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What role do environmental factors play in the development of neurodegenerative diseases? A narrative review.

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Abstract
Introduction and purposes: Degenerative diseases of the nervous system, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS). Environmental influences are significant contributors to the development of these conditions. The primary objective of this research was to examine key environmental factors that are suspected of their impact on the development of diseases, specifically lifestyle, medical conditions, diet and exposure to environmental pollution.

Materials and Methods: A systematic literature search was conducted using PubMed and Google Scholar. The search employed terms such as 'Alzheimer's disease,' 'Parkinson disease,' 'amyotrophic lateral sclerosis,' 'environment,' 'pollution,' 'diet,' 'traumatic brain injury,' 'alcohol,' 'obesity,' 'lifestyle factors'. The search included articles published from 2014 to 2024.

Results: Among environmental factors with regard to lifestyle choices, a healthy diet has a protective effect against these diseases, while alcohol consumption was not clearly categorised as harmful or protective. Among past illnesses, an increase in AD, PD after head injury was confirmed, but more research is required as to the impact on ALS incidence. Lipid metabolism disorders affect ALS morbidity, for the AD and PD, studies do not reach consensus. Similarly, with regard to body weight, studies do not clearly indicate whether it is relevant. On the contrary, when it comes to pollution, a lot of studies showed a correlation.

Conclusion: In summary, research studies varied in size and quality, so caution must be exercised in drawing conclusions. This review suggests that there is a relationship with the environment, and future research may focus on exploring these connections.

Keywords: 'Alzheimer's disease,' 'Parkinson disease,' amyotrophic lateral sclerosis,' 'neurodegenerative disease,' 'environment,' epidemiology,' 'pollution,' 'diet,' 'traumatic brain injury,' 'alcohol,' 'obesity,' 'heavy metals,' 'lifestyle factors'

Introduction and purpose

Neurodegenerative diseases which include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) involve many problems in their course, often contributing to death. Worldwide, neurological disorders are being more widely acknowledged as the second leading cause of death after cardiovascular diseases. [1] In 2016, approximately 280 million individuals globally were affected by neurological disorders, resulting in 9 million fatalities. They are also the primary cause of disability-adjusted life-years (DALYs). [2] The total number of deaths and DALYs attributed to all neurological disorders combined rose from 1990 to 2019, indicating a growing burden of neurological disorders. [1] In the year 2019, approximately 50 million individuals globally were affected by neurodegenerative disorders, frequently leading to dementia. It is projected that this figure will escalate to 152 million by the year 2060. [3] Such serious consequences as dementia make them a significant problem not only for patients and their families, but also for national healthcare systems. [4]

Neurodegenerative diseases like AD,PD, and ALS often arise without any known family history. [5] The majority of cases of discussed conditions are multifactorial in which interactions among external environmental and inner genetic risk factors work cumulatively over a lifespan to establish the 'allostatic load' of a patient. Over 60 environmental risk factors were pinpointed in AD and organised into various categories including air quality, heavy metals, trace elements, occupational exposure, and miscellaneous. [6] Although there is less data on risk factors in other conditions, environmental links certainly exist. Understanding the mechanisms through which a wide variety of seemingly different risk factors promote the onset of these disorders remains a constant challenge. [7]

The purpose of this review is to outline the impact of lifelong environmental exposures, including lifestyle factors, on the risk and the subsequent course of AD, PD and ALS. Since there is no complete treatment for many neurodegenerative diseases, identifying factors potentially involved in the genesis of pathology offers promising opportunities for primary prevention.

Methods

A comprehensive review of the literature was performed by searching through databases such as PubMed and Google Scholar. Search included specific terms to ensure a thorough examination of the available research: 'Alzheimer's disease,' 'Parkinson disease,' amyotrophic lateral sclerosis,' 'neurodegenerative disease,' 'environment,' epidemiology,' 'pollution,' 'diet,' 'traumatic brain injury,' 'alcohol,' 'obesity,' 'heavy metals,' 'lifestyle factors'. The search included articles published from 2014 to 2024, as well as frequently cited publications from over a decade ago. The criteria for inclusion were papers, case series, meta-analysis and reports that focused on epidemiology and research related to AD, PD, and ALS, specifically examining the influence of individual modifiable factors on disease development. Only publications in the English language were considered for inclusion.

Traumatic brain injuries and AD

As the average age of the population continues to rise, it is expected that the prevalence of AD and its related socioeconomic impact will also increase. AD is prevalent among the elderly and stands as the primary culprit behind dementia, responsible for the majority of cases, estimated to be between 60-70%. [8] Although ageing and genetic factors are significant contributors to the development of AD, recent research highlighted the importance of lifestyle choices, physical health, medical conditions, and diet as potential influencers of the disease. These environmental risk factors have the potential to either hasten or slow down the onset and progression of AD.

Numerous studies showed correlation of Traumatic brain injury (TBI) and AD. TBI is classified by the International Classification of Diseases (ICD) as mild, known as concussion, or severe, which includes skull fractures, brain swelling, damage, or bleeding. Injury commonly occurs as a result of accidents involving cars, motorcycles, and bicycles, as well as from military service, boxing, horseback riding, and various recreational activities. [9] In a large-scale study conducted in Denmark by Fann et al., researchers examined the health records of almost 3 million individuals aged 50 years and above.

The study spanned over a period of 10 years on average. The findings revealed a heightened risk of developing dementia (hazard ratio (HR)1.2, 95% confidence interval (CI) 1.2-1.3) and AD (HR 1.2, CI 1.1-1.2) in this population. Notably, the risk of dementia was most pronounced in the six months following a TBI, with a substantially higher risk (HR 4.1, CI 3.8-4.3). Moreover, the risk of dementia was found to increase with the number of TBIs experienced by an individual, with those having multiple TBIs showing the highest risk (≥5 TBIs HR 2.8, CI 2.1-3.8). [10] In a study conducted by Nordström et al. on 21,963 individuals in the Swedish population aged 50 years or older, it was discovered that TBI significantly increased the risk of developing dementia within one year. The risk was found to be 3.5 times higher with (CI 3.2-3.8). Furthermore, the risk of dementia remained elevated over a period of 30 years, although it was slightly reduced to 1.3 (CI 1.1-1.4). The study also revealed that a single mild TBI, as defined by the ICD, posed a lower risk of dementia compared to severe TBI. Additionally, the risk of dementia increased with the number of TBIs experienced, with a higher risk associated with more severe TBIs. The odds ratios (ORs) were 1.6 (CI 1.6-1.7) for a single TBI, 2.1 (CI 2.0-2.2) for more severe TBI, and 2.8 (CI 2.5-3.2) for multiple TBIs. [11] Tolppanen et al. conducted a study focusing on early-onset AD within a specific population and also found TBI to be a significant risk factor for developing dementia. The risk increased with both the number and severity of TBIs experienced. Notably, a higher risk of dementia was observed closer to the time of the TBI, particularly in individuals with early-onset AD. [12]

Blood pressure and AD

Numerous research studies on the effectiveness of blood pressure medications in reducing high blood pressure showed a potential link to lower rates of dementia. The findings indicated a decrease in the risk of developing any form of dementia, including clinically diagnosed AD, among individuals who receive the interventions. A meta-analysis was conducted by Tully et al. on 15 trials and observational studies involving 52,599 individuals who were taking diuretics. The participants had a median age of 76 years and were followed up for a median of 6.1 years. The results showed a reduced risk of dementia (HR 0.8, 95% CI 0.8–0.9) and AD (HR 0.8, 95% CI 0.7–0.9) in this population. [13] Ding et al. incorporated in meta-analysis data from six different observational studies, focusing on individual participants. After closely monitoring individuals with high blood pressure for an extended period, it was found that using any antihypertensive medication that effectively lowered blood pressure significantly decreased the likelihood of developing dementia.[14]

Vascular risk factors and AD

Research indicated that vascular risk factors do not necessarily increase the risk of AD pathology. [15,16,17] This suggests that while vascular risk factors do contribute to dementia, they may not do so through the AD pathway. A comprehensive analysis by Kivimäki et al. of 19 observational studies involving nearly 405,000 younger adults found that those who were physically inactive in the decade leading up to their diagnosis were more likely to develop all-cause dementia and AD. However, this increased risk was not seen in individuals with comorbid cardio-metabolic disease. The average age of participants at the start of the studies was 45.5 years, with an average follow-up period of 14.9 years.

Overall, the findings suggest that maintaining physical activity levels may play a role in reducing the risk of dementia later in life, particularly for those without underlying health conditions. [18]

Body Mass Index and AD

Numerous studies suggested a link between higher body mass index (BMI) in middle-aged individuals and an increased risk of developing AD, while overweight or obesity in older age may actually have a protective effect on cognitive function. [19,20] A study conducted by Tolppanen et al. showed that individuals with a higher BMI in late-life have a lower risk of developing AD, with a hazard ratio of 0.89 (HR 95% CI 0.81–0.98), compared to a 20% increased risk for those who experienced significant weight loss from midlife to late-life. [19] Additionally, studies by Sun Z et al. found that obese elderly individuals tend to have lower levels of amyloid beta (Aβ) plaques and larger hippocampal volumes. [20] One possible explanation for these findings is the role of leptin, a hormone primarily produced by fat cells, which was proven to promote the growth of new brain cells in the hippocampus in animal models of AD. [21] It is important to consider age when assessing the relationship between obesity and AD. While young adults should strive to maintain or lose weight within a healthy range (18.5–24.9 kg/m2), older individuals should be cautious about losing too much weight, as this may have negative implications for cognitive health.

Diet and AD

Extensive research indicates a significant link between dietary habits and the development and progression of dementia and AD. [22] Commitment to nutritious eating habits, such as following the Mediterranean diet (MeDi), Dietary Approach to Stop Hypertension (DASH), and the Mediterranean-DASH diet Intervention for Neurodegenerative Delay (MIND), were linked to positive health outcomes. These dietary patterns, while sharing similarities, prioritise the consumption of plant-based foods and limit the intake of red meat. Research indicated that adherence to these diets may lead to a decreased risk of cognitive decline and lower chances of developing dementia and AD. [23,24,25,26,27,28] When it comes to nutrition, utilising a variety of nutritional strategies to improve insulin resistance, dyslipidemia, decrease abdominal obesity, lower oxidative stress and inflammation is more effective than relying on single nutrient supplements. This holistic approach is believed to be a better method for preventing and managing the risk of AD, as nutrients found in foods work together in a synergistic manner. [29, 30] A trial in Spain known as the PREDIMED study tested the impact of the MeDi compared to a low-fat diet on 522 individuals with a high risk of vascular issues. The participants, with an average age of 74.6 years during cognitive assessment, were split into two groups: one following the MeDi with either extra virgin olive oil (1 L/week) or mixed nuts (30 g/day), and the other following a low-fat control diet. After 6.5 years, the study found that participants on the MeDi showed improved cognitive function based on tests like the Mini Mental State Examination (MMSE) and the Clock-Drawing Test. [24] A study conducted by Wengreen et. al discovered that maintaining a high adherence to the DASH diet was linked to consistently better cognitive function levels over an 11-year period in 3,831 participants aged 65 and above. Cognitive function was evaluated using the Modified Mini-Mental State Examination (3MS) on four separate occasions. [26]

Tangney et al. conducted a study that focused on the health of 826 participants, with an average age of 81.5 years, revealed that those who followed the MeDi and DASH diets more closely experienced a decelerated rate of cognitive decline. The participants were monitored over a period of 4.1 years through a combination of food frequency questionnaires and cognitive tests. [25]

Alcohol and AD

Excessive alcohol consumption was long linked to alterations in the brain, decreased cognitive function, and an increased risk of developing dementia. [31] A comprehensive analysis conducted by Anstey et al. in 2019 examined a total of 91 articles that investigated 36 different risk factors associated with AD. [32] The researchers found that alcohol consumption, particularly light to moderate intake compared to abstaining, was associated with a decreased risk of Alzheimer's disease. The risk ratio ranged from 0.43 (HR 95% CI 0.17–0.69) [33] to 0.72 (HR 95% CI 0.61–0.86). [34] In the field of research on alcohol consumption and AD, many studies showed a pattern where moderate alcohol consumption is associated with a lower risk of developing AD. [35,36,37] However, there are limitations in the methodology of these studies, particularly in relation to the impact of alcohol consumption on cognitive function. Additionally, the potential health risks and societal costs associated with alcohol consumption must be taken into consideration.

It is not definitive that light or moderate alcohol consumption can protect against dementia or cognitive decline. The World Health Organization's (WHO) guidelines from 2022 do not advocate for the general use of alcohol as a protective measure against AD. [38]

Pollution of the environment and AD

Air Pollution

Air pollution refers to the alteration of the atmosphere by the introduction of various harmful substances, including chemicals, physical particles, and biological agents. This pollution was long ago linked to respiratory and cardiovascular illnesses, and recent research even found a connection between air pollution and AD. The National Ambient Air Quality Standards (NAAQS) in the United States have identified six key pollutants that pose a threat to human health: ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulphur dioxide (SO2), and lead (Pb).

Studies conducted on animals and cellular models demonstrated that exposure to high levels of air pollution can lead to damage in the olfactory mucosa, bulb, and frontal cortex - similar to the effects seen in AD. Individuals exposed to air pollutants showed increased oxidative stress, neuroinflammation, and neurodegeneration, as well as the presence of hyper-phosphorylated tau and Aβ plaques in the frontal cortex. Furthermore, air pollution was found to contribute to the formation, accumulation, and impaired function of Aβ42, a protein associated with AD. [39,40] A research conducted in Northern Sweden found that individuals living in areas with higher levels of air pollution from traffic had a 38% increased risk of developing AD. This risk was observed when comparing those exposed to the highest quartile of NOx levels (≥26 μg/m3) with those in the lowest quartile (≤9 μg/m3). The study highlights the potential impact of residential traffic-related air pollution on the development of AD. [41]

Exposure to heavy metals

Metals can be categorised into two groups: bio-metals, which play a vital role in the functioning of living organisms (such as copper, zinc, and iron), and toxicological metals, which do not serve any biological purpose (like aluminium (Al) and Pb). [42] Al is widely used in various industries including processed foods, cosmetics, and medical products. In the body, Al is bound to plasma transferrin and citrate molecules, which help transport it to the brain. Research showed that Al accumulates in specific brain areas like the cortex, hippocampus, and cerebellum, where it interacts with proteins and leads to misfolding and aggregation. [43] Pb, on the other hand, competes with essential bio-metals like calcium and can quickly penetrate the blood-brain barrier, impacting neural development and causing significant harm. Studies linked acute lead exposure to AD by increasing β-secretase expression and Aβ accumulation. Cadmium (Cd), a water-soluble metal known for its carcinogenic properties, can also cross the blood-brain barrier and contribute to neurological disorders like AD. Research findings indicated that Cd ions play a role in the formation of Aβ plaques and the aggregation of tau proteins in the brain of AD. The growing body of evidence suggested that metals may play a role in the development of AD. [44]

Traumatic brain injury and PD

PD is the second most prevalent neurological disorder affecting movement, following closely behind AD. The majority of PD cases, around ninety percent, are considered sporadic in nature. [45] The prevalence of PD is estimated to affect 1 to 2 individuals per 1000 in the general population at any given time. The likelihood of developing PD tends to rise with age, with approximately 1% of individuals aged 60 and above being affected by the disease. [46] It is projected that due to the ageing population, the number of individuals with PD will double again to reach 12.9 million by the year 2040.[47] Additionally, other factors such as exposure to pesticides, chemicals, air pollution, and decreased smoking rates may contribute to a further increase in the prevalence of PD. The incidence of PD is currently rising at a faster rate than the overall ageing of the population, particularly in newly industrialised regions across the globe. [48]

The precise causes and mechanisms underlying PD are still not fully understood, which poses a challenge for researchers in creating successful methods for prevention and treatment. Currently, there are no known ways to efficiently avoid or cure PD, but some medications may help in reducing the symptoms associated with the condition. There are various elements that play a role in the likelihood of developing PD and conditioning of its progress, such as genetic factors, gender, environmental influences, and personal habits. [49, 50,51,52] Better knowledge of them offers hope of reducing the incidence of this. Therefore, this review investigated some of the most frequently mentioned modifiable factors affecting morbidity and course of PD.

TBI is a significant non-genetic risk factor for the development of PD, according to epidemiological studies. [53] The relationship between TBI and PD has been a widely debated subject for an extended period. It is still unknown exactly how TBI influences the development of the condition, but Impellizzeri et al. found numerous links between TBI and the development of PD in mice.

They noted significant changes in the dopamine transporters in the substantia nigra, as well as a notable increase in neuroinflammatory factors like cyclooxygenase-2 and nitric oxide. [54] A recent in-depth analysis involving over 420,000 individuals revealed that individuals with a previous TBI have a significantly higher likelihood of developing PD. A meta-analysis was conducted by Mohammad Balabandian et al. and revealed that the OR of TBI among individuals with PD compared to controls, based on data from 23 studies using a random-effects model, was significantly higher. However, there was a high level of heterogeneity across the selected studies. Their subgroup analysis indicated that in individuals over 70 years of age, the OR for TBI among PD patients and controls was not significant. In contrast, for individuals under 70 years of age, the risk ratio for TBI was significant. Additionally, the OR for TBI among PD patients and controls in Europe and North America was found to be significant. The overall prevalence of TBI, based on data from 14 studies, was 18% with high heterogeneity. Furthermore, the prevalence of TBI among PD patients in studies with individuals under 70 years of age was 24%, whereas in studies with individuals over 70 years of age, it was 9%. Moreover, the analysis revealed that the history of TBI was more prevalent in PD patients from North America compared to those from Europe. [55]

Blood cholesterol and hypertension and PD

Research on hypercholesterolaemia leads to inconsistent conclusions. A study conducted by de Lau et al. in the Rotterdam cohort found that individuals with high blood cholesterol had a lower risk of developing PD. [56] The risk reduction was reported to be 0.77 per mmol/L increase in cholesterol levels. Similarly, the HAAS study showed a 0.6 risk ratio for individuals with 135 mg/dL of cholesterol compared to those with 85 mg/dL. [57] On the other hand, a significant increase in Pd risk was observed in a study cohorts included 24,773 Finnish men and 26,153 women, with a risk ratio of 1.9 for individuals with 7 mmol/L or higher cholesterol levels.[58] Contradictory findings were reported in the Nurses' Health Study and HPFS, where PD risk decreased with increasing self-reported blood cholesterol levels. However, there was no association between PD risk and a history of diagnosed hypercholesterolemia, hypertension, or high blood pressure. [59] These conflicting results suggest that there may be unknown factors influencing the relationship between blood cholesterol levels and PD risk.

Body-mass index and PD

Most long-term studies didn’t find a link between BMI and the risk of PD [60,61,62,63,64] It was confirmed by a meta-analysis carried out by Yun-Liang Wang et al. They noted that for every 5 kg/m² increase in BMI, there was no significant change OR 1.0 (HR 95% CI 0.9 -1.1) in the risk of PD. [65] However, in a study conducted by Hu et. al. in Finland, a particular group stood out as having a higher risk of developing PD. Individuals in this cohort who were classified as overweight (with a BMI of 27-29.9) or obese (with a BMI of 30 or higher) were found to have a significantly increased risk compared to those with a lower BMI of less than 23. The HR for developing PD was 2.0 for both the overweight and obese groups in comparison to the lower BMI group. [66] Research showed that individuals with high triceps skinfold thickness [62] or waist-to-hip ratio [67,66] may have a higher risk of developing PD.

This indicates that the distribution of body fat could be a more accurate predictor of PD risk than simply looking at overall body weight.

Diet and PD

In potential areas of action to reduce the risk of PD and slow the progression of the disease is to change diet. In a study conducted by Mischley et al. the dietary habits of 1053 individuals in the United States diagnosed with idiopathic PD were examined. The results showed a clear correlation between the severity of PD and the intake of certain foods. Specifically, individuals who consumed higher amounts of coconut oil, fish, fresh fruits, fresh vegetables, nuts, olive oil, spices, and wine tended to have less severe symptoms of PD. On the other hand, those who consumed beef, canned fruits, canned vegetables, cheese, yoghourt, ice cream, fried foods, and diet soda had more severe symptoms. [68]

While some research indicated that increasing vegetable intake can lower the risk of developing PD, other studies suggested that the type of dairy product consumed may also play a role in affecting the risk of PD. [69,70,71] The eating habits of 249 PD patients and 368 control subjects from various hospitals in Japan were investigated by Okubo et al. using factor analysis.They discovered three distinct dietary patterns linked to the risk of PD: a healthy diet, a western diet, and an easy-to-digest diet. The healthy diet consisted of higher intake of vegetables, seafood, and tea, along with low alcohol consumption. The western diet included high amounts of beef, pork, chicken, vegetable oil, and salt. The easy-to-digest diet was characterised by bread, pasta, dairy products, fruit, soft drinks, and sugar. The study indicated that following a healthy diet could potentially lower the risk of developing PD. [72]

The cohort study carried out by Liu et al. used the Dietary Screening Tool (DST) to investigate the link between diet quality and the risk of PD in a group of 3653 men and women aged over 65 in the United States. Over the course of nearly seven years, 47 participants were diagnosed with PD. The findings showed a clear correlation between higher diet quality and a lower risk of developing PD. This suggests that following a healthy diet can help reduce the likelihood of developing PD. However, further research is necessary to understand how diet quality, as assessed by the DST, affects PD risk in various populations and regions. [73]

Multiple studies demonstrated a reduced risk of developing PD in individuals who regularly consume coffee compared to those who do not. [74,75,76]

Alcohol and PD

There is conflicting evidence regarding the link between alcohol consumption and PD. While some studies implied that alcohol may have a protective effect against PD or not effect at all [77] , other experimental animal studies pointed out that chronic heavy alcohol consumption is likely to have a neurotoxic effect on dopamine levels [78] . Researchers showed that long-term exposure to alcohol can lead to a decrease in dopamine levels [79] and an increase in α-synuclein, a protein associated with the development of PD [80].

Evidence from epidemiological studies by Paul et al. showed that in comparison to individuals who consume alcohol moderately, those who abstain from liquor completely and those who drink heavily have a higher chance of developing Hoehn and Yahr stage 3 (mild to moderate bilateral involvement, some postural instability but physically independent).

The risk was significantly increased for non-drinkers (HR 3.48 95% CI 1.90–6.38) and moderately increased for heavy drinkers (HR 2.16 95% CI 1.03,-4.54). [81] A comprehensive analysis of various studies on the connection between alcohol consumption and PD, conducted by Zhang and colleagues, revealed interesting findings. The analysis, which included data from 32 studies involving a total of 677,550 participants, suggested that beer consumption may have a protective effect against PD (HR 0.59, 95% CI: 0.39–0.90), particularly in males (HR 0.65, 95% CI: 0.47–0.90), but not in females. Surprisingly, the same protective effect was not observed with wine or liquor. However, the researchers noted a lack of studies that delved into the dose-response relationship between different types of alcohol and their impact on PD. [77] There is an intricate connection between alcohol consumption and PD that requires more in-depth research to fully understand.

Pollution of the environment and PD

The aftermath of industrialization could potentially be playing a role in the increasing prevalence of PD. Many of the by-products produced during the Industrial Revolution, such as certain pesticides, solvents, and heavy metals, were associated with the development of PD. [82] Nations that have experienced swift industrial growth witnessed a significant rise in the occurrence of PD. A prime illustration of this phenomenon is evident in China, where the adjusted prevalence rates of PD surged dramatically between 1990 and 2016, surpassing the rates of any other country and even doubling in magnitude. [83] Research conducted by Wang et al. showed a possible link between pesticides and PD, with studies pointing to the ubiquitin-proteasome system (UPS) as playing a role in the development of the disease. Exposure to pesticides was found to hinder the UPS, increasing the likelihood of developing PD. To investigate the impact of pesticides on proteasome activity, experiments were conducted using SK-N-MC neuroblastoma cells that were engineered to overexpress a green fluorescent protein (GFP) tagged proteasome degradation signal, GFPu. [84]

Furthermore, there is a forecasted annual growth of 2% in the worldwide usage of the solvent, with a more significant increase of 4% per year specifically in China. Despite numerous publications highlighting the harmful effects of trichloroethylene dating back to as early as 1932, including a letter that was published in the Journal of the American Medical Association. [85]

ALS and TBI

ALS is a devastating degenerative condition that affects motor neurons in the brain, brainstem, and spinal cord, ultimately leading to paralysis and death. [86] Disease has a significant prevalence, with approximately a 1 in 350 chance of developing the disease in one's lifetime. [87] Although the occurrence of ALS remains consistent among European populations, there is a projected 69% global increase in ALS cases by the year 2040. This increase is primarily driven by a 34% rise in the United States due to the ageing population. [88] In the majority of cases where there is no family history of ALS, it is estimated that genetic factors contribute between 20-60% to the development of the disease. Even in cases where a genetic mutation is present, other factors are needed to trigger the disease, as not all carriers of the mutation will develop ALS. [89]

In particular, external factors in the environment, combined with inherited predispositions and alterations in cells as a result of getting older. [90]

TBI is a valid environmental factor that increases the risk of developing neurodegenerative diseases associated with ageing. [4] ALS was not definitively proven to be associated with TBI, whereas there is strong evidence linking TBI to PD and AD. Several studies showed a higher likelihood of developing ALS in former professional athletes who participated in contact sports like football, soccer, and rugby. [91,92,93] Although individuals with TBIs are more prevalent in certain populations compared to the general public, previous studies failed to consider the participants' prior history of TBI. However, a study conducted by Kurtzke et al. in 1980 on World War II veterans revealed that those who later died of ALS were more likely to have experienced a TBI 15 or more years before their death compared to the control group. [94] Additional research demonstrated a higher likelihood of developing ALS in individuals who experienced a brain injury within one, in a study carried out by Turner et al. [95] or ten, in a study conducted by Chen et al. [96] years before the onset of the disease. However, no significant correlation was found between TBI and ALS when considering all time frames. The complexity lies in determining the cause-and-effect relationship due to the fact that ALS is linked to motor symptoms that increase the risk of falls. Interestingly, a study conducted by Chen et al. found no connection between other physical injuries resulting from falls (such as injuries to the trunk, arms, or legs) and ALS, indicating that the association is specific to TBI.[96] In general, a comprehensive analysis, conducted by Armon et al. of research from 1980 to 2011 revealed limited evidence to suggest a connection between a lone TBI and ALS. [97] Furthermore, a separate investigation by Fournier et al. revealed that a prior TBI does not exacerbate the advancement of illness or abnormality in individuals diagnosed with ALS. [98]

Therefore, the connection is frequently brought up but still lacks clarity. TBI has the potential to trigger ALS. This degenerative condition specifically targets the loss of motor neurons. Studies on animals conducted by Wright et al. showed that TBI leads to a gradual shrinking of the motor cortex and breakdown of the corticospinal tracts, leading to muscle wasting and impaired motor function similar to neurodegenerative conditions. [99] ALS commonly manifests with specific motor symptoms that start in one or multiple muscle groups and progress to nearby muscles. A study done by Rosenbohm et al. involving 18 cases of sporadic ALS after frontotemporal cortical lesions revealed that the location of the lesion often appeared on the opposite side of where symptoms first appeared. This indicates that TBI may play a role in triggering the disease alongside various genetic and non-genetic factors. [100]

Blood lipids and ALS

Several researchers recently conducted an extensive Mendelian randomization (MR) study to investigate the impact of blood lipids on the development of ALS. Among these researchers, Bandres-Ciga et al. carried out a thorough MR analysis to identify environmental factors that could potentially influence the risk of ALS. By analysing a large dataset consisting of 345 published and 290 unpublished genome-wide association studies (GWAS), they found that only three factors were significantly associated with ALS risk: low-density lipoprotein (LDL) cholesterol levels (OR 1.12, 95% CI 1.03–1.20), coronary heart disease (OR 1.06, 95% CI 1.0–1.13), and self-reported high cholesterol (OR 2.39, 95% CI 1.48–3.84). [101]

Another comprehensive study conducted by Zeng and Zhou explored the impact of high-density lipoprotein (HDL) cholesterol, triglycerides, LDL cholesterol, and total cholesterol on ALS. The study's strength lay in the validation of results across both European and East Asian populations. In the European population, after applying a rigorous Bonferroni correction for multiple tests, only LDL cholesterol was found to be significantly associated with ALS risk (OR 1.14, 95% CI = 1.05–1.24). The relationship between LDL cholesterol and the risk of ALS was found to be significant in the East Asian population. [102] Finally in a study conducted by van Rheenen et al., a larger GWAS involving 29,612 ALS patients and 122,656 controls revealed a significant positive correlation between total cholesterol levels and the risk of developing ALS. The findings suggest that higher total cholesterol levels may increase the likelihood of developing ALS. [103]
In general, there is convincing MR evidence supporting a connection between higher levels of LDL cholesterol and total cholesterol and a genetic predisposition to ALS. However, there is no such evidence for triglycerides or HDL cholesterol.

BMI and ALS

The significance of BMI in relation to ALS remains a topic of debate, with its potential role as a protective factor still largely unexplored. Various studies showed a positive correlation between BMI and survival time in ALS patients. [104,105,106,107,108] For instance, research by Nakken et al. found that individuals with high BMI levels at a young age had a lower risk of developing ALS several decades later. [109] Similarly, a study led by Goutman et al. indicated that a higher premorbid BMI was linked to a slower progression of ALS and improved survival rates, suggesting BMI could serve as an indicator of disease severity. [110] Conversely, in study by Park et al a decrease in BMI was associated with increased disease severity. [111] The favourable survival outcomes observed by Wills et al. in ALS patients with higher BMI levels raise the possibility that nutritional interventions leading to weight gain could potentially enhance prognosis in these patients. [112] It is noteworthy that obesity rates are significantly higher in Sweden compared to China and South Korea [**113**] , with a higher incidence of ALS onset in Sweden. Additionally, there is a greater prevalence of ALS in males despite the fact that obesity rates are higher in males as compared to females. [105] Further research is warranted to better understand the relationship between obesity and the onset as well as the progression of ALS.

Diet and ALS

Research on the impact of diet on ALS as a potential preventive or modifying factor is limited. A recent extensive study, stemming from the findings of a large-scale American project called ALS COSMOS, was the first of its kind to thoroughly examine the relationship between diet and patient function. The study analysed data from 302 individuals with ALS, revealing that a diet high in fibre, antioxidants, and carotenes from fruits and vegetables (considered "good" foods) was linked to better function as measured by the ALS Functional Rating Scale Revised (ALSFRS-R) and Forced Vital Capacity scores. [114] Previous research also suggested that consuming a healthy diet may help lower the risk of developing ALS, with individuals who consumed high amounts of fibre [115], vegetables, and citrus fruits [116,117] showing a decreased risk of the disease.

Studies by Nelson et al. and Huisman et al. suggested a potential link between a diet high in glutamate and fat and an increased risk of developing ALS. [115,118] However, other research conducted by Fitzgerald et al. and Veldink et al. actually found that a high-fat diet may decrease the likelihood of developing ALS by up to 34% and could possibly delay the onset of the disease. This protective effect is believed to be due to the high-fat diet's ability to counteract the hypermetabolic phenotype associated with ALS. [119,120] Both human epidemiological studies and animal models of ALS by Fergani et al. showed that a high-fat diet can have a positive impact on the progression of the disease. In mice with a SOD1 mutation, a high-fat diet led to a decrease in levels of triglyceride-rich lipoproteins after meals, a condition known as postprandial lipemia. This reduction in lipoproteins was associated with neuroprotection and improved health outcomes. Overall, these findings suggest that a high-fat diet could potentially be beneficial for individuals at risk of developing ALS or those already diagnosed with the disease. Further research is needed to fully understand the mechanisms behind the protective effects of a high-fat diet in ALS. [121] Studies conducted by Verburgh et al. and Pupillo et al. found a link between higher consumption of protein from meat and the development of age-related diseases in the elderly population. [122,117] In addition, the WHO recommends a healthy diet that includes limiting intake of free sugars and trans-fats, which includes natural trans-fats found in meat and dairy products from ruminant animals.

Interestingly, previous research by Felmus et al. and Pierce-Ruhland et al. showed that individuals with ALS consumed more milk compared to control subjects. [123,124] This aligns with findings from Nieves et al., which demonstrated a negative association between consumption of "unhealthy" foods, with milk being a major component, and ALSFRS-R score. [114] Furthermore, consumption of dairy products was also linked to an increased risk of other age-related diseases, is studies by Grant et al. and Hughes et al. [125,126]

Alcohol and ALS

Consuming alcohol is a frequently changeable habit, and understanding its potential link to ALS can provide insight into the disease's root causes. This knowledge is crucial for creating successful prevention and treatment approaches. However, research findings on the relationship between alcohol intake and ALS were inconclusive.

Research conducted by D’Ovidio et al. indicated that consuming alcohol does not appear to impact the likelihood of developing ALS. [127] With a relatively low incidence rate of 1-2 cases per 100,000 individuals annually, the available cohort and case-control studies were sparse, making it challenging to reach a definitive conclusion. [128] However, the study conducted by van Rheenen et al. did not find any association between the consumption of alcoholic drinks per week and the risk of developing ALS. Their analysis, which included both the Inverse Variance Weighting (IVW) method and robust measures, did not show any significant results. It is crucial to acknowledge that van Rheenen et al. conducted a study on the consumption of 'alcoholic drinks per week' without specifying the exact units or grams of ethanol consumed, resulting in a less accurate measurement of actual ethanol intake. [104]

The same findings were made in the 2019 Euro-Motor research by D'Ovidio et al., which delved into the connection between alcohol consumption and the likelihood of developing ALS, found that both overall alcohol consumption and specifically red wine consumption did not show a significant link to the risk of ALS. In fact, the study concluded that alcohol intake did not appear to increase the risk of developing ALS. [127] Meng et al. conducted a study that suggested that consuming alcohol may have a protective effect against developing ALS. This comprehensive analysis of data from various epidemiological studies, including a cohort study and seven case-control studies. The findings of their meta-analysis indicated that the risk of developing ALS was lower among individuals who consumed alcohol (OR 0.57, 95% CI 0.51–0.64). However, the relationship between the amount of alcohol consumed and the risk of ALS was not clearly established due to limited studies on this topic. [129] De Jong et al. conducted a study on 494 patients with incident ALS and 1,599 controls to explore the relationship between smoking, alcohol consumption, and ALS. They found that individuals who used to drink alcohol (OR 0.67, 95% CI 0.40–1.13) and those who currently drink alcohol (OR 0.52, 95% CI 0.40–0.75) were less likely to develop ALS, suggesting that alcohol consumption may have a protective effect against the risk of developing ALS. [130]
On the other hand, Yu et al. in study demonstrated a starkly contrasting correlation. Yu et al. investigated the correlation between daily alcohol consumption in grams and the likelihood of developing ALS. Utilising tools from extensive genome-wide association studies, researchers conducted a thorough MR analysis and discovered a causal link between alcohol consumption and an increased risk of ALS. Specifically, they found that for every approximately 10g/day increase in alcohol intake, there was a 1.5-fold higher risk of developing ALS (95% CI 1.4–3.4). These results indicate that ongoing alcohol consumption could play a significant role as a risk factor in the development of ALS. [131]

Pollution of the environment and ALS

Heavy Metals

Exposure to metals was long thought to play a role in the development of sporadic amyotrophic lateral sclerosis (sALS) in a complex and individualised manner. [132,133,134] Certain occupational exposures linked by Peters et al. to a higher risk of ALS, such as precision-tool manufacturing workers (OR 1.68, 95% CI 1.11-2.52) and glass, pottery, and tile workers (OR 1.76; 95% CI: 1.03-3.00). [134] Research studies showed a clear link between exposure to metals and the onset of ALS. A study conducted in Scotland by Chancellor et al. found that occupational exposure to Pb was significantly more common in ALS patients compared to control subjects (OR 5.7). [136] In a study conducted by Currier et al. involving 31 ALS cases, it was discovered that 24 of those individuals had a history of metal exposure before experiencing initial symptoms of ALS. [137] Additionally, research studies by Chio et al. and Johnson et al. also reported connections between metal exposure and ALS. [138,139] Notably, in 2017, a team of German medical experts claimed to have achieved complete remission in an ALS patient by treating them for mercury (Hg) intoxication. [140] Recent studies also (Andrew A. S. et al., 2021; Andrew et al., 2022; Mitsumoto et al., 2022; Wang et al., 2023) confirmed Pb as a risk factor for condition. [141,142,143,144] Duan et al. conducted a thorough review of relevant literature.

A total of 230 eligible studies were included in the analysis, with 67 studies focusing on 22 non-genetic factors and 163 studies focusing on genetic factors. The team investigated four main aspects of non-genetic factors, which included lifestyle choices, environmental and occupational exposures, pre-existing diseases/comorbidities, medical exposures, and other miscellaneous factors. The findings revealed that exposure to heavy metals (OR 1.79) was identified as one of the eight significant risk factors. [145]

Pesticides

The widespread utilisation of pesticides across the globe is primarily attributed to their significant advantages in enhancing agricultural productivity and controlling vector-borne diseases to safeguard public health. However, continuous and extensive application of pesticides in agricultural regions was identified as a major contributor to environmental contamination. Consequently, living in close proximity to farmlands treated with pesticides may potentially jeopardise human health. [146] Several research studies identified pesticides as a potential risk factor for ALS. [147,148,143] A meta-analysis conducted by Qiaochu et al. found that exposure to pesticides was associated with an increased risk of ALS (OR 1.96, 95% CI 1.7-2.26). Individuals who were exposed to pesticides had a 1.96 times higher risk of developing ALS compared to those who were not exposed. [149] The examination of the previously mentioned studies by Duan et al. validated that being exposed to pesticides increases the risk factor by 1.46 times, making it one of the eight major factors contributing to the risk. [145]

Conclusion

In light of the increasing burden on healthcare systems globally and the lack of effective treatments, it is crucial to develop credible hypotheses that can explain the development of neurodegenerative diseases and offer new avenues for treatment. Understanding the role of environmental factors in these conditions is essential, as it is a modifiable risk factor, even for individuals with a strong family history or known genetic predisposition. The gene-time-environment hypotheses propose that a combination of genetic susceptibility, age-related cell damage, and environmental stresses contribute to the onset of neurodegenerative diseases. Various factors are believed to play a role in the pathogenesis of these diseases, suggesting that lifestyle modifications, disease prevention, and limiting exposure to harmful substances like pesticides and heavy metals could help curb the rising trend of these illnesses.

However, studying the impact of environmental exposures on disease development is challenging due to the long-term accumulation of exposures and the difficulty in pinpointing specific causative factors. Research in this area is time-consuming, costly, and has a low success rate. Identifying genetic factors and understanding metabolic pathways may help pinpoint potential environmental triggers for further investigation.

Large-scale population-based studies that involve collaboration between national registries and standardised data collection methods are essential to improve the quality of research, the level of evidence obtained, and the reliability of conclusions drawn.

Disclosure
Conceptualization, JL, and KC; methodology, JL; software, KK; check, MK, KK and MK; formal analysis, MK; investigation, JL; resources, KK; data curation, MK; writing - rough preparation, JL, MK; writing - review and editing, KC, MK, KK; visualization, MK, KC, MK, KK, JL; supervision, KC; project administration, KC; receiving funding, MK
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