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REVIEW OPEN ACCESS

Risk Factors of Amyotrophic Lateral Sclerosis (ALS): An Updated Systematic Review

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease impacting the voluntary motor nervous system. While the origin of ALS remains unclear, existing literature suggests multifactorial pathogenesis. Most cases appear sporadically, implicating the existence of environmental factors, while others suggest an underlying genetic mechanism. This study aims to summarize risk factors associated with the onset and progression of ALS.

Methods: Three reviewers searched Medline database for English-language articles published between January 1, 2017 and November 6, 2021. Keywords included, but were not limited to, ALS, motor neuron disease, biomarkers, expos*, risk factors, and others. Included studies directly examined the effect of risk factors on ALS patients. Results were summarized descriptively following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Results: Overall, 310 unique articles were identified, of which 66 articles spanning 18 countries met the inclusion criteria. Thirty-five articles discussed environmental factors and reported 3 personal characteristics, 13 lifestyle factors, and 22 clinical factors being associated with ALS. Nineteen different genes were also discovered to be associated with ALS, while 13 genes were found to have no association.

Discussion: Among environmental factors, lower socioeconomic status occupations were found to have a higher occurrence of ALS. Traumatic brain injuries are another clinical risk factor commonly associated with ALS. There are inconsistent associations between alcohol intake and ALS, and the link between ALS and viruses needs to be further explored due to a potential causal relationship. Some of the genes identified in this review are definitive ALS genes, but others are novel or have little supporting evidence, necessitating further research.

Conclusion: With over 90% of ALS cases appearing sporadically, a great amount of research has gone into identifying the risk factors of the fatal illness. This study provides an updated systematic review that encompasses findings from 66 of the most current articles surrounding environmental and genetic risk factors of ALS. This paper provides researchers with a comprehensive summary of these risk factors to provide a springboard for future studies.

Keywords: amyotrophic lateral sclerosis; environmental; genetic; etiology; onset; progression; lifestyle; clinical; risk factors

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative condition impacting the voluntary motor nervous system, originating either sporadically with no obvious cause or familial, where multiple family members are affected. ALS may result in increasing disability, rapid disease progression, and often death in three to five years after symptoms begin [1]. The majority of affected individuals often die as a result of respiratory complications, while few ALS patients (10%) may survive longer than ten years [1].

Presently, the specific pathophysiology and associated cellular mechanisms are unknown. However, there are several theroies that have been proposed to explain the cellular underpinnings of ALS ranging from the dying forward hypothesis which implicates cortricomotoneuronal hyperexcitability and the dying backward hypothesis implicating lower motor neuron dysfunction. An intermediate to the aforementioned theories has been proposed whereby the random and independent degeneration of lower and upper motor neuron occurs [2].

Risk factors associated with the onset and progression of ALS remain primarily unknown, though previous research has been conducted to investigate potential causes. Environmental factors, genetic factors, or a combination or interaction between them have often been cited as risk factors behind the onset and progression of ALS. Environmental risk factors involve lifestyle factors primarily occupational related exposures to volatile compounds, combustion particles, heavy metals, silicia and lead that increase a patient's risk of developing ALS. Some previous review also cite alcohol consumption, smoking, and cardiovascular disease as

predictors of ALS [3]. On the other hand, genetic risk factors are also commonly correlated with ALS as they involve changes to the genome of the patient that increase their risk of developing ALS. Interactive factors describe more nebulous factors that likely result as a combination of environmental and genetic factors.

Most studies do not provide a holistic review of the risk factors associated with ALS, often focusing on either environmental or genetic risk factors. The most recent systematic review summarizing this research was written in 2016 [3], leaving five years for new knowledge to have surfaced. This review paper seeks to update the last review [3] following a similar literature search and systematic review process to provide a comprehensive understanding of the diverse variety of risk factors associated with the onset and progression of ALS.

Methods

Search Strategy

This study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting (PRISMA) guidelines (Figure 1). A literature search was conducted by three reviewers using the Medline database for English-language articles published between January 1, 2017, and November 6, 2021. To identify studies using different terms for the disease, the terms amyotrophic lateral sclerosis, motor neuron disease, muscular atrophy, primary lateral sclerosis, spinal muscular atrophy, and Lou Gehrig's disease were used. To identify studies focusing on onset and progression of the disease, the terms biomarkers, expos*, etiology, risk factors, risk, genetic association studies, onset, progress*, prognos*, incidence, prevalence, survival, and survival rate were used. To identify studies analyzing environmental factors, the terms lifestyle, cholesterol, obesity, overweight, smoke, cigarette, tobacco products, alcohol, virus*, bacteri*, metals, workplace, sports, toxic, infection*, wounds and injuries, trauma, and oxidative stress were used. The asterisks used in these search terms indicate truncation. Finally, to identify studies analyzing genetic factors, the terms genetic factor, genetic polymorphism, and single nucleotide polymorphism were used. Relevant articles were exported into Rayyan.ai software for further evaluation and review. Articles were independently screened by each reviewer based on title and abstract for inclusion. Some articles were further excluded during data extraction of full texts. Conflicts were resolved by discussion between reviewers.

Study Selection

Studies were included that directly examined the effect of risk factors on human ALS patients. This includes studies measuring changes in either onset or progression, as well as studies measuring either genetic or environmental risk factors. Studies only discussing the pathology or specific treatment of risk factors were excluded. Case controls, cohort studies, cross-sectional studies, and observational studies were included. Case studies were also included, despite their sample size, to ensure all potential risk factors are included. Systematic reviews and meta-analyses were excluded as the focus of this paper was to review only primary articles. Studies using animal models or cell cultures were excluded as their findings cannot always be generalized to humans.

Data Extraction and Synthesis

Three reviewers independently extracted data on study design, the type of risk factor, description of the risk factor, if the risk factor was associated with onset, progression, or both, and the risk factor's effect. Studies were then categorized as environmental, genetic, or interactive. Environmental studies were further grouped by individual risk factors such as personal, clinical, and lifestyle characteristics. These groups were further subdivided into factors associated with onset and factors associated with progression. Results were summarized using descriptive analysis and data were presented as numbers and percentages.

Results

Study Characteristics

The systematic search yielded 310 unique articles, of which 66 papers met the inclusion criteria. The studies were conducted in a total of 18 countries spanning globally across North America, Europe, and Asia. Studies were most frequently from the United States (16.7%) [4–14] and China (15.1%) [15–24]. A majority of the studies were observational studies including case-control design (68.2%) [4,6,10,12–52], cross-sectional (12.1%) [9,11,53–58], cohort studies (6.0%) [59–62], and case studies (12.1%) [7,8,63–68], One study was experimental [5] and one was a Mendelian randomized study [69]

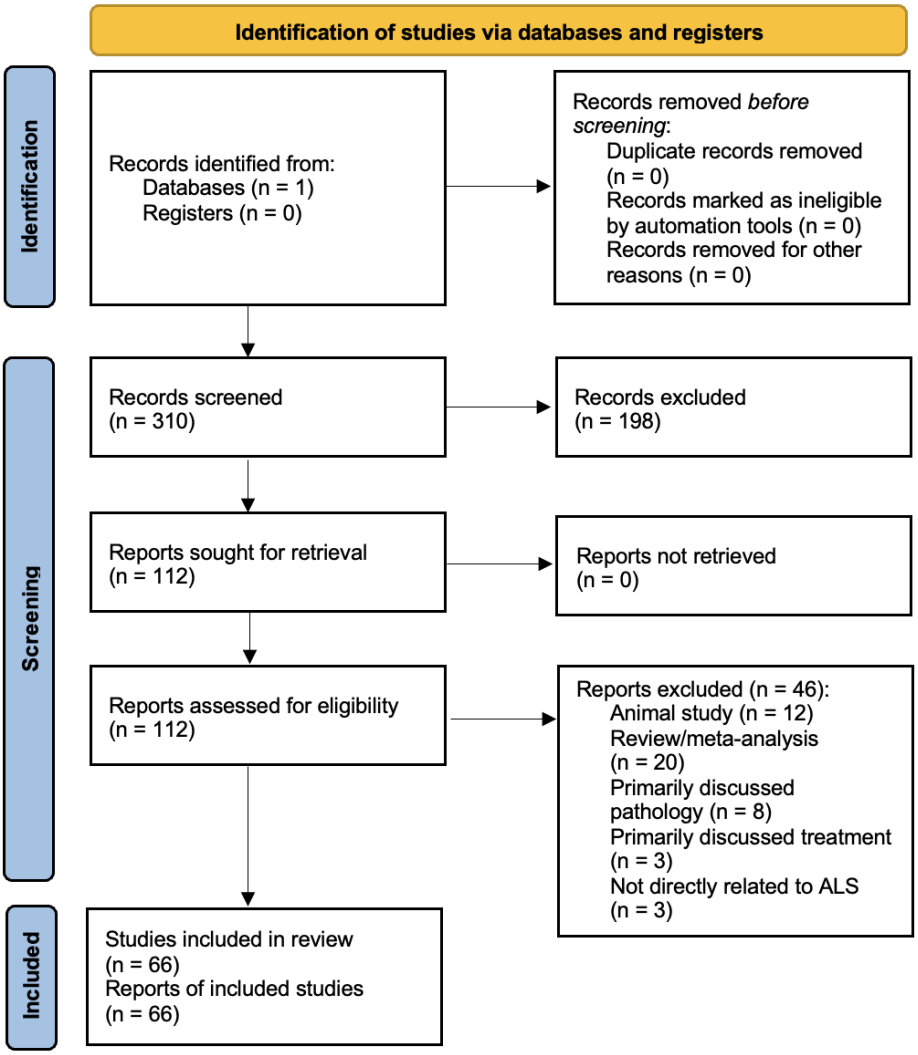

Figure 1. PRISMA flow diagram for the study selection of this systematic review. This figure was made using Google Drawings.

Environmental Risk Factors

Overall, 35 articles reported environmental factors which can be categorized into personal characteristics, lifestyle, and clinical factors [7–9,12-14,16,18,26–29,32–34,37–40,41,44,47,48,51,52,56,59,60,62,63,66,68,69]. Of the 35 articles, 2 (5.7%) [18,52] reported 3 different personal characteristics factors, 20 (57.1%) [8,9,13,14,18, 27,28,32,34,37–41,47,48,51,52,56,60,62] reported 21 lifestyle factors and 20 (57.1%) [7,12–14,18,25,26,29, 33,40,44,45,52,56,59,62,63,66,68,69] reported 26 clinical related factors.

Personal Factors

Of the 2 articles discussing personal characteristics, 2 (100%) mentioned family history of ALS or other neurological disorders [18,52], 1 (50%) [18] reported body mass index (BMI) and 1 (50%) [52] reported dominant handedness or footedness. Among these, only one out of two articles associate a family history of ALS or other neurological disorders as a risk factor for ALS [52]. These studies found that individuals with a low BMI or non-right dominant hand or foot are at a higher risk of ALS.

Lifestyle Factors

Of the 21 articles reporting lifestyle factors, 7 (33.3%) discussed occupation [9,14,18,32,38,48,51], 5 (23.8%) alcohol intake [18,41,47,52,56], 5 (23.8%) cigarette smoking [18,28,40,48,52], 3 (14.3%) physical activity [18,27,56], 2 (9.5%) competitive sports [52,60], 1 (4.8%) air pollution [37], 1 (4.8%) eating fish [52], 1 (4.8%) drinking wine [52], 1 (4.8%) amino acid and selenium containing supplements [52], 1 (4.8%) mercury exposure from seafood [39], 2 (9.5%) amalgam fillings [39,52], 1 (4.8%) use of private wells for drinking water and chemical exposures specifically [52], 1

(4.8%) silica exposure [38], 1 (4.8%) volatile compound exposure [8], 2 (9.5%) heavy/transition metal exposure [34,62], 1 (4.8%) low frequency magnetic field exposure [62], 1 (4.8%) lead exposure [13], 1 (4.3%) pesticide, herbicide, insecticide, and fungicide exposure [62].

Among these articles, lifestyle factors independently associated with increased risk of ALS were: type of occupation (7 out of 7 studies) [9,14,18,32,38,48,51], alcohol consumption (2 out of 5 studies) [18,47], cigarette smoking (3 out of 5 studies) [18,28,52], physical activity (1 out of 3 studies) [27], competitive sports (2 out of 2 studies) [52,60], air pollution (1 out of 1 study) [37], amino acid and selenium containing supplements (1 out of 1 study) [52], amalgam fillings (1 out of 1 study) [52], use of private wells for drinking water (1 out of 1 study) [52], silica exposure (1 out of 1 study) [38], heavy/transition metal exposure (2 out of 2 studies) [34,62], lead exposure (1 out of 1 study) [13], and low frequency magnetic field exposure (1 out of 1 study) [62].

Of the 7 articles reporting occupation-related exposures, 3 (3 out of 7 studies) [13,18,51] reported lower socioeconomic status occupations such as agriculture, farming, hunting, forestry, fishing, construction, mechanics, painting, while 1 (1 out of 7 studies) [9] reported higher socioeconomic occupations such as computer and mathematics, architecture and engineering, legal, education, training and library-related jobs. One (1 out of 7 studies) [38] article reported occupational exposure to combustion products and particulates, and 1 (1 out of 7 studies) [14] article reported occupational exposure to organic solvents with higher odds of ALS in men and women but occupational exposure to lead associated with higher odds of ALS only in women. 1 (1 out of 7 studies) [32] article also reported occupations related to general public exposure as being a risk factor.

Clinical Factors

Of the 20 articles reporting clinical factors, 5 (25.0%) reported traumatic brain injury [13,18,25,52,56], 3 (15.0%) electric injury/shock [13,52,62], 1 (5.0%) diabetes [14], 1 (5.0%) cardiovascular disease [14], 1 (5.0%) hypermetabolism [45], 1 (5.0%) obesity [14], 1 (5.0%) fracture [52], 1 (5.0%) surgery [52], 1 (5.0%) spinal anesthesia [52], 1 (5.0%) antibiotic usage [44], 1 (5.0%) influenza infection [63], 1 (5.0%) human immunodeficiency virus (HIV) [59], 1 (5.0%) reported Brucellosis infection [66], 1 (5.0%) exposure to Mycobacterium avium subspecies paratuberculosis [7], 1 (5.0%) study reported creatinine, uric acid, and albumin levels [16], 1 total proteins (5.0%) [16], 1 (5.0%) total cholesterol [16], 2 (10.0%) LDL levels [12,69], 2 (10.5%) HDL levels [12,16], 1 (5.0%) exogenous estrogens and progestogens [26], 1 (5.0%) blood trace metals [33], 1 (5.0%) polio vaccines [52], 1 (5.0%) human papillomavirus (HPV) vaccines [68], and 1 (5.0%) more broadly oxidative stress [29].

Among these articles, we found that traumatic brain injury (4 out of 5 studies) [13,18,25,52], electric injury/shock (2 out of 3 studies) [13,52], cardiovascular disease (1 out of 1 study) [14], hypermetabolism (1 out of 1 study) [45], fracture (1 out of 1 study) [52], antibiotic usage (1 out of 1 study) [44], blood trace metals (1 out of 1 study) [33] specifically significant differences in level of arsenic, LDL (low-density lipoprotein) levels (1 out of 2 studies) [69] HDL (high-density lipoprotein) levels (1 out of 2 studies) [12], Mycobacterium avium subspecies paratuberculosis exposure (1 out of 1 study) [8], and oxidative stress (1 out of 1 study) [29] are risk factors of ALS. Some case studies also found possible associations between ALS and HIV (1 out of 1 study) [59], influenza infection (1 out of 1 study) [63], brucellosis infection (1 out of 1 study) [66], and the HPV vaccine (1 out of 1 study) [68]. 1 (1 out of 5 studies) [56] article found head injuries to be an extrinsic factor for accelerated neurodegeneration in ALS. Creatinine, uric acid, and albumin (1 out of 1 study) [16], total protein (1 out of 1 study) [16], total cholesterol (1 out of 1 study) [16], HDL levels (1 out of 2 studies) [16] were also found to be correlated with ALS disease stages and progression. 1 article found exogenous estrogens and progestogens were found to be protective factors against ALS [26].

Genetic Risk Factors

Overall, 26 papers reported on genetic risk factors of ALS, discussing variants and mutations of genes. 19 of these papers found certain genes were associated with the risk of onset or the progression of ALS. Genes *DCTN1* (5.3%), *GNE* (5.3%), *HFE* (5.3%), *NEK1* (5.3%), and *TBK1* (10.5%) were associated with increased risk of onset of the disease, genes *ABCC8* (5.3%), *ABCC9* (5.3%), *C6orf10* (5.3%), *CX3CR1* (5.3%), *CYP1A2* (5.3%), and *SCFD1* (5.3%) were associated with faster progression of the disease, and genes *UNC13A* (5.3%), *C9orf72* (5.3%), *FUS* (5.3%), *HLA-DRA/HLA-DRB5* (5.3%), *PON1* (5.3%), *PXK* (5.3%), *SOD1* (5.3%), and *ZNF208* (5.3%) were associated with both risk of onset and faster progression of the disease [4,10,15,19,21,23,30,31,35,36,43,46,49,50,53–55,58,61,64,67]. 7 papers found that genes *CELF1* (14.3%), *CTSD* (14.3%), *FERMT2* (14.3%), *HNMT* (14.3%), *KIFAP3* (14.3%), *MTHFR* (14.3%), *NMD3* (14.3%), *PTK2B* (14.3%), *SIRT2* (14.3%), *SREBF1* (14.3%), *STK39* (14.3%), *TMEM106B* (14.3%), and *VMAT2* (14.3%) were not found to be associated with risk of onset or faster progression of ALS [11,17,20,22,24,42,57].

Interactive Risk Factors

Overall, five studies found interactive factors implicated in the onset and progression of ALS. One study reported altered gut microbiomes as a risk factor [5], having studied the 16s rRNA sequence in human patients and paralleling this to mouse models with the *SOD1* gene mutation. Another study proposed a causal relationship between elevated levels of LDL C and total cholesterol levels and linked this as a risk

factor for ALS [5]. Another study suggests oxidative stress as a risk factor [30], citing the polymorphism rs591486 in *ERCC6L2* as the main causal agent. A case study revealed that certain underlying genetic mutations, yet to be further investigated, remain dormant and may cause impairment in cognitive functions and parkinsonian symptoms in the later years of life after one leaves an ALS endemic area [65]. One study reported both environmental and genetic factors together, discussing how both intricately work together in the onset and progression of ALS [50]. ALS patients without the *C9orf72* mutation had a lower BMI with a slower increase over time compared to patients with the *C9orf72* mutation [50]. They also smoked more and consumed more alcohol, possibly indicting causal effects.

Discussion

Our paper identified 66 articles summarizing environmental, genetic, and interactive risk factors associated with the onset and progression of ALS. Lifestyle related environmental risk factors such as occupation were the most reported risk factors of ALS. Other clinical risk factors such as traumatic brain injury, electric injury/shock, among others, were independently associated with ALS. Genetic mutations and polymorphic variants were also associated with the risk of onset or ALS progression. Biological and environmental factors interplay with genetic factors, further complicating ALS onset. More robust studies are required to classify factors associated with ALS progression and onset.

Certain occupations are associated with higher risk of ALS. Of the different occupations discussed in our review, lower socioeconomic status occupations reported higher risk of ALS, which may be attributed to higher chance of exposure to chemicals, heavy metals or change of workplace injuries from manual labor. Although our findings did not show military service was a risk factor, the meta-analysis by Wang et al. (2017) discusses it extensively. Their findings show wars are associated with the onset of ALS, which can be attributed to the extensive organic phosphorus compounds present in explosives and other chemicals soldiers are exposed to, along with war associated trauma and injuries [3]. A 2020 review by McKay et al. further looked at the specific exposures during military service that might influence its association with ALS [70]. They found that exposure to pesticides like Agent Orange, exhaust, burning agents, and heavy metals along with head trauma increased the risk of ALS amongst military personnel and veterans [70]. Thus, there are often interactions between different environmental factors in different capacities, making it challenging to accurately associate a causal relationship of a risk factor to ALS.

Our study found inconsistent reporting of alcohol as a risk factor (2 out of 5 studies) which is in parallel to the findings from Wang et al.'s meta-analysis in 2017 [3]. Although their work showed no association between alcohol drinking and increased ALS risk, the authors mention the possibility of there being an inverse association based on other observational studies. A recent 2020 review by Peng et al. also found inconsistent findings between alcohol consumption and ALS [71]. Studies imply that either alcohol drinking has a protective effect, although this proposition is weakly supported, or that there is no association between alcohol consumption and ALS risk. This suggests that further research is required to understand the etiological involvement of alcohol intake, especially considering that alcohol consumption is one of the most common practices in the world [71].

We found traumatic brain injury to be commonly associated with the risk of ALS (80%) in our included studies. Likewise, a 2017 study by Wang et al. found a positive association between head trauma and ALS. However, in the same year, Watanabe and Watanabe conducted a meta-analytic evaluation focusing on the association between head injury and ALS [72]. Based on findings from 16 included studies, they confirmed a significant association between a history of head injuries and the occurrence of ALS. However, when considering the possibility of reverse causation, the association was marginally or not significant at all. The Watanabes believe the association between traumatic head injuries and ALS might have been overestimated [72]. More recently, a 2020 review by Gu et al. further confirmed that head trauma increases the risk of ALS, especially repeated trauma [73].

Our findings also reveal a possible association between ALS and viruses such as HIV [59] or influenza infection [63], but this relationship was only reported in one study each. In general, an etiological link between viruses and ALS has not been established, but connections have been proposed. A 2018 study by Castanedo-Vazquez et al. investigated links between infectious agents and ALS and found an association between retroviruses like HIV with ALS-like syndromes [74]. ALS-like syndromes differ only from classic ALS in that they are usually seen in younger patients, possibly with the presence of cerebrospinal fluid pleocytosis and no symptoms of inexorable progress [74]. Another 2018 study by Celeste and Miller found that although substantial efforts have been made to associate viruses with ALS, there is very little evidence suggesting a causal role [75]. Though, common viral infections have the potential to trigger stress pathways that are already dysfunctional as a result of prior genetic predisposition [75]. This possibility, according to Celeste and Miller, is often overlooked in studies aiming to find an association between ALS and viruses [75].

Countless genetic risk factors have been previously studied in the context of ALS, but new research continues to identify mutations and variants associated with the onset and progression of the disease. These factors can be transmitted as either genetic polymorphisms or through Mendelian inheritance patterns, though the majority of familial ALS cases are currently attributed to monogenic mutations in definitive ALS genes. *C9orf72*, *SOD1*, and *TARDBP* are three of the

genes most commonly identified in familial ALS cases, and both *C9orf72* and *SOD1* were again cited as risk factors for ALS in this review. However, the development of ALS is an exceedingly complex process, and novel genetic variants associated with ALS in genes such as *DCTN1*, *FUS*, and *TBK1* continue to be discovered, as we found in this review [19,36,67]. The ALSoD database tracks over 120 genes associated with the onset of ALS [76], ranging from definitive ALS genes to genes with little to no supporting evidence, yet our review identified three genes not yet listed in the database. Furthermore, our review found studies indicating an association between the onset of ALS and two genes for which ALSoD suggests there exists only tenuous evidence [19,54,76].

This study is not without limitations. Although an extensive review of various environmental, genetic, and interactive risk factors of ALS was explored, a clear difference between clinical factors and biomarkers was not established. As a result, factors like oxidative stress and LDL levels were categorized under clinical factors, they may be better defined as a separate group, especially due to their relationship with genetics and the pathogenesis of ALS. For example, oxidative stress is a biomarker produced by environmental exposures but could itself be a causal factor behind ALS. Furthermore, several studies used in this updated systematic review consisted of case studies, potentially rendering our conclusions from these studies as ungeneralizable to a wider population. There was no overlap between any genetic studies, as only one gene (*TBK1*) was identified as a potential risk factor in more than one paper in our review. Some of the environmental risk factors also had only one to two articles reporting the same associations, such as air pollution, low-frequency magnetic fields, viruses, or cardiovascular disease.

Future research should attempt to corroborate the tenuous findings of the articles included in this review, particularly novel risk factors identified in only one independent study. While many studies have examined environmental and genetic risk factors of ALS separately, further research into the interaction of both factors is required. Gaining a more holistic understanding of the risk factors implicated in the onset and progression of both familial and sporadic ALS will equip clinicians with the proper knowledge needed to improve the diagnosis and prognosis for ALS patients.

Conclusions

ALS is a neurodegenerative disease whose etiology remains poorly understood. More than 90% of cases appear to occur sporadically, prompting endless scientists to attempt to uncover risk factors for the fatal illness. Our study reviews the latest reports of potential ALS risk factors and attempts to provide an updated systematic review. We identified 66 articles that summarize environmental, genetic, and interactive risk factors that are associated with the onset and progression of ALS. Lifestyle-based factors such as occupation were the most reported risk factor of ALS, along with other clinical risk factors like traumatic brain injury or electric injury/shock that were also independently associated with ALS. We also found various mutations and polymorphic variations of genes as being associated with the risk of ALS onset. Our work provides researchers with a centralized coverage of potential environmental and genetic associations of ALS to better investigate the onset and progression of ALS in both familial and sporadic cases.

List of Abbreviations Used

ALS: amyotrophic lateral sclerosis
BMI: body mass index
HDL: high-density lipoprotein
HIV: human immunodeficiency virus
HPV: human papillomavirus
LDL: low-density lipoprotein
PRISMA: preferred reporting items for systematic reviews and meta-analyses

Conflicts of Interest

The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

As this paper is a review, no ethics approval was required.

Authors' Contributions

VB: made equal contributions to the entirety of the manuscript as well as the extraction of data and is to be held equally accountable for all aspects.
CK: made equal contributions to the entirety of the manuscript as well as the extraction of data and is to be held equally accountable for all aspects.
MB: made equal contributions to the entirety of the manuscript as well as the extraction of data and is to be held equally accountable for all aspects.

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