



In what ways has social isolation during the COVID-19 pandemic influenced the onset of dementia on people from different socio-economic backgrounds?

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Abstract

Alzheimer's disease (AD) is a growing public health concern and a sharp increase in the number of Alzheimer's patients has been observed in the 21st century. Unfortunately, the molecular pathology driving AD remains poorly understood. However, evidence suggests that both societal and environmental factors play an important role in the cognitive decline and reduction in quality of life associated with AD.

This review aims to summarise the available literature on the factors that affect AD patients from different socio-economic backgrounds. The paper will also discuss the impact of social isolation during the COVID-19 pandemic on Alzheimer patients and their caregivers. The pathology of AD and its hallmarks, the impact of genetic factors and traumatic brain injury on AD, the impact of socio-economic conditions, social isolation, and the pandemic on Alzheimer patients have been explored in this review.

Methods

A literature review was conducted using previously published papers on Google Scholar and PubMed. Papers on the pathology of Alzheimers, the genetic factors of Alzheimers, the effect of traumatic brain injury, socio-economic background(education, stress and comorbidities), access to healthcare and lifestyle factors such as aerobic exercise, smoking, alcohol consumption and exposure to polluted environments were reviewed. Papers on the impact of COVID-19 on Alzheimer patients and care-givers as well as the impact of social isolation and loneliness on cognitive function were reviewed. A survey of high school students in Mumbai, India was conducted. The survey received 83 results and comprised the University of California Los Angeles (UCLA) loneliness scale and question about the impact of social isolation and the COVID-19 pandemic on the academic performance and learning rates of adolescents.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that results in gradual cognitive decline and memory loss. This neuropathological condition is characterised by neuronal loss and the development of neurofibrillary tangles and amyloid beta plaques. (Trejo-Lopez et al., 2022). AD is classified into sporadic late-onset (prevalent in 85-90% of cases), familial early-onset, familial late-onset, and AD associated with Down's syndrome (Cvetkovi et al., 2001).

AD is a growing public health concern, with 55 million cases reported in 2020. The incidence of AD is predicted to increase among senior citizens (65+ years of age) from 420 million in 2000 to nearly 1 billion by 2030. This number is expected to almost double every 20 years, reaching 78 million in 2030 and 139 million in 2050 (Lanclet, 2022.). Developing countries in eastern sub-Saharan Africa such as Sudan, Djibouti and Ethiopia are expected to see the largest increase in AD patients with cases going up by 357% . The prevalence of AD patients in these countries is predicted to rise from 59% to 71% by 2050. This is believed to be the result of poor education and unhealthy lifestyle (Lanclet, 2022). However, taken together, this evidence suggests that AD is a major and growing public health concern with substantial increases projected in the future, particularly in low-to-middle-income countries, making it an impending epidemic.

Clinical Pathology of AD

Morphological changes in AD include cortical atrophy with narrowing of gyri and widening of sulci. Gyri is the name of the bumps and ridges of the cerebral cortex while the sulci are grooves on the brain surface. The most severely affected regions include the temporal lobe (region of the brain associated with memory, hearing and emotion) especially its substructures such as the hippocampus, parahippocampus, and amygdala. This is followed by the frontal lobe (associated with voluntary movement, language and higher order executive functions) and parietal lobes (associated with receiving and processing sensory input). The occipital lobes (associated with visuospatial processing, distance and depth perception) and motor cortex that generates signals for body movement are usually spared. (Cvetkovi et al., 2001)

The disease is characterised by the deposition of beta-amyloid protein in the cerebral cortex and the dramatic loss of neurons and synapses. (Cvetkovi et al., 2001)

The neuropathological hallmarks of AD include (Figure 1):

- 1) Neurofibrillary tangles (NFTs), which are primarily composed of microtubule-associated tau protein due to abnormal phosphorylation. NFTs in general are flame or globoid in shape. They comprise highly insoluble and proteolysis-resistant paired helical filaments (PHFs), along with straight filaments and amorphous material. They are found mainly in pyramidal neurons of the medial temporal lobe and certain subcortical neurons. Pyramidal neurons are those that are found in the subcortical regions of the brain such as the hippocampus and amygdala. They are named so because of their rounded pyramid or tear drop shape. They transform sensory input into action potentials. (Bekkers, 2011)
- Neuritic plaques (NPs) include foci of enlarged axons, synaptic terminals, and dendrites, associated with extracellular beta/A4 amyloid. However diffuse plaques are a classic presentation in AD patients.
- 2) Neuropil threads (NTs), which appear as an argentophilic network of fragmented and twisted fibres in the neuropil and are often associated with NFTs in patients.

- 3) Hirano's bodies (HBs) which are eosinophilic intraneuronal structures found in hippocampal pyramidal neurons in AD patients. They represent age-related alterations of the micro filamentous system of the brain. A greater number of Hirano bodies indicate a higher age of a person. The number of Hirano bodies increases in patients suffering from Alzheimer's. (Dickson et al., 2014)
- 4) Cerebral amyloid (conophilic) angiopathy (CAA), which involves the accumulation of beta/A4 amyloid filaments within the walls of small arteries and arterioles in the brain in patients (Cvetkovi et al., 2001).

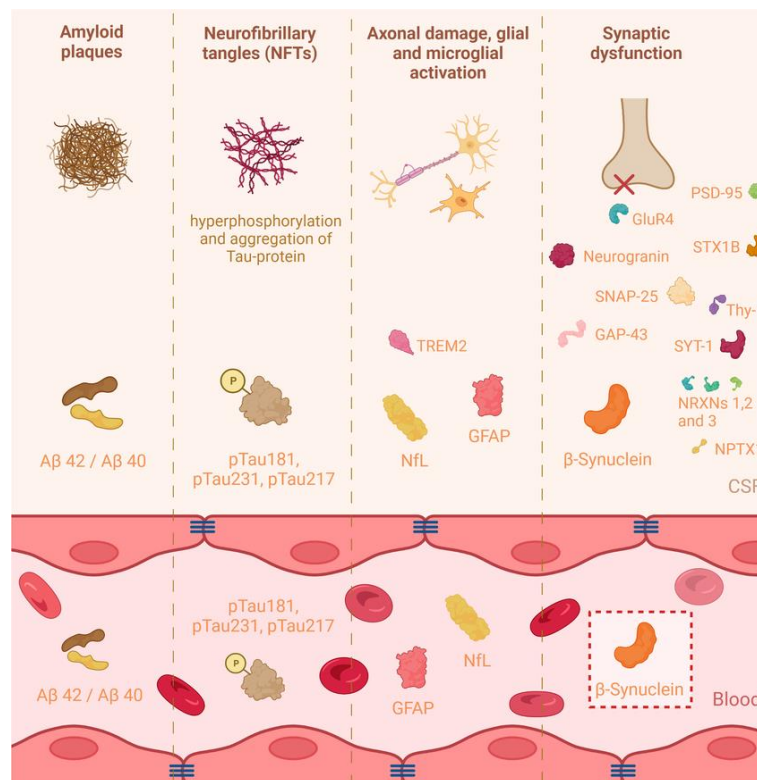


Fig.1 The hallmarks of AD pathology (Mohaupt et al., 2022). This figure shows amyloid plaques and neurofibrillary tangles whose development is a hallmark of Alzheimers. Synaptic dysfunction, axonal damage, glial and microglial activation depicted are also hallmarks of Alzheimer's pathology.

The AD clinical phenotype follows a stage known as mild cognitive impairment (MCI) that is usually, but not exclusively, characterised by memory loss (amnesic MCI = aMCI). Early identification and treatment of MCI improves patient prognoses. Lifestyle factors such as obesity, lack of exercise, smoking, and low cognitive activity along with medical factors like cardiovascular diseases, diabetes, thyroid dysfunction, and hypercholesterolemia have also been implicated in the development and progression of MCI and AD (Rossini et al 2020).

An electroencephalogram (EEG) is a test that can measure electrical activity in the brain with electrodes adhered to the scalp. Neuronal circuits in the human brain communicate via synchronous firing patterns known as oscillations. EEG rhythms reflect these dynamics, measuring functional connectivity between brain areas through synchronisation, coherence, and phase-locking. Synchronisation is seen in an EEG when brain wave activity is coordinated in different brain regions. This is seen in an EEG in the form of rhythmic patterns or waves in different brain areas. Coherence is the degree of synchronisation and phase-locking is defined as the timing when the neuronal activity synchronises. Hence, EEG recordings help in the diagnosis of dementia. Alpha rhythms in an EEG have been defined as rhythms between 8 and 13 Hz observed during

wakefulness across the posterior regions of the head, typically exhibiting increased voltage over the occipital areas.(Aich, 2014). They are best examined when a person is in a state of physical relaxation and relative mental inactivity such as meditation or daydreaming. Delta rhythms are high-frequency, low-amplitude fluctuations exclusively associated with sleep, particularly during slow-wave sleep when the body undergoes restorative functions such as repair and memory consolidation (Sachdev et al., 2015). Higher beta density in EEGs represents increased mental activity. Theta waves are associated with certain cognitive processes, such as memory formation, creativity, and spatial navigation along with certain stages of sleep such as rapid eye movement (REM) and drowsiness. (Schacter, 1977). In the context of AD, the EEG of patients with dementia shows abnormalities such as excessive delta (δ) rhythms and a significant decrease in posterior alpha (α) rhythms. The EEGs of AD patients under the power spectrum also show increased delta and theta (θ) density and decreased alpha and beta (β) density, with a lowering of the alpha power density peak compared to individuals of a similar age but without AD.

These patterns allow EEGs to help detect AD in patients. Alzheimer's disease leads to a reduction in the complexity of EEG signals and changes in EEG synchrony. These modifications in EEG recordings are used for AD diagnosis (Houmani et al., 2018). EEGs also provide information on the activity of localised brain regions such as the precuneus (associated with recollection and memory, responses to pain and memory retrieval) and posterior cingulate(associated with autobiographical memory, imagining the future, spatial navigation and scene processing). These two regions show reduced activity in Alzheimer's patients. Hence, reduced activity of these regions shown in the EEG, indicates the presence of AD in the patient.

The impact of genetic factors and severe brain injuries on Alzheimer's

The molecular pathology of Alzheimer's is still not universally accepted. However, the most universally accepted hypotheses include the aggregation and deposition of misfolded proteins like aggregated beta-amyloid (A β) peptide in the form of extracellular senile (or neuritic) "plaques," and hyperphosphorylated tau (t) protein in the form of intracellular neurofibrillary "tangles" (NFTs) (Bertram et al., 2010). These pathognomonic changes are often accompanied by abundant microvascular damage, including vascular amyloid deposits, and pronounced inflammation of the affected brain regions (Bertram et al., 2010).

Inherited AD genes increase the risk of the development of the disease. The examination of thousands of single nucleotide polymorphisms (SNPs) using microarray technology (Chouraki and Seshadri, 2014) has revealed that the β -amyloid precursor protein (β APP) gene (on chromosome 21), the presenilin 1 (PSEN1) gene (on chromosome 14), and the presenilin 2 (PSEN2) gene (on chromosome 1) are all associated with early-onset AD. (St George-Hyslop, 2000). Presence of these increases the risk of AD development by 50% (Science Direct). The ϵ 4 allele of apolipoprotein E (APOE) is associated with an increased risk for late-onset AD(St George-Hyslop, 2000). People carrying one ϵ 4 allele(heterozygous) showed a 3 fold increased risk of AD while those carrying two alleles (homozygous) showed a 15 fold increased risk of developing the disease (Gharbi-Meliani et al., 2021).

Positional cloning has led to the identification of rare mutations in APP, PSEN1, and PSEN2 that play a role in the development of Alzheimer's (Bertram et al., 2010). The expression of the $\epsilon 4$ allele of APOE (APOE4) results in intracellular cholesterol accumulation and impairment of A β clearance in astrocytes. Astrocytes are a subtype of glial cells that make up a majority of neurons of the central nervous system (CNS). They perform functions like promotion of synapse formation, regulation of the blood-brain barrier and clearing of excess neurotransmitters (Wei, 2023). APOE4 disrupts neuron-astrocyte coupling and is associated with impaired lipid and fatty acid metabolism. This fatty acid accumulation in neurons hinders fatty acid oxidation and lipid dysregulation in astrocytes. This in turn affects A β clearance and may contribute to increased AD risk (Raulin, 2022).

The catalytic centre of γ -secretase is encoded by PSEN1 and PSEN2. γ -secretase mediates the final cleavage that liberates A β amyloid plaques, a hallmark of AD thereby contributing to the development of Alzheimer's (Hur, 2022).

This convergence of genetic and molecular evidence supports the "amyloid hypothesis," which states that the abnormal production of A β is the initial step in triggering the pathophysiological cascade that eventually leads to AD (Bertram et al., 2010).

Despite prior research, most of the genetic drivers of AD remain inexplicable, known as "missing heritability." Therefore, the exact genetic mechanism causing AD cannot be accurately elucidated.

Traumatic Brain Injury

Traumatic brain injury significantly contributes to the development of dementia by causing cerebrovascular dysfunction. Cerebrovascular dysfunction (CVD) is a key element in the development of neurodegeneration due to initiation of molecular events leading to neurodegeneration (Nelson et al., 2016). Cerebrovascular disruption can lead to accumulation of neurotoxic circulating molecules that may directly initiate neuronal injury (Nelson et al., 2016). Traumatic brain injury is a major public health concern. Additionally, severe or repeated traumatic brain injury (TBI) causes haemorrhages, oedema, vasospasms, coagulopathy, and chronic inflammation (Ramos-Cejudo et al., 2018) that induces long-term neurodegeneration with similar hallmarks to Alzheimer's disease neuropathology.

The term "punch drunk" has been used to describe syndromes experienced by players of contact sports such as boxing. The effects are witnessed after years and include facial characteristics of Parkinsonian syndrome, marked mental deterioration, and repeated loss of consciousness. Hence, it can be said that a history of TBI accelerates the onset of dementia in later life (Ramos-Cejudo et al., 2018).

Encephalopathy is defined as either a temporary or permanent change in brain function. An infection or an underlying condition are possible causes of encephalopathy. Chronic traumatic encephalopathy (CTE) occurs in the latter lives of patients who suffered from traumatic brain injuries. Cerebrovascular pathology represents a link between A β /tau deposition-related dementia and chronic traumatic encephalopathy.

CTE exhibits symptoms similar to Parkinson's, Alzheimer's, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). More specifically, this includes the deposition of $\alpha\beta$ plaques (characteristic of Alzheimer's) around the lesion site (Ramos-Cejudo et al., 2018). Hypoxia, brain ischemia stress and reduced blood flow

also stimulate the deposition of α plaques (Ramos-Cejudo et al., 2018). TBI plays a role in secondary injury cascades including cerebrovascular damage, oxidative stress, mitochondrial damage, and endothelial cell death or dysfunction (Ramos-Cejudo et al., 2018). A characteristic feature of CVD is the deposition of hyperphosphorylated tau protein as NFTs, particularly around small blood vessels of the cortex and in the depths of the sulci. This leads to the formation of neurofibrillary tangles that lead to AD pathology. Microtubules in axons provide a structural backbone for dendrites and axons. They allow them to maintain their specialised morphologies (Baas et al., 2016). Mechanical stress, following trauma, beyond certain thresholds can disrupt microtubule networks within axons causing hyperphosphorylation, extracellular accumulation, and tau release (Ramos-Cejudo et al., 2018). All in all, traumatic brain injury may increase the risk of developing Alzheimer's.

Socio-economic status and its impact on Alzheimers

The behavioural and neural differences associated with lower socioeconomic status (SES) are multifaceted. Discrepancies may be observed in language processing, executive function, memory systems, and social cognitive processing among children from different socioeconomic backgrounds (Raizada and Kishiyama, 2010). There is a strong correlation between lower education levels and the risk of Alzheimer's disease and other forms of dementia. Childhood SES, a measure of the availability of material and social resources, is one of the strongest predictors of future well-being. Higher SES is associated with lower exposure to stress, and greater access to cognitive enrichment, such as education, books, and toys. Lower SES is associated with faster thinning and blunted brain functional remodelling during childhood and adolescence. It has been observed that children from lower SES tend to be academically weaker than their counterparts from higher socio-economic backgrounds. Studies show that they are more likely to perform lower on standardised tests, drop out of school, fail, or be placed in special school for academically weaker or specially abled students (Raizada and Kishiyama, 2010). These trends are likely due to childhood environments that lacked cognitive enrichment.

Individuals from lower socio-economic backgrounds are also more likely to develop Alzheimer's due to poor access to healthcare and education. This includes a greater likelihood of developing clinical risk factors of AD such as hypertension, obesity, poor sleep quality, low physical activity, and diabetes.

Lower SES is also associated with greater chronic stress that requires repeated use of stress detection regulation circuitry, including the amygdala and medial prefrontal cortex. Animal studies have shown that chronic stress or glucocorticoid administration, which simulates the effects of chronic stress, can lead to decrease in size, complexity and activity (Tottenham and Sheridan, 2010) of the hippocampus and amygdala (brain regions associated with long term memory and fear, emotions respectively) (Pagliaccio et al., 2014). Stress may also contribute to the faster ageing of the body by increasing glucocorticoid levels and allostatic load and by promoting the activation of inflammatory processes. This causes individuals from lower SES to enter puberty earlier, driven most strongly by experiences of threat. It may also accelerate brain development as young individuals process threats as an overall signal of lack of support and protection thus requiring environmental maturity. Hence, children from such sections of society tend to demonstrate accelerated cortical maturation at the expense of cognitive development.

Early childhood adversity, particularly seen in children from lower SES, was associated with poor baseline cognitive performance in African American participants in a research study conducted in 2021 (Majoka and Schimming, 2021).

Specific neuropsychological assessments and neuroimaging have revealed differences in neurocognitive systems between children from low SES backgrounds and those from higher SES backgrounds. SES was also associated with grey matter structure in the brain's developmental trajectories (Tomasi and Volkow, 2021). Lower SES is also associated with reductions in grey matter volume, thickness, as well as surface area, particularly in the frontal and subcortical regions (Tomasi and Volkow, 2021). The absence of cognitive enrichment leads to accelerated synaptic pruning in brain regions that process complex cognitive and social stimuli, causing these individuals to potentially be predisposed to Alzheimer's and other forms of dementia.

Furthermore, early investigations in animal models have shown that enriched environments and stimulation lead to brain growth. Animals (rats) raised in enriched environments comprising other animals, objects to explore, ladders to climb, toys to learn have been observed to learn better than genetically identical animals reared in environments without enrichment due to higher levels of the neurotransmitter acetylcholine. Higher amounts of acetylcholine are also seen in rats trained on difficult spatial problems such as food- rewarded maze problems than in rats exposed to simpler problems. An increase in brain weight by 5% in the cerebral cortex of animals was seen on exposure to the enriched environments mentioned above. Training or stimulation increased neuronal size, connectivity, and blood supply by 25% as compared to a person/animal without training or stimulation. Postmortem examinations revealed that an increased number of neuron branches led to an increase in the volume and the thickness of the cortex. This in turn reinforces the brain against AD pathology (Doidge, N. (2008), *The brain that changes itself*. Penguin Books.)

A study published in January, 2008 was carried out to understand why some patients with AD pathology maintain normal cognitive function for longer. It was found that more educated individuals showed less severe cognitive decline than patients with poorer education even with the presence of AD pathology. More educated refers to patients who were complete or partial high school graduates and those who completed more education after high school as compared to those patients who did not reach high school. This proves that education (and by proxy, socio-economic status) can provide some level of protection against the development of AD symptoms even in the presence of AD pathology (Fotenos et al., 2008). It was also found that cognitive leisure activities (CLA) and education reduce the risk of MCI and AD. However, the association between SES and AD have proved to be inconsistent over many experiments as various factors fall under the umbrella term of SES (Sattler et al., 2012).

Alzheimer's disease adversely impacts the care-givers of the patient as well. Studies addressing the socio-economic conditions and background of caregivers provide us with insight into the background of patients. A study investigating the impact of socio-economic factors and family stigma on patients and their caregivers in urban areas reported that caregivers of patients with EOAD (early onset Alzheimer's disease) had a higher frequency of socioeconomic risk factors. It was also found that caregivers of patients with frontotemporal dementia (FTD) experienced higher levels of family stigma and more negative outcomes.

This study also found that family stigma caused caregiver burden and reduced the quality of life (QoL) of caregivers. There was a strong relationship between family stigma and negative outcomes such as caregiver burden, fatigue, emotional well-being, and anxiety (vellila et al ., 2022).

The neurological impact of SES is significant. Interventions targeting low SES children have shown short-term cognitive gains. Though "fade-out" effects of these interventions are also reported, long-term follow-up studies suggested that some interventions can lead to enduring neural changes that correlate with improved life outcomes (Raizada and Kishiyama, 2010).

AD risk factors associated with socio-economic status

Stress

Lower SES is commonly associated with high-stress levels. Stress is critically involved in the development and progression of disease. Physiological processes driven by stress have a detrimental effect on the ability to heal and maintain a high quality of life (Justice, 2018). Stress plays a pivotal role in the development and progression of neurodegenerative diseases, especially Alzheimer's. Neurodegenerative diseases are not only exacerbated by stress but also disrupt neural circuits that mediate stress responses which in turn results in emotional and aggressive behaviour, anxiety, depression, and insomnia. This occurs due to the activation of the hypothalamic-pituitary-adrenal (HPA) axis which elevates circulating corticosteroid (Cort) levels (Justice, 2018). The feed forward relationship between disease and stress has been coined the "Vicious Cycle of Stress" (Justice, 2018). This cycle can be divided into two arcs and can be seen in Figure 2: the right arc which represents the influence of stress on disease progression and the left arc representing how the prognosis of the disease disrupts neural and endocrine circuits involved in the stress response, leading to neuropsychiatric symptoms (Justice, 2018).

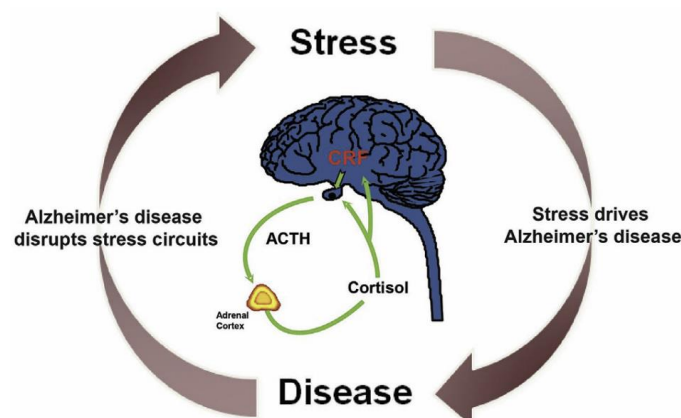


Figure 2: The vicious cycle of stress. Stress drives AD which in turn disrupts stress circuits. Stress stimulates the release of the Adrenocorticotrophic hormone which inturn stimulates the release of cortisol(a glucocorticoid) from the adrenal cortex. Cortisol is the primary stress hormone and its high levels have deleterious effects on the brain causing neurodegenerative diseases like Alzheimer's(Justice, 2018).

Animal models show that stress exacerbates AD. In rats with higher stress levels, an increased expression of amyloid precursor protein (APP) and generation of A β peptide along with exacerbated amyloid plaque deposition and neurofibrillary tangle deposition are seen (Justice, 2018). Excessive secretion of cortisol and corticotropin-releasing factors (CRF) that contribute to AD are also seen. Clinical studies have shown that elevated cortisol levels and stress-related conditions are seen in patients in the early stages of AD and in patients with mild cognitive impairment (MCI). Higher levels of distress and anxiety positively correlate with accelerated loss of brain tissue density and an increased likelihood of conversion of MCI to AD/dementia (Justice, 2018). A higher score on the childhood trauma questionnaire resulted in a 1.7-fold increase in the possibility of the development of AD. This suggested that patients with more traumatic childhoods were more likely to develop AD. Stress can also increase amyloid β precursor protein and tau phosphorylation which are involved in the impairment of synapses and neuronal death, which in turn catalyses AD (Caruso et al., 2018). Hence, it can be concluded that an increase in stress levels may accelerate the development of AD.

Diabetes and hyperglycemia

The World Health Organization reports that type 2 diabetes (T2D) is the most prevalent metabolic disease and affects approximately 422 million people worldwide. Epidemiological studies report that T2D is associated with increased susceptibility to AD and vascular dementia across various populations (Santiago and Potashkin, 2021). A study found a significantly lower cognitive performance among diabetic patients as compared to a healthy control group, over 4 years, which resulted in a 2-3-fold increase in dementia development (Santiago and Potashkin, 2021). Interestingly, patients with prediabetes also displayed an increased risk of dementia, suggesting that early alterations in glucose metabolism can trigger neurodegeneration (Santiago and Potashkin, 2021). Islet amyloid, a hallmark of diabetes, was found in patients with Alzheimer's disease, pointing towards the correlation between the two diseases. Just like with other factors causing Alzheimer's, the exact mechanism of how diabetes affects Alzheimer's is not clearly known. However, numerous hypotheses exist. These include impaired glucose metabolism, vascular abnormalities, impaired insulin signalling, amyloidosis, and inflammation. The most popular hypothesis is the impaired insulin signalling hypothesis. Patients with T2D are more susceptible to cerebral amyloid angiopathy (Lee et al., 2018), a condition associated with brain infarcts and AD. Induction of acute hyperglycemia in certain animals and mice subsequently increased amyloid beta in hippocampal interstitial fluid and amyloid beta plaques in aged mice. The immune system also plays a pivotal role in the development of both AD and T2D as shown by the existence of increased proinflammatory cytokines in both diseases. The risk of dementia in diabetic individuals may also be influenced by genetic factors such as the presence of the APOE ϵ 4 allele (Lee et al., 2018). Even though these findings vary, it is most commonly believed that diabetes catalyses the prognosis of NDDs like AD. Notably, it has been found that lower SES is associated with a higher prevalence of diabetes potentially due to limited healthcare access and poor health-related behaviours such as poor diet, poor physical activity. (Rabi et al., 2006).

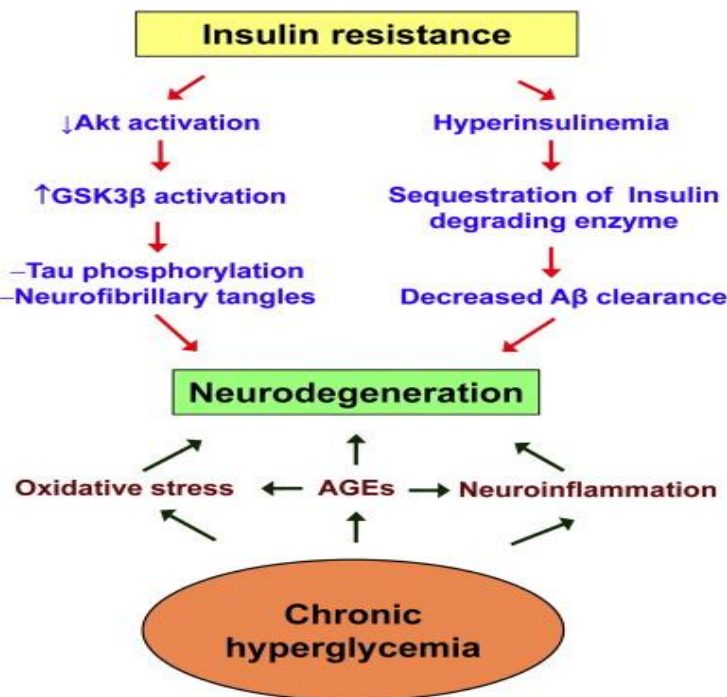


Figure 3: The relationship between insulin resistance, neurodegeneration and chronic hyperglycemia. Insulin resistance causes decreased amyloid beta clearance and increase in neurofibrillary tangles and tau phosphorylation. These are hallmarks of AD and increase AD risk. Chronic hyperglycemia on the other hand causes oxidative stress and neuroinflammation which in turn causes neurodegeneration (Pugazhenthir et al., 2017).

Cardiovascular diseases and hypertension

It has been found that cardiovascular diseases and hypertension contribute to AD development and pathology (Stampfer, 2006). Several cardiovascular risk factors are also risk factors for AD and dementia. These include hypertension, high LDL cholesterol, low HDL cholesterol, and diabetes. Elevated blood pressure (hypertension) during an individual's midlife is associated with the development of neuritic plaques and neurofibrillary tangles, hallmarks of AD pathology. Severe white matter lesions have also been found in highly hypertensive individuals. Studies of both clinical cardiovascular diseases (CVD) and subclinical CVD have reported associations with impaired cognitive function (Stampfer, 2006). CVD, hypertension, and high cholesterol levels are said to be more prevalent in those with lower SES and positively correlate with AD development and prognosis. It has also been found that the use of antihypertensive drugs is associated with a lower incidence of AD and dementia along with reduced cognitive decline (Santiago and Potashkin, 2021). Therefore, it can be concluded that cardiovascular diseases that are more prevalent in lower SES positively correlate with AD development.

Obesity

Obesity has been recognised as a crucial factor in the pathogenesis of Alzheimer's disease. In the context of AD, adipocyte (fat cells i.e. the primary cell type in adipose tissues) dysfunction and subsequent alteration in adipocyte-derived protein secretion are key obesity-related mechanisms that lead to the development of AD (Letra et al., 2014).

A longitudinal study of 6583 individuals that measured the sagittal abdominal diameter was conducted over a period of 9 years. The study revealed that individuals with the largest diameter had nearly a three-fold risk of developing dementia as compared to those with the smallest diameter (Whitmer et al., 2008). Another study revealed that a larger hip-waist ratio was associated with decreased hippocampal volume (Pugazhenthhi et al., 2017). Additionally, another study reported that the odds of overweight individuals (body mass index (BMI) >25-30) developing dementia were 1.71. In comparison, the risk of obese individuals (BMI >30) developing dementia was 3.88 (Pugazhenthhi et al., 2017). This evidence strongly implicates obesity in AD development and progression.

High-fat diet, a major cause of obesity, results in elevated levels of circulating free fatty acids. These elevated levels cause low-grade inflammation that plays a pivotal role in insulin resistance which, in some cases, results in AD pathology. This inflammation is due to the activation of Toll-like receptor 4 (TLR4) by saturated fatty acids. The activation causes the generation of cytokines in astrocytes and the induction of an inflammatory response in the hypothalamus. Loss of TLR4 function or its inhibition protects against diet-induced obesity. Though fatty acids have limited passage through the blood-brain barrier (BBB), they still are able to accumulate in the brain of obese patients leading to AD pathology such as glial activation. (Pugazhenthhi et al., 2017). Obesity is more common among members of lower SES and positively correlates with AD pathology (Anekwe et al., 2020).

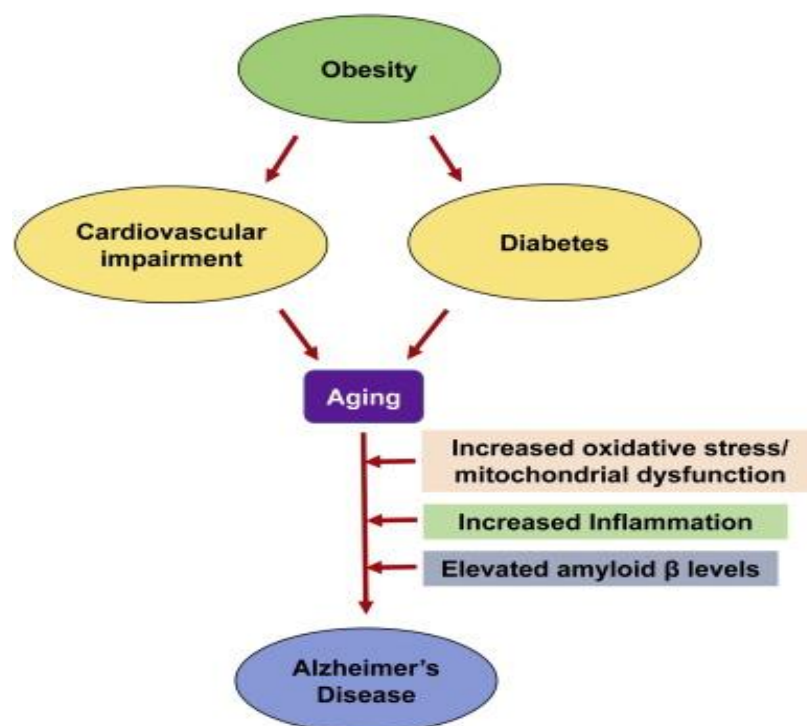


Figure 4: The figure depicts the relationship between obesity and its side-effects and the manner in which they affect ageing and Alzheimer's disease neurodegeneration (Pugazhenthhi et al., 2017). Obesity causes cardiovascular impairment and diabetes that lead to elevated amyloid beta levels, increased inflammation and increased oxidative stress/mitochondrial dysfunction. These in turn increase the risk of Alzheimer's disease. Hence, it can be said that obesity may be one of the factors of AD.

Access to healthcare and the impact of lifestyle (aerobic exercise, consumption of alcohol, smoking, and exposure to environmental toxins) on AD

Patients from higher SES tend to have better and quicker access to healthcare which leads to early detection of Alzheimer's disease. Detection of AD during the preclinical phase may reduce the prognosis and extent of damage caused by the disease. The preclinical phase refers to the asymptomatic phase that ranges from 2 to 15 years in length. During this phase, neuropathological changes occur but the cognitive ability of the patient remains broadly unaffected (Dubois et al., 2016). Early detection of AD can avoid or delay secondary medical complications (Valcour and Blanchette, 2001), emphasising the importance of early detection methods. Early detection provides the patient with time to benefit from available treatments, enrol in clinical trials, organise the required care, prepare their families, manage legal and financial aspects of their personal lives, and seek counselling to manage future behavioural changes. Hence, patients from higher SES have an advantage due to quicker access to healthcare (Colizzi, 2020).

Interestingly, a study in 1992 suggested that mild-to-moderate consumption of alcohol is not substantially related to the incidence of Alzheimer's disease and that smoking does not increase the risk of the disease (Hebert et al., 1992). Another study showed the presence of plausible pharmacological mechanisms that link smoking and drinking to AD. In addition, it concluded that epidemiological reports on the relationship between alcohol/smoking and AD have been inconsistent. (Vallée, 2023)

In contrast to this, evidence collected over 3 years suggested that tobacco and alcohol use may not only individually affect AD but may also modify each other's effects (Myers et al., 2006). A study in 2020 showed that cigarette smoking is associated with a higher risk of AD. It concluded that smokers performed worse on verbal memory tests, especially the Rey Auditory Verbal Learning Test (RAVLT), both in terms of learning score and delayed recall, as compared to non-smokers. Smokers exhibited lower levels of hippocampal volume (HpVR) as compared to non-smokers. Smokers were also found to have lower levels of cerebral glucose metabolism as compared to non-smokers. However, no significant difference was found in cerebrospinal fluid (CSF) levels of Alzheimer's disease (AD) pathologies, including A β 42, t-tau, or p-tau, between non-smokers and smokers (Wu et al., 2020). Another paper published in the same year found no differences in the rate of cognitive decline by smoking status (Deal et al., 2020).

Aerobic exercise has been shown to favourably modify the accumulation, degradation, and removal of AD hallmark amyloid- β and hyperphosphorylated tau in animal models. This is achieved by the stimulation of the production and function of brain-derived neurotrophic factors (BDNF). BDNFs contribute to neurogenesis, especially in the hippocampus. It increases neuronal survival, enhances synaptic plasticity, and mediates memory improvement (Yu et al., 2021). Aerobic exercise also appeared to impact AD non-hallmark pathology such as neuroinflammation, oxidative stress, and glucose hypometabolism. Exercise may help mitigate the decline in overall cognition function among older adults with mild-to-moderate AD dementia. (Yu et al., 2021b). The study by Yu and colleagues, conducted in 2021, investigated whether aerobic exercise may reduce the decline in hippocampal volume, cortical thickness, and white matter hyperintensity. However, the extent of the effect of aerobic exercise was found to be limited with positive effects reversing if patients stopped exercising (Yu et al., 2021a). Aerobic exercise is a promising therapy for the behavioural changes that accompany AD. (Yu et al., 2013).

Since patients from higher SES tend to engage more in activities such as aerobic exercise due to the availability of more time for leisure activities, it can be concluded that the extent of behavioural changes associated with AD might be less in patients from this section of society who tend to exercise.

Environmental factors and toxins

Environmental factors affect neurodegenerative diseases. It has been recently hypothesised that exposure to various environmental factors enhances the risk of AD. Exposure to air pollutants, heavy metals, pesticides, nanoparticles containing metals, and industrial chemicals accelerates the progression of AD. This results in tau hyperphosphorylation, leading to the initiation of senile plaques and neurofibrillary tangles. This causes the death of neurons (Mir et al., 2020). Human exposure to such chemicals can be measured in human tissues and body fluids using Human Biomonitoring (HBM) (Elonheimo et al., 2021). A scoping review conducted in 2021 showed that exposure to pesticides positively correlated with the advancement of AD (Elonheimo et al., 2021). Even though conclusive data on the impact of cadmium (Cd) on Alzheimer's disease is not known, a previous study has found elevated levels of Cd circulation in patients with AD (Xu et al., 2018). A study also correlated arsenic exposure with amyloid, vascular, and inflammatory hypotheses of AD. However, a conclusion has not been accepted due to a lack of evidence. Lead exposure has a weak to moderate correlation with AD and occupational exposure to mercury has associations with adversely affected cognitive functions (Elonheimo et al., 2021).

No clear association of AD with NO₂/SO₂ emissions was seen among residents living near industrial areas (Cakmak et al., 2022). In contrast, a study published in 2017 showed that people living in heavy traffic zones in urban areas showed a higher rate of AD development (Chen et al., 2017). A study also found that environmental factors may interact with genetic factors to accelerate AD development. (Campdelacreu, 2014).

Thus, we can conclude from various studies that the risk of AD can be reduced slightly if not significantly by engaging in regular exercise, avoiding smoking and excessive use of alcohol, living in non-polluted and toxin-free environments, and remaining free from comorbidities by following a healthy diet and exercising. Low educational status, social isolation, stress, and cognitive inactivity may hasten the advancement of AD.

Social isolation and its impact on Alzheimer's

Loneliness has been defined as a condition associated with increased risk for premature mortality and neurodevelopment disorders like AD. Humans are primarily social animals and require social connections and relationships, in the absence of which, loneliness or perceived social isolation occurs (Lieberz et al., 2021). Humans may have evolved to feel lonely to meet the need for new social connections, similar to how hunger is felt to promote ingestion (Lieberz et al., 2021). Social engagement has been reported to have a protective effect against Alzheimer's disease-related dementias (ADRDs). Social connection and engagement have been found to preserve cognitive function (Majoka and Schimming, 2021). Individuals with strong social connections are 50% more likely to live longer after their diagnosis of AD than lonely patients (Drinkwater et al., 2022).

Perceived social isolation, or loneliness, affects physical and mental health, cognitive performance, overall life expectancy, and increases vulnerability to Alzheimer's disease-related dementias (Spreng RN, 2021). Social isolation caused by disparity and discrimination has been linked to poor global cognitive function and a faster rate of cognitive decline. Minority ethnic populations, including African American and Hispanic populations, have been found to have a higher incidence and prevalence of dementia compared to their white counterparts (Spreng RN, 2021). Additionally, these minority populations often present with greater levels of cognitive impairment and experience a faster decline in cognition. Residential segregation results in limited access to resources and healthcare, limited educational opportunities, and decreased socio-economic mobility. This may increase the rate of development of AD (Majoka and Schimming, 2021).

Loneliness can include everything from the subjective perception of social isolation or the discrepancy between one's desired and perceived levels of social connection. The health burden of loneliness is pervasive and it is closely related to morbidity, hypertension, immune system dysfunction, and increased risk of suicide. Higher-order social intelligence is associated with the collection of brain regions, including the medial prefrontal and medial temporal lobes, the temporoparietal junction, and the posteromedial parietal cortex (Spreng RN, 2021). Collectively, these regions are thought to form the core of the "social brain." The effects of loneliness on the brain are more pronounced in males as compared to females. (Spreng RN, 2021).

Social isolation has been found to result in abnormalities in brain structures such as the prefrontal cortex (PFC), amygdala, and hippocampus (Xiong et al., 2023). These abnormalities present as reduced total grey and white matter volumes in the PFC and hippocampus. While the effects on amygdala volume are inconsistent, relative amygdala volume was found to be larger among socially isolated individuals, which may be a potential cause for emotional dysregulation (Xiong et al., 2023). EEG reports have shown a delay in cortical maturation among socially isolated infants and toddlers. Further, altered structural connections between brain regions were also observed, with reductions in global and local connectivity, particularly in the ventromedial PFC. White matter integrity in the uncinate fasciculus (that allows temporal based mnemonic associations and processing of novel information. It connects the limbic system of the temporal lobe to the orbitofrontal cortex) and other white matter tracts involved in limbic and frontostriatal circuitry(that connects the frontal lobe to the basal ganglia and regulates motor, cognitive and behavioural functions) among children under institutional care was also compromised (Xiong et al., 2023).

A study using amyloid-beta positron emission tomography (PET) imaging found a significant association between amyloid-beta burden and greater loneliness. In healthy adults, increased tau pathology in the entorhinal cortex (related to memory formation and consolidation of spatial memory. It is located in the medial temporal lobe) on PET imaging was significantly associated with greater loneliness. Loneliness, even 5 years before death, predicted significant up-and down-regulation of AD-associated genes in the dorsolateral prefrontal cortex, independent of cognitive decline and AD pathology (Drinkwater et al., 2022). The study also found that cognitive function remained higher for participants with larger social network sizes, even among those with more severe levels of global AD pathology. However, the results of the study cannot be considered definitive due to several reasons. AD pathological markers, such as amyloid-beta plaques and neurofibrillary tangles, may not always correlate well with the extent of cognitive decline or clinical dementia. Instead, synaptic loss and neuronal death are considered the strongest neurobiological correlates of cognitive

impairment and dementia severity in AD. Further, certain studies have found no correlation between social interaction and AD pathology. It is also unclear if social isolation causes AD or if AD leads to social isolation. The latter may be caused due to social withdrawal and emotional disengagement after the onset of the disease (Drinkwater et al., 2022).

Studies in AD mouse models, such as APP/PS1 and Tg2576 mice, have shown that social isolation can lead to increased plaque formation and worsened memory. Additionally, social isolation has been associated with induced spatial memory deficits, tau hyperphosphorylation, and reduced synaptic protein expression in rodents (Drinkwater et al., 2022). Furthermore, other pathological features of AD, including exacerbated hippocampal atrophy, synapse loss, and glial neuroinflammatory changes, have been observed in socially isolated mice compared to their non-socially isolated counterparts (Drinkwater et al., 2022).

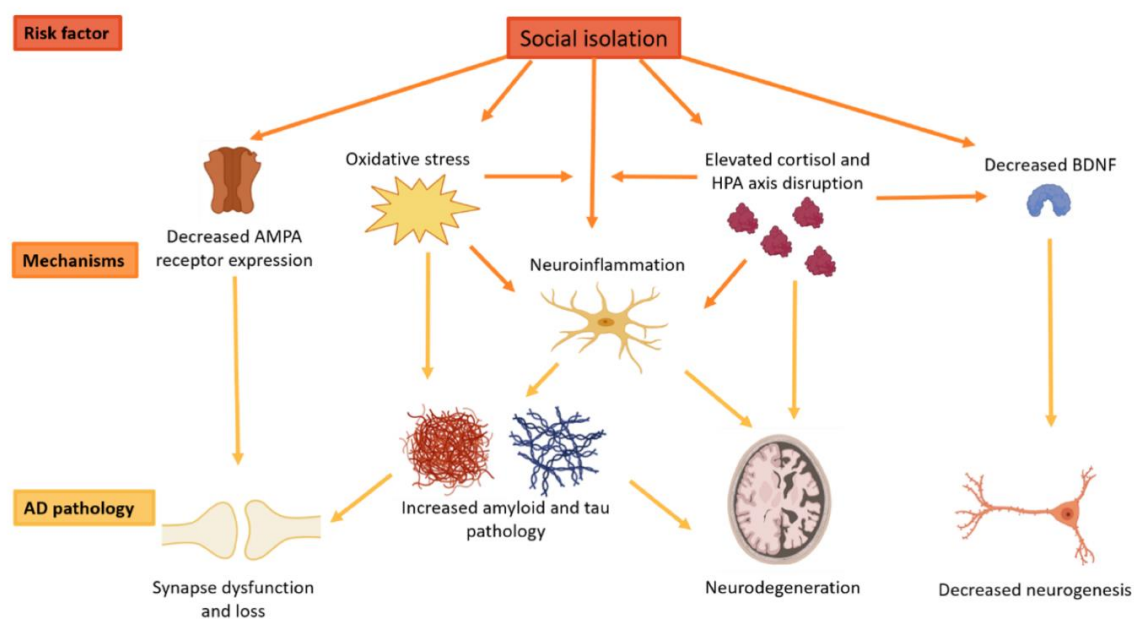


Figure 5: This figure shows the mechanisms through which social isolation contributes to AD pathology ((Mohaupt et al., 2022), Science Direct, ResearchGate). Social isolation causes oxidative stress, decreased brain derived neurotrophic factor (BDNF), neuroinflammation, elevated cortisol levels, disruption of the hypothalamic- pituitary-adrenal axis and decreased AMPA receptor expression. These in turn contribute to AD pathology such as neurodegeneration, decreased neurogenesis, increased amyloid and tau pathology as well as synapse dysfunction and loss. Therefore, social isolation contributes to AD pathology.

Social isolation during the COVID pandemic

The COVID-19 pandemic has had a significant impact on the health, social, and economic aspects of the world. The advent of COVID-19 exacerbated the effect of social isolation on the human brain and increased the rate of onset of dementia. COVID-19 pandemic lockdowns resulted in significant behavioural and psychiatric symptoms of relevance in patients with COVID and Alzheimer's disease. It was reported that delirium was found in patients who were asymptomatic for COVID-19. Caregivers of patients reported worsening neuropsychiatric symptoms and reported the development of agitation, apathy, depression, irritability, and aberrant motor behaviour symptoms in AD patients. (Manca et al., 2020). Patients affected with Alzheimer's or other forms of dementia showed an increased susceptibility to severe COVID infection.

This is because the APOE $\epsilon 4\epsilon 4$ allele is associated with dementia and increases the risk of severe COVID-19 infection, especially when the patient has other comorbidities like diabetes, hypertension, obesity, and cardiovascular disease (Gan et al., 2021, p. 19). The COVID-19 pandemic worsened the condition of Alzheimer's patients as they were socially isolated from their families and caregivers. They were not able to comprehend the sudden changes in their routine due to the lockdown, affecting their quality of care and accelerating the progression of AD (Gan et al., 2021, p. 19). The cognitive and psychiatric abilities of patients deteriorated during the pandemic. Studies have revealed the neuroinvasive potential of SARS-CoV-2 which led to neurological conditions such as lethargy, headache, or even cognitive impairment. The central nervous system (CNS) complications have been observed in more than 30% of individuals with COVID-19, particularly in cases of higher infection severity. The presence of viral RNA and proteins in the brains of deceased COVID-19 patients seen in postmortem confirm the ability of SARS-CoV-2, the virus responsible for COVID-19, to invade the CNS. The virus was also detected in the CSF of infected individuals. This invasion of the central nervous system by the virus would lead to neuroinflammation, disruption of the BBB, and alterations in neurovascular and cognitive functions. These in turn increase the progression of AD (Chen et al., 2022).

The pandemic was an onerous time for not only AD patients who faced challenges in the hospital, health care settings, care homes, their community at large but also for students. Students were subjected to social isolation and were left with no option but to attend online classes. This in turn affected their academic performance. To investigate the impact of COVID-19 related social isolation on loneliness and academic performance a survey was conducted among 83 high school student most whom were early adolescents during the pandemic. Participants were asked about the learning abilities and academic performance during the pandemic as compared to before/after it. It also included questions on whether social isolation during a short span affected learning abilities. The survey used the University of California Los Angeles (UCLA) loneliness scale to measure the loneliness of the participants to identify any direct impacts of loneliness on perceived academic performance. This loneliness scale comprises 20 questions and is designed to measure one's subjective feelings of loneliness as well as feelings of social isolation. Participants rated each item as either O ("I often feel this way"), S ("I sometimes feel this way"), R ("I rarely feel this way"), N ("I never feel this way"). O was given a numerical value of 4, S was given a numeric value of 3, R was given a numeric value 2 and N was given a value of 1. The total loneliness index was calculated by summing up the numeric value of all 20 questions. The total value ranges from 20-80 with 20-34 indicating a low degree of loneliness, 35-49 indicating a moderate degree of loneliness, 50-64 indicating a moderately high degree of loneliness and 65-80 indicating a high degree of loneliness.

As seen in figure 6, the survey showed that the performance of adolescents in Math appeared to be better before and after the pandemic as compared to during the pandemic. It is also interesting to note that the highest number of students showing no difference in learning rates before/after the pandemic also belonged were the ones who showed low loneliness levels.

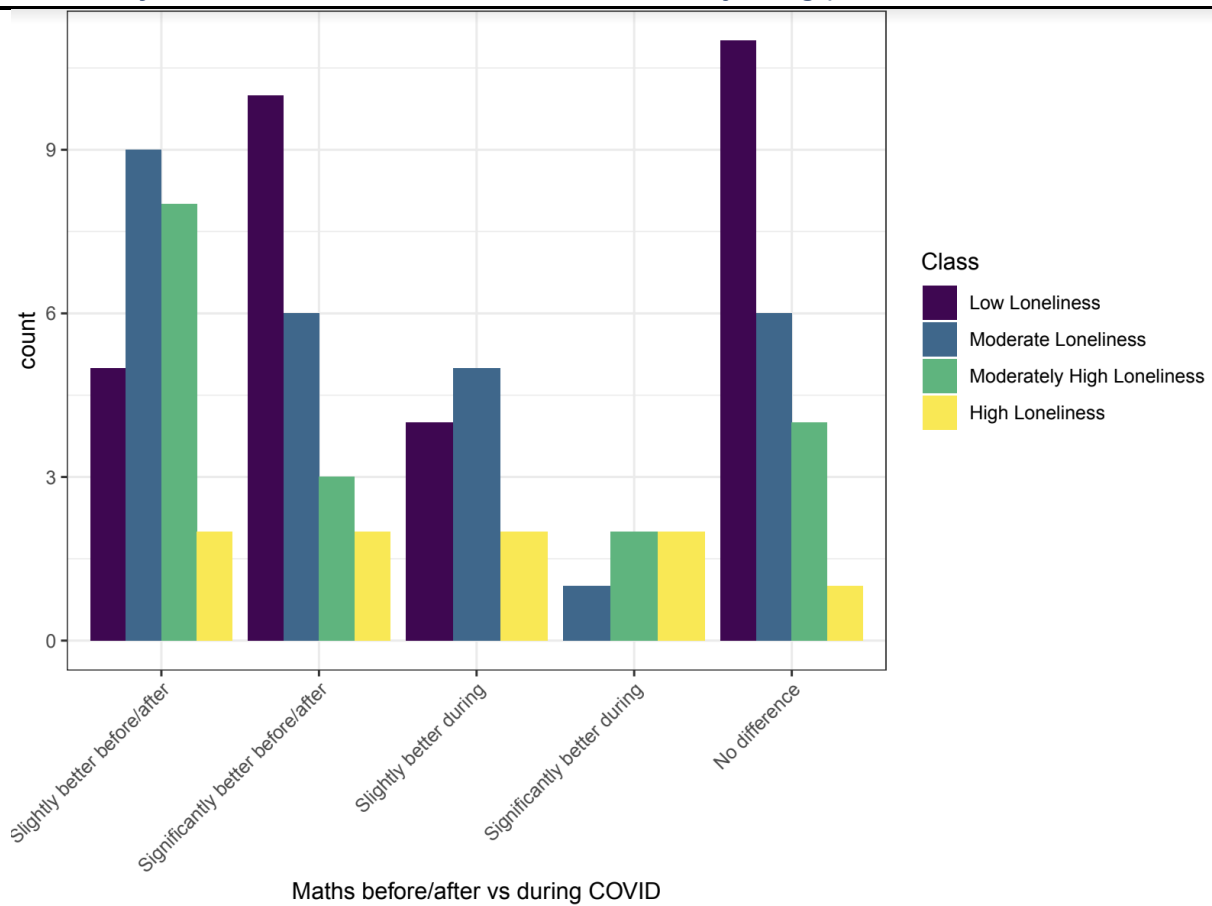


Figure 6: Relationship between loneliness levels and academic performance in Maths before/after vs during COVID.

As seen in figure 7, the maximum number of students showing no difference in forgetfulness before/after vs during COVID belonged to the group showing low levels of loneliness.

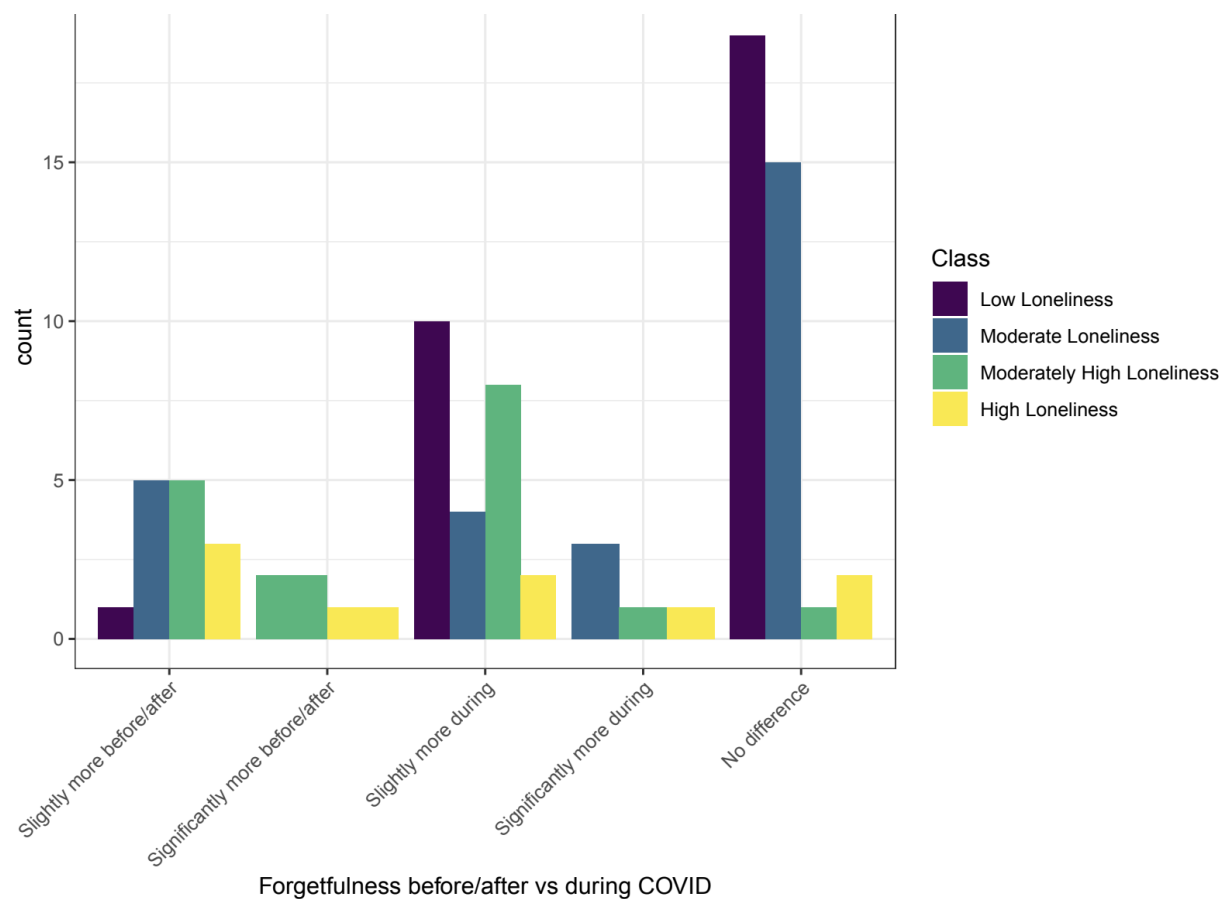


Figure 7: Relationship between loneliness and forgetfulness before/after vs during COVID

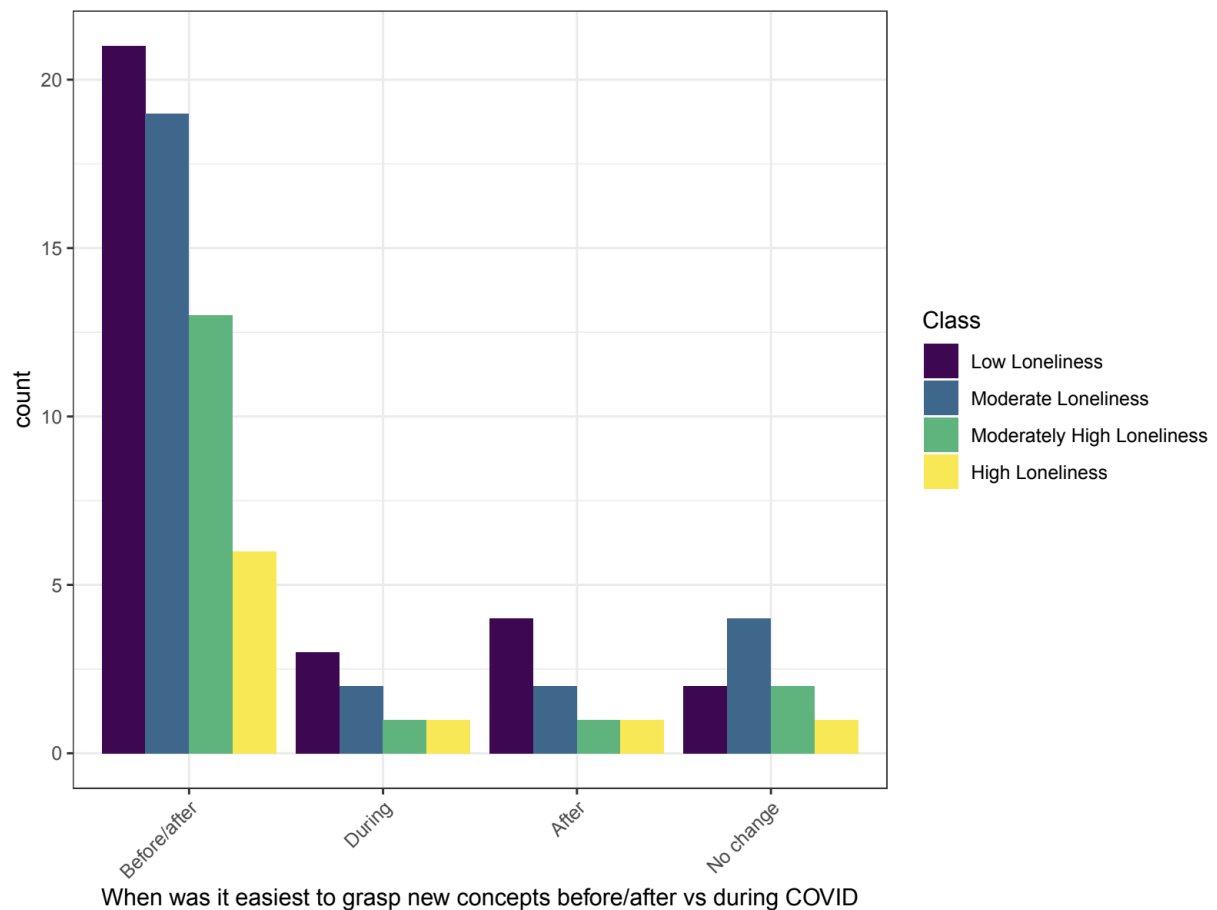


Figure 8: Relationship between loneliness and ability to grasp new concepts before/after vs during COVID

As seen in figure 8, students with moderate loneliness found it the easiest to grasp new concepts before/after vs during the pandemic. They were followed by students showing low loneliness.

As seen in figure 9, students with low loneliness showed no change in studying abilities after 48 hours of isolation whereas students with moderate loneliness were the largest group to exhibit improved studying abilities after 48 hours of isolation.

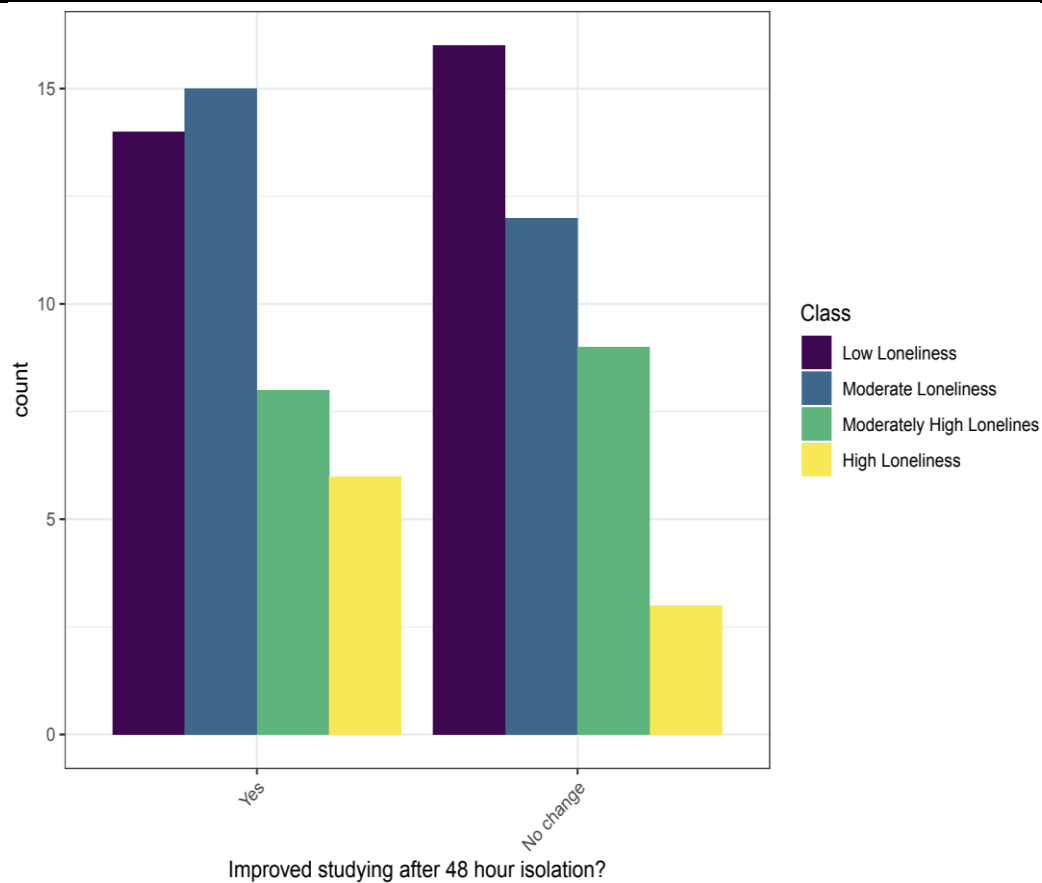


Figure 9: Relationship between loneliness and the ability to study after 48 hours of isolation

As seen in figure 10, the students with the lowest loneliness levels found it the easiest to learn new things while the students with the highest loneliness levels found it most difficult to learn new things.

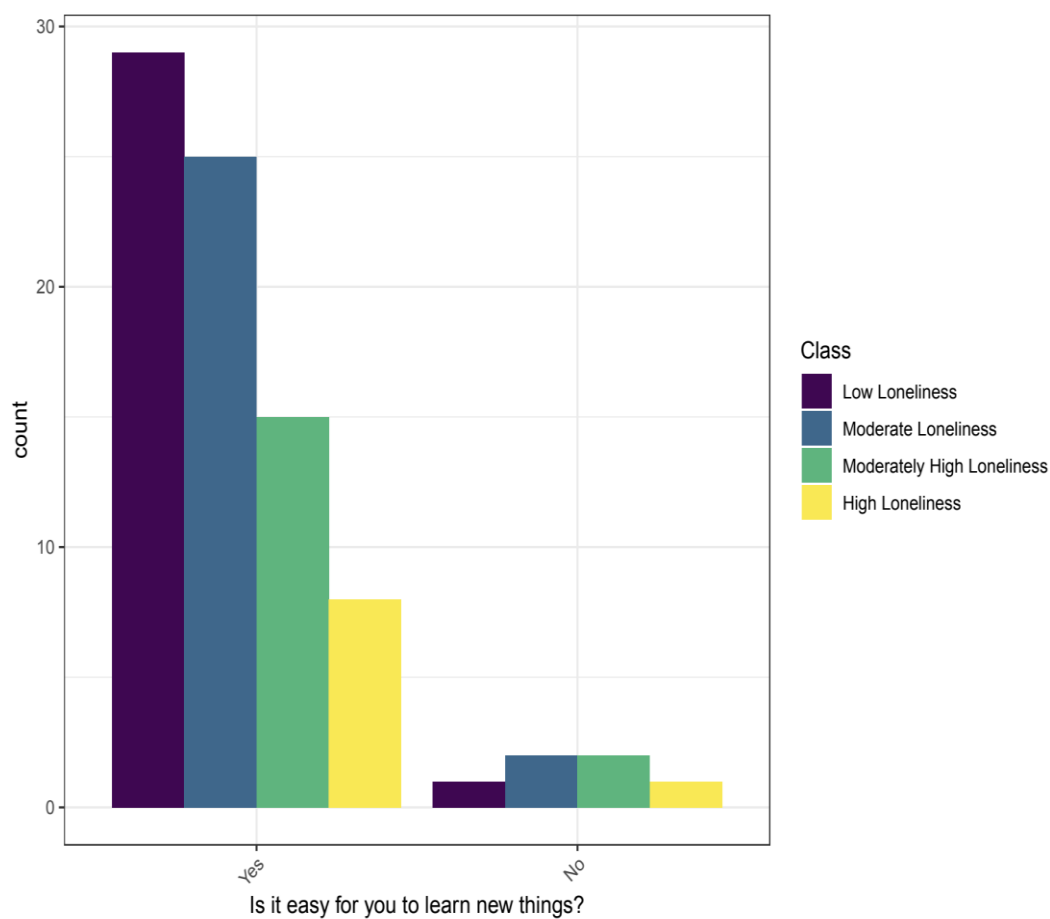


Figure 10: Relationship between loneliness and ability to learn new things

How was your academic performance in Maths before/after covid as compared to during the pandemic?(Please answer this question keeping in m...question aims to assess your cognitive abilities)

83 responses

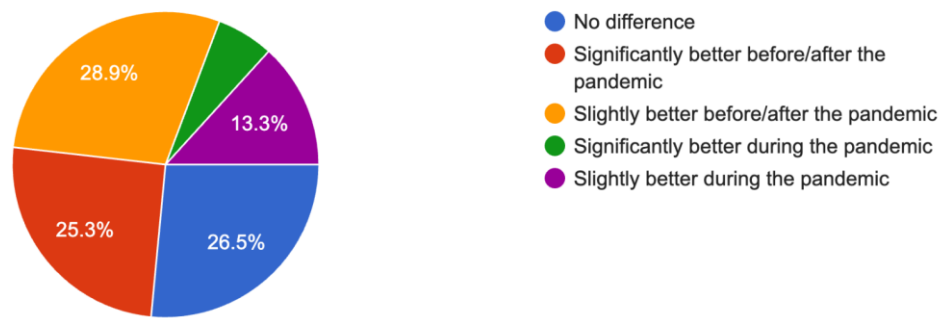


Figure 11: Responses of students on their academic performance in Math before/after vs during COVID

Were you able to grasp the same concept better during the lockdown or before/after the lockdown?

83 responses

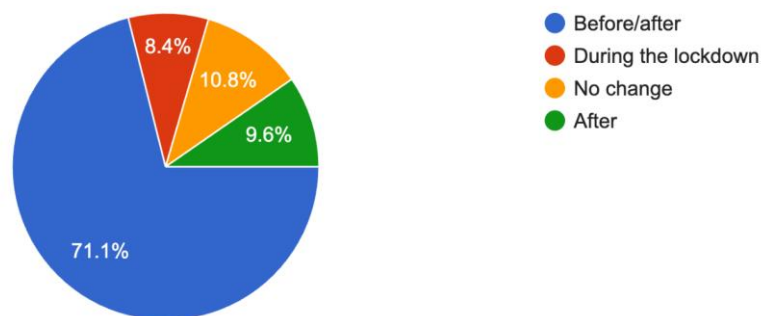


Figure 12: Responses of students on their ability to grasp a concept before/after vs during the pandemic

The survey also revealed that the performance of 28.9% of the participants in Mathematics was better before/after the pandemic as compared to during the pandemic (as seen in figure 11). Further, 71.1% of the participants found it easier to grasp the same concept before/after the lockdown (as seen in figure 12) thus suggesting that the social isolation during the pandemic, the high levels of stress and anxiety, and the inability to concentrate on an online medium adversely affected their academic performance.

Do you think your ability to learn increases when you are around people?

83 responses

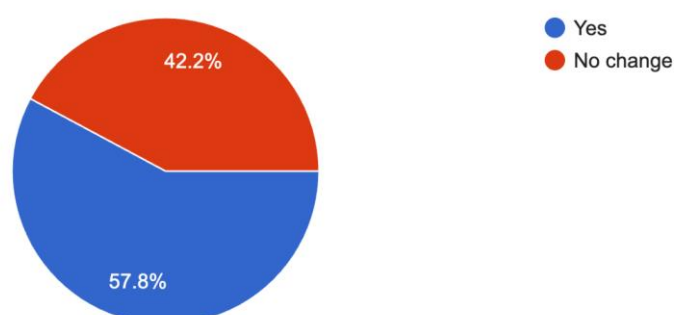


Figure 13: Responses of students on their ability to learn around people

As seen in figure 13, 57.8% of the participants said that their ability to learn increases when they are around people. This suggests that the presence of social company boosted the learning abilities among the study participants.

Conclusion

The exact cause of Alzheimer's disease is not certain even though several theories exist on its pathology and hallmarks are known. Genetic factors and traumatic brain injury hasten the advancement of AD. People from lower socio-economic backgrounds are more susceptible to the disease due to lack of access to education, cognitive training, easy access to treatment, and higher stress levels. People from lower SES are also more susceptible to comorbidities which negatively impact the prognosis of AD. AD progression can also be increased by polluted environments or the presence of toxins. Aerobic exercise helps alleviate the negative effects of AD. Social isolation or perceived social isolation and loneliness can accelerate neurodegeneration and contribute to the development of AD. Loneliness during the COVID-19 pandemic adversely affected Alzheimer's patients as well as caregivers. The sudden change in routine, the loneliness, the lack of appropriate care due to the isolation of caregivers, and the inability to meet families enhanced the adverse effects of AD. Adolescent students found it easier to learn the same things in a proper classroom setup with their peers rather than when they were secluded and locked down during the pandemic. It cannot be certainly said that the COVID pandemic affected more Alzheimer patients from lower SES as compared to higher SES. In fact, no such definitive conclusion can be made. However, eating the correct food (fruits, vegetables, fat free diet), managing comorbidities, regular exercise, regular check ups, enough sleep, preventing and correcting hearing loss, activities to increase cognition and higher levels of education and social interaction can help protect individuals from Alzheimers. Studies in the field of Alzheimer's are rapidly progressing and they are being assisted by better imaging tools and the advent of Artificial Intelligence. We can hope that this rising pandemic is curbed at the earliest and that this enigmatic mystery is soon unravelled.

Limitations

The survey conducted was limited only to the students of a particular age group of a high school. Since Alzheimer's has many confounding factors, it can not be certainly said that a certain factor is a definite cause of the condition. These factors do not follow a regular trend in all patients across the globe. The condition has its own distinct mark on each patient. It cannot be certainly said that the COVID pandemic affected more Alzheimer's patients from lower SES as compared to higher SES.

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