that, if studied empirically, may yield substantial results.

Clinical Implications and Potential Treatments

Increasing cholinergic functioning would ameliorate AD and COVID-19 effects separately [7], and potentially as a shared factor by lowering COVID-19-induced inflammation [24] and therefore the expression of APP [18]. Conversely, it could also lower the immune activation caused by AD that would worsen the COVID-19 inflammatory response [13]. Furthermore, as high flow oxygen therapy helped protect against longitudinal cognitive decline [28], it is possible that this treatment could also guard against a similar decline in MCI, though this remains to be empirically investigated. High flow oxygen therapy could also help counteract hypoxia-induced damage to the cerebral cortex in COVID-19 patients [7], and therefore may decrease potential AD risk.

Limitations

Some studies were limited in the scope of their data. For example, some studies used Biobank UK data [19,27,29], which were collected from participants living in the UK. Such limitations in geographic diversity may conceal factors in the COVID-19 and AD relationship that are generalizable to a wider population. Additionally, most studies reviewed were observational, so it was not always possible to establish causality. For example, while it was found that COVID-19 can result in tau pathology [3], it is unknown whether the reverse is true. Future research may opt to examine this relationship using cell culture or animal models to explore causal mechanisms. One review suggested telemedicine for clinical care, which may be especially appropriate for studying COVID-19-positive patients [32]. Telephone-oriented studies may prove useful in future studies as they are not constrained by physical location and could thus gather data from more geographically diverse samples in comparison to databases like UK Biobank.

As research on COVID-19 and AD is still developing, this paper cannot put forth concrete conclusions, but instead aims to clarify possible directions of research suggested by the current literature. Most pertinently, cognitive effects and neurologic symptoms, which arise from biological mechanisms, may be most effectively interpreted as

indicators of the direction of further empirical neuropathological research. Furthermore, while Aβ is implicated in the progression of AD, the uncertainty in its particular role [11] consequently limits the certainty with which the potential Aβ-mediated link between COVID-19 and AD can be interpreted.

Conclusions

The literature suggests that COVID-19 may worsen or increase the risk of AD development by increasing APP (though this link is currently uncertain), increasing odour and memory deficits, increasing demyelination, and causing tau hyperphosphorylation. COVID-19-induced cognitive decline may point to another link between AD and COVID-19 through MCI. Possible feedback loops between COVID-19 and AD may involve demyelination, immune activation, the APOE e4 genotype, and ACE2 gene expression—though this last potential loop requires greater investigation.

This review enriches existing knowledge on COVID-19 and AD by connecting these two fields of research. Although the shared factors and interactions between COVID-19 and AD may increase risk of development for each, they also offer more potential treatments, specifically with regards to cholinergic functioning and oxygen therapy. However, as these findings are new and sometimes weak, they should be interpreted as general guidelines for the direction of future research.

Further research could be done on whether tau pathology might increase risk for COVID-19, whether delirium could be a shared factor, and on the neurological basis of delirium. Future research could also consider the role of Aβ in AD and the effect of COVID-19 on APP processing, as current evidence is mixed. Since COVID-19 is a relatively new phenomenon, the suggestion to conduct longitudinal follow up studies looking at biomarkers [30] may yield valuable information. However, the suggestion to conduct further research on increased COVID-19 mortality in those with AD [31] has already been addressed by some articles [15-17]. Furthermore, these articles produce mixed findings, which could suggest that directly investigating the relationship between COVID-19 and AD may be more valuable than observing mortality outcomes.

Delirium and "brain fog" are respectively associated with APOE e4 and tau and can be measured quickly and non-invasively. Instead of analyzing biological samples, these symptoms could potentially be used as indicators for the presence of APOE e4 and tau pathology, and therefore the possibility of heightened risk for AD development from COVID-19.

List of Abbreviations Used

ACE2: angiotensin converting enzyme 2
ACh: acetylcholine
AChEI: acetylcholinesterase inhibitor
AD: Alzheimer's disease
APOE: apolipoprotein E
APP: amyloid precursor protein
Aβ: beta-amyloid
BBB: blood-brain barrier
CNS: central nervous system
COVID-19: severe acute respiratory syndrome coronavirus 2
MCI: mild cognitive impairment
MRI: magnetic resonance imaging
NFT: neurofibrillary tangle
NPS: neuropsychiatric symptoms
p-tau181: phosphorylated tau-181
RyR2: ryanodine receptor 2
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Conflicts of Interest

The author (NC) declares no conflict of interests.

Ethics Approval and/or Participant Consent

This study was a literature review that only assessed pre-existing studies and articles, and therefore did not require ethics approval nor participant consent.

Authors' Contributions

NC: made substantial contributions to the design of the study, collected and interpreted data, drafted the manuscript, and gave final approval of the version to be published.

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References

[1] WHO coronavirus (COVID-19) dashboard [Internet]. World Health Organization. World Health Organization; 2022 [cited 2022 Dec1]. Available from: https://covid19.who.int/
[2] Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (covid-19): A Multicenter European Study. European Archives of Oto-Rhino-Laryngology. 2020 Aug;277(8):2251–61. https://doi.org/10.1007/s00405-020-05965-1
[3] Reiken S, Sittenfeld L, Dridi H, Liu Y, Liu X, Marks AR. Alzheimer's-like signaling in brains of COVID-19 patients. Alzheimer's & Dementia. 2022 May;18(5): 955–65. http://doi.org/10.1002/alz.12558

[4] Flores-Silva FD, García-Grimshaw M, Valdés-Ferrer SI, Vigueras-Hernández AP, Domínguez-Moreno R, Tristán-Samaniego DP, et al. Neurologic manifestations in hospitalized patients with COVID-19 in Mexico City. Chen T-H, editor. PLOS ONE. 2021;16(4). https://doi.org/10.1371/journal.pone.0247433

[5] Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host–virus interaction, and proposed neurotropic mechanisms. ACS Chemical Neuroscience. 2020 Apr;11(7):995–8. http://doi.org/10.1021/acschemneuro.0c00122

[6] Steardo L, Steardo L, Zorec R, Verkhratsky A. Neuroinfection may contribute to pathophysiology and clinical manifestations of COVID-19. Acta Physiologica. 2020 Jul;229(3). http://doi.org/10.1111/apha.13473

[7] Rahman MA, Islam K, Rahman S, Alamin M. Neurobiochemical cross-talk between COVID-19 and Alzheimer's disease. Molecular Neurobiology. 2021 Mar;58(3):1017–23. https://doi.org/10.1007/s12035-020-02177-w

[8] Sheppard O, Coleman M. Alzheimer's Disease: Etiology, neuropathology and pathogenesis. In: Huang X, editor. Alzheimer's disease: Drug discovery. Brisbane, Australia: Exon Publications; 2020. p. 1–21. https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ch1

[9] Lyketsos CG, Carrillo MC, Ryan JM, Khachaturian AS, Trzepacz P, Amatniek J, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimer's & Dementia. 2011 Sep 1;7(5):532–9. http://doi.org/10.1016/j.jalz.2011.05.2410

[10] Zhang Y-wu, Thompson R, Zhang H, Xu H. APP processing in Alzheimer's disease. Molecular Brain. 2011 Jan 7;4(1). http://doi.org/10.1186/1756-6606-4-3

[11] Morris GP, Clark IA, Vissel B. Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer's disease. Acta Neuropathologica Communications. 2014Sep18;2(1). http://doi.org/10.1186/s40478-014-0135-5

[12] Papuć E, Rejdak K. The role of myelin damage in Alzheimer's disease pathology. Archives of Medical Science. 2020 Feb;16(2):345–1. https://doi.org/10.5114/aoms.2018.76863

[13] Hwang J-moon, Kim J-H, Park J-S, Chang MC, Park D. Neurological diseases as mortality predictive factors for patients with COVID-19: A retrospective cohort study. Neurological Sciences. 2020;41(9):2317–24. https://doi.org/10.1007/s10072-020-04541-z

[14] Frontera JA, Boutajangout A, Masurkar AV, Betensky RA, Ge Y, Vedvyas A, et al. Comparison of serum neurodegenerative biomarkers among hospitalized COVID-19 patients versus non-covid subjects with normal cognition, mild cognitive impairment, or Alzheimer's dementia. Alzheimer's & Dementia. 2022 May;18(5):899–910. http://doi.org/10.1002/alz.12556

[15] Gao Y, Chen Y, Liu M, Niu M, Song Z, Yan M, et al. Nervous system diseases are associated with the severity and mortality of patients with COVID-19: A systematic review and meta-analysis. Epidemiology and Infection. 2021 Feb 15;149:1–12. https://doi.org/10.1017/S0950268821000376

[16] Hariyanto TI, Putri C, Arisa J, Situmeang RF, Kurniawan A. Dementia and outcomes from coronavirus disease 2019 (covid-19) pneumonia: A systematic review and meta-analysis. Archives of Gerontology and Geriatrics. 2021;93. http://doi.org/10.1016/j.archger.2020.104299

[17] Saragih ID, Saragih IS, Batubara SO, Lin C-J. Dementia as a mortality predictor among older adults with COVID-19: A systematic review and meta-analysis of observational study. Geriatric Nursing. 2021;42(5):1230–9. http://doi.org/10.1016/j.gerinurse.2021.03.007

[18] Camacho RC, Alabed S, Zhou H, Chang SL. Network meta-analysis on the changes of amyloid precursor protein expression following SARS-COV-2 infection. Journal of Neuroimmune Pharmacology. 2021 Dec;16(4):756–69. https://doi.org/10.1007/s11481-021-10012-9

[19] Kuo C-L, Pilling LC, Atkins JL, Masoli JA, Delgado J, Kuchel GA, et al. Letter to the editor: ApoE e4e4 genotype and mortality with covid-19 in UK Biobank. The Journals of Gerontology: Series A. 2020 Sep 16;75(9):1801–3. http://doi.org/10.1093/gerona/glaa169

[20] Hultman K, Strickland S, Norris EH. The *APOE* ε4/ε4 genotype Potentiates Vascular Fibrin(Ogen) deposition in amyloid-laden vessels in the brains of Alzheimer's disease patients. Journal of Cerebral Blood Flow & Metabolism. 2013 Aug;33(8):1251–8. http://doi.org/10.1038/jcbfm.2013.76

[21] Lim K-H, Yang S, Kim S-H, Joo J-Y. Letter to the editor: Elevation of ACE2 as a SARS-COV-2 entry receptor gene expression in Alzheimer's disease. Journal of Infection. 2020 Sep;81(3). http://doi.org/10.1016/j.jinf.2020.06.072

[22] Kehoe PG, Wong S, AL Mulhim N, Palmer LE, Miners JS. Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-β and tau pathology. Alzheimer's Research & Therapy. 2016 Nov 25;8(1). http://doi.org/10.1186/s13195-016-0217-7

[23] Stanciu GD, Luca A, Rusu RN, Bild V, Beschea Chiriac SI, Solcan C, et al. Alzheimer's disease pharmacotherapy in relation to cholinergic system involvement. Biomolecules. 2019 Dec 26;10(1):40. http://doi.org/10.3390/biom10010040
[24] Hoover DB. Cholinergic modulation of the immune system presents new approaches for treating inflammation. Pharmacology & Therapeutics. 2017 Nov;179:1–16. http://doi.org/10.1016/j.pharmthera.2017.05.002
[25] Sharma K. Cholinesterase inhibitors as Alzheimer's therapeutics. Molecular medicine reports. 2019 Aug 1;20(2):1479-87. https://doi.org/10.3892/mmr.2019.10374
[26] Gowayed MA, Refaat R, Ahmed WM, El-Abhar HS. Effect of galantamine on adjuvant-induced arthritis in rats. European Journal of Pharmacology. 2015 Oct 5;764:547–53. http://doi.org/10.1016/j.ejphar.2015.07.038
[27] Kuo C-L, Pilling LC, Atkins JL, Fortinsky RH, Kuchel GA, Melzer D. *APOE* e4 genotypes increase risk of delirium during COVID-19-related hospitalizations: Evidence from a large UK cohort. The Journals of Gerontology: Series A. 2022 Apr;77(4):879–80. http://doi.org/10.1093/gerona/glab184
[28] Liu Y-H, Wang Y-R, Wang Q-H, Chen Y, Chen X, Li Y, et al. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. Molecular Neurodegeneration. 2021 Jul 19;16(1). http://doi.org/10.1186/s13024-021-00469-w
[29] Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, et al. SARS-COV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022 Mar 7;604(7907):697–707. https://doi.org/10.1038/s41586-022-04569-5
[30] Ciaccio M, Lo Sasso B, Scazzone C, Gambino CM, Ciaccio AM, Bivona G, et al. COVID-19 and Alzheimer's disease. Aguado F, editor. Brain Sciences. 2021 Feb 27;11(3). http://doi.org/10.3390/brainsci11030305
[31] Hardan L, Filtchev D, Kassem R, Bourgi R, Lukomska-Szymanska M, Tarhini H, et al. COVID-19 and Alzheimer's disease: A literature review. Reiss AB, editor. Medicina. 2021 Oct 25;57(11). http://doi.org/10.3390/medicina57111159
[32] Iodice F, Cassano V, Rossini PM. Direct and indirect neurological, cognitive, and behavioral effects of COVID-19 on the healthy elderly, mild-cognitive-impairment, and Alzheimer's disease populations. Neurological Sciences. 2021 Jan 7;42(2):455–65. https://doi.org/10.1007/s10072-020-04902-8
[33] Roalf DR, Moberg MJ, Turetsky BI, Brennan L, Kabadi S, Wolk DA, et al. A quantitative meta-analysis of olfactory dysfunction in mild cognitive impairment. Journal of Neurology, Neurosurgery & Psychiatry. 2017 Mar;88(3):226–32. http://doi.org/10.1136/jnnp-2016-314638
[34] Mahalakshmi AM, Ray B, Tuladhar S, Bhat A, Paneyala S, Patteswari D, et al. Does COVID-19 contribute to development of neurological disease? Immunity, Inflammation and Disease. 2021 Mar;9(1):48–58. http://doi.org/10.1002/iid3.387

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