QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

ZIĘBA, Natalia, CZAPIŃSKI, Olgierd, BRODOWSKA, Anna, KNAPIK, Anna, BIAŁOWĄS, Patrycja, PYSIEWICZ, Mateusz, KUŚ, Justyna, CIESIELSKI, Maciej, TOMICKA, Ewa, STADNICKA , Olga and CZECH, Mateusz. Interaction of Environmental Factors and Physical Exercise in the Development of Amyotrophic Lateral Sclerosis and the Potential of Pharmacology and Targeted Therapies - a Narrative Review. Quality in Sport. 2026;56:72469. https://doi.org/10.12775/QS.2026.56.72469

ARTICLE TIMELINE
Received: 23.05.2026 Revised: 26.05.2026
Accepted: 26.05.2026 Published: 30.05.2026

INDEXING & EVALUATION
MEiN points: 20 Unique ID: 201398
Disciplines: Economics & Finance; Management & Quality Sciences

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Economics and Finance (Social Sciences); Management and Quality Sciences (Social Sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Interaction of environmental factors and physical exercise in the development of amyotrophic lateral sclerosis and the potential of pharmacology and targeted therapies - a Narrative Review

Natalia Zięba
ORCID: https://orcid.org/0009-0005-4554-9536
natalia.zieba03@gmail.com
Medical University of Lublin,
Lublin, Poland

Olgierd Czapiński
ORCID: https://orcid.org/0009-0007-7894-7201
olgierd.czapinski@gmail.com
Institute of Dentistry of the Central Clinical Hospital of the Medical University of Lodz,
ul. Pomorska 251, 92-213 Łódź, Poland

Anna Brodowska
ORCID: https://orcid.org/0009-0008-9227-2869
annabrodowska2001@gmail.com
Medical University of Lublin,
Al. Racławickie 1, 20-059 Lublin, Poland

Anna Knapik
ORCID: https://orcid.org/0000-0002-9556-7514
aknapik14@gmail.com
Medical University of Silesia in Katowice
St. Poniatowskiego 14, 40-055 Katowice

Patrycja Białowąs
ORCID: https://orcid.org/0000-0002-8913-3656
bialowaspatrycja@gmail.com
Andrzej Frycz Modrzewski University, Kraków, Poland

Mateusz Pysiewicz
ORCID: https://orcid.org/0009-0007-0094-2857
dreo@outlook.com
Norbert Barlicki Memorial Teaching Hospital No. 1
Stefana Kopcińskiego 22 St., 90-153 Łódź, Poland

Justyna Kuś
ORCID: https://orcid.org/0009-0006-5562-8702
k.justynna@gmail.com
Medical University of Lodz
Lodz, Poland

Maciej Ciesielski
ORCID: https://orcid.org/0009-0002-4191-3474
maciejciesielski58@gmail.com
Medical University of Lodz
Lodz, Poland

Ewa Tomicka
ORCID: https://orcid.org/0000-0001-6492-4729
ewa.tomicka@vp.pl
Non-public Health Care Facility “Lecznica MEDEA”
Warsaw, Poland

Olga Stadnicka
ORCID: https://orcid.org/0009-0008-9058-0868
olgastadnicka1999@gmail.com
Central Clinical Hospital in Łódź
ul.Pomorska 251, 92-213 Łódź

Mateusz Czech
ORCID: https://orcid.org/0009-0008-6980-6930
mateuszcz102@gmail.com
Medical University of Lublin,
Lublin, Poland

Corresponding Author: Natalia Zięba, natalia.zieba03@gmail.com

Abstract

Background: Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease leading to motor neuron degeneration and muscle atrophy. Its etiology remains unclear, although environmental and lifestyle factors may contribute to disease development.

Aim: This review analyzed the influence of environmental factors and physical activity on ALS risk, as well as current and emerging treatment strategies.

Material and methods: Articles published between 2017 and 2026 were reviewed using PubMed, GeneReviews, StatPearls, and Google Scholar databases. Original studies and review papers concerning ALS risk factors and therapies were included.

Results: Exposure to chlorinated pesticides, cadmium, lead, tobacco smoke, and cigarette smoking was associated with increased ALS risk. Studies on air pollution produced inconclusive findings. A higher ALS incidence was observed among NFL players, although the direct role of physical activity remains uncertain. Some large population studies suggested that regular physical activity may lower ALS risk. Despite available disease-modifying therapies, ALS remains incurable.

Conclusions: Exposure to pesticides and toxic metals may increase ALS risk and should be minimized. Evidence regarding physical activity and ALS is inconsistent and requires further research. Continued development of therapies targeting ALS pathogenesis is necessary.

Key words: ALS, ALS treatment, ALS risk factors, pesticides and ALS, Physical activity and ALS

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease of the nervous system that leads to the atrophy of skeletal muscles. It is characterized by degeneration of the anterior horn cells of the spinal cord, the motor nuclei of the cranial nerves in the medulla oblongata, as well as the neurons of the pyramidal tract. Unfortunately, the etiology of ALS remains unknown [1].

ALS is a polymorphic disease. Depending on the site of initial symptoms, limb-onset and bulbar-onset forms can be distinguished, as well as sporadic and familial forms according to the underlying causative factor. The first symptoms of the disease include muscle weakness of the upper and lower limbs, speech disturbances, swallowing difficulties, and respiratory impairment. In the final stage, the disease leads to complete paralysis of all voluntary muscles throughout the body [2].

Many factors that may influence the development of this disease have been identified [3]. In recent years, an increasing number of studies have investigated potential factors contributing to the development of ALS, although some of them remain a subject of ongoing debate.

ALS is an incurable disease. Current therapeutic options are limited and are mainly focused on symptomatic treatment; therefore, the search for new therapies is essential. In order for patient care to be effective, it should involve a multidisciplinary team of specialists, which may prolong survival and improve the patient's quality of life [4]. The dynamic development of research on new drugs provides considerable hope, particularly in the fields of gene therapy and molecularly targeted treatment, which may enable a more individualized approach to patient care.

The aim of this paper is to summarize current knowledge regarding physical activity and environmental exposure as potential risk factors for ALS, as well as to present current treatment options for amyotrophic lateral sclerosis and discuss the latest directions in research on disease-modifying therapies and gene therapies.

2. Materials and methods

2.1 Literature Search and Study Selection

This paper is a narrative review aimed at summarizing current knowledge regarding risk factors for ALS, particularly physical activity and environmental exposure, as well as pharmacology and innovative therapeutic approaches in ALS, with special emphasis on drugs that may prove effective in the treatment of this incurable and fatal disease.

The literature review was conducted using publications available in the PubMed, GeneReviews, StatPearls, and Google Scholar databases, mainly covering the years 2017-2026. The search strategy was based on keywords such as: ALS, ALS treatment, ALS risk factors, pesticides and ALS, Physical activity and ALS.

The analysis included epidemiological studies, meta-analyses, systematic reviews, and selected experimental studies. The selection of publications was selective and focused on articles relevant to the subject of this paper, with particular emphasis on the most recent scientific reports. Due to the narrative and cross-sectional nature of the study, no formal quality assessment or statistical analysis was performed.

2.2 AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Research results

3.1 Epidemiology of ALS

Amyotrophic lateral sclerosis is a rare disease occurring worldwide. According to epidemiological data, the incidence rate across all continents is low and ranges from 0.73 to 2.56 per 100,000 individuals. The highest incidence occurs in Oceania and North Africa, while the lowest incidence is observed in Asia [5]. The current lifetime risk of developing ALS is estimated to be 1 in 347 for men and 1 in 436 for women [6]. The mean age of symptom onset is variable and ranges from 58 to 60 years [7].

In the limb-onset form, the average survival time has been reported to range from 3 to 5 years, whereas in the bulbar-onset form it ranges from 2 to 3 years. Studies have also shown that sporadic ALS occurs far more frequently than familial ALS. Familial ALS accounts for

approximately 5–10% of cases, while sporadic ALS constitutes as many as 90–95% of all cases. The risk of developing sporadic ALS is approximately twice as high in men as in women, whereas the risk of familial ALS is similar in both sexes [1].

The initial symptoms of ALS and the patient's age are factors that may help predict the course of the disease. For example, early spinal cord involvement in young men is associated with a more slowly progressive and milder disease course [8]. Therefore, the progression of ALS is influenced by multiple factors, including the presence of genetic mutations such as C9orf72, SOD1, and FUS, as well as lifestyle and place of residence. Epidemiological data indicate that living in rural areas is associated with a higher risk of developing ALS compared with urban and suburban areas [9].

3.2 Clinical Presentation

The clinical presentation of ALS may vary considerably between patients. The classical form involves both upper and lower motor neuron degeneration. Initial manifestations of the classical type may present as limb-onset, bulbar-onset, or respiratory-onset ALS. Although ALS is primarily associated with motor neuron involvement, neurodegeneration may also occur in the frontal and temporal lobes [10].

Pseudobulbar syndrome is associated with the clinical presentation of ALS. This syndrome results from bilateral damage to the corticobulbar tracts of cranial nerves V, VII, IX, X, and XII. Such damage leads to dysphagia, dysarthria, exaggerated palatal and pharyngeal reflexes, absence of muscle atrophy, absence of fasciculations, an increased jaw jerk reflex, positive frontal release signs, and pathological emotional reactions. Emotional disturbances manifest as uncontrolled laughing or crying that is disproportionate to the patient's actual emotional state [10]. Damage may also occur at the level of the cranial nerve nuclei themselves (V, VII, IX, X, and XII), leading to bulbar syndrome, which is characterized by dysarthria, dysphagia, muscle atrophy, fasciculations, weakened palatal and pharyngeal reflexes, and a diminished jaw reflex [11].

Degeneration of the upper motor neuron in the limbs manifests with pathological reflexes such as the Babinski and Rossolimo signs. Patients may also present with hyperactive deep tendon reflexes, spasticity, and muscle weakness. In contrast, lower motor neuron involvement leads to muscle atrophy, decreased muscle tone, weakened tendon reflexes, absence of pathological reflexes, and fasciculations [12]. The disease may begin in either the cervical or lumbar spinal cord region, initially affecting one limb before progressively spreading to other parts of the

body. As the disease progresses, patients experience difficulty walking, inability to perform precise movements, and frequent falls. Furthermore, progressive muscle weakness eventually involves the diaphragm, leading to respiratory failure [13].

The course of the disease is generally continuous and steadily progressive [1]. Functional abilities in ALS patients are most commonly assessed using the ALS Functional Rating Scale-Revised (ALSFRS-R), which evaluates speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency.

ALS should mainly be differentiated from other motor neuron diseases, spinal cord disorders, neuromuscular junction diseases, myopathies, metabolic and toxic disorders, as well as paraneoplastic syndromes. The diagnosis of ALS is primarily based on clinical examination. The Gold Coast criteria are helpful in establishing the diagnosis. The first criterion is progressive motor impairment preceded by normal motor function, based on patient history or repeated neurological examination. The second criterion involves determining whether both upper and lower motor neurons are affected in at least one body region, or whether lower motor neuron dysfunction is present in at least two body regions. The third criterion requires exclusion of alternative diagnoses. Additional investigations useful in diagnosing ALS include blood tests, electromyography (EMG), nerve conduction studies, magnetic resonance imaging (MRI), and chest X-ray examination.

3.3 Pathophysiology of disease

ALS is a disease with a complex pathomechanism, and its etiology remains not fully understood. It is considered a multifactorial disorder in which several factors usually need to coexist for the disease to develop. Environmental exposure, lifestyle, occupation, and genetic predisposition all contribute to the development of ALS. Identifying new risk factors is important because ALS remains an incurable disease in which prevention plays a crucial role, and certain factors may influence prolonged survival in affected patients.

3.3.1 Localization of degeneration

The name “amyotrophic lateral sclerosis” reflects the pathological processes occurring in this disease. The term “sclerosis” refers to gliosis, i.e., the proliferation of glial cells at the site of injury, where the tissue becomes scarred and consequently harder. “Amyotrophic” refers to muscle atrophy, while “lateral” indicates the localization of lesions within the pyramidal tracts, i.e., the corticospinal tracts running in the lateral columns of the spinal cord.

Degeneration occurs in the Betz pyramidal cells of the motor cortex, as well as in the anterior horns of the spinal cord and the motor nuclei of the cranial nerves in the medulla oblongata. In these structures, abnormal protein aggregates are deposited, most commonly TDP-43 in sporadic cases of the disease, and occasionally in familial forms [1].

3.3.2 Genetic factors

Approximately 15% of all ALS cases represent genetically confirmed forms of the disease. Several types of inheritance can be distinguished. Monogenic inheritance with low penetrance refers to mutations that increase disease risk, although not every carrier will develop the disease. In contrast, monogenic inheritance with high penetrance means that nearly all individuals carrying the mutation will eventually develop the disease. Oligogenic and polygenic inheritance patterns, as well as risk genes, are also recognized.

More than 40 genetic mutations associated with an increased risk of ALS have been identified. The most common genes involved in ALS include C9orf72, SOD1, TARDBP, FUS, and TBK1 [14]. Mutations in the open reading frame 72 of chromosome 9 (C9orf72) lead to an expansion of GGGGCC hexanucleotide repeats. This mutation is characteristic not only of ALS but also of frontotemporal dementia. In these conditions, abnormal proteins accumulate, exerting neurotoxic effects [15]. The most commonly deposited protein is TDP-43 in neurons, which leads to abnormal mRNA processing [16].

The SOD1 gene (superoxide dismutase 1) was the first gene identified in association with ALS. More than 180 variants of this gene have been described, which may result in different phenotypes. Mutations in SOD1 may be inherited in either an autosomal dominant or recessive manner [17]. The TARDBP mutation also presents with various phenotypes, differing in symptom severity, while life expectancy is highly variable and remains an individual feature. Early symptoms often include speech and swallowing disturbances [18].

3.3.3 Oxidative stress, including endoplasmic reticulum stress, and mitochondrial dysfunction

Studies have shown that in ALS there are disturbances in mitochondrial respiration due to decreased activity of complex I and complex II [19]. Dysfunctional mitochondria contribute to the increased production of reactive oxygen species, which promote damage to cellular components, including genetic material and neuronal membrane lipids. Mitochondrial dysfunction also leads to a reduced production of ATP, which is essential for proper neuronal function.

3.3.4 Glutamate excitotoxicity

In a population with the SOD1 mutation, an experimental study demonstrated increased expression of the AEG-1 protein. This stimulates astrocytes to produce inflammatory factors and leads to impaired glutamate transport due to decreased expression of the EAAT2 protein, which is responsible for glutamate uptake. As a result, glutamate accumulates in the synaptic space, leading to excitotoxicity [20].

3.3.5 Inflammatory process

Neuroinflammation occurs in ALS and is associated with reduced activity of regulatory T cells and Th2 cells. As a result, the regulation of inflammatory processes is impaired, leading to a predominance of pro-inflammatory mechanisms. Astrocytes produce TGF-β1, while Th1 and Th2 cells produce IFN-γ, which acts on microglia and contributes to the release of pro-inflammatory factors such as TNF-α, IL-1β, NF-κB, and reactive oxygen species, all of which damage motor neurons [21].

3.3.6 Proteostasis impairment and disturbances in axonal transport, cytoskeletal structure, and function

Impairment of proteostasis is a key pathogenic mechanism in ALS. Proteins accumulate excessively within cells due to disturbances in the genetic material responsible for their synthesis, but also as a result of failure of the ubiquitin–proteasome system and autophagy processes. The lack of efficient protein degradation systems leads to neurodegeneration [22].

Neuronal transport is responsible for the movement of organelles, signaling molecules, cargo, and cytoskeletal components. Impaired axonal transport in neurons occurs even before the onset of clinical symptoms. This observation has been supported by studies conducted in mouse models [23].

3.4 Significance of environmental factors and physical activity in the development of ALS

3.4.1 Environmental factors

Exposure to environmental factors such as particulate matter, volatile organic compounds, metals, diesel engine exhaust, and vehicle emissions is considered a potential risk factor for the development of ALS. Metal exposure appears to have the most detrimental effect on disease development [24].

In a prospective cohort study from the UK Biobank, which included 501,308 participants aged 40–69 years, long-term exposure (2006–2021) to nitrogen dioxide, nitrogen oxides, fine

particulate matter, and coarse particulate matter was analyzed. No association was found between air pollution and the development of ALS [25].

In a cohort study of postmenopausal women from the Women's Health Initiative, it was shown that the risk of ALS associated with earlier or later exposure to PM2.5 and PM10 particulate matter was low, and no causal relationship could be inferred [26].

At the University of Michigan, a survival analysis of individuals with ALS was conducted for the period 2009-2022. Indoor air pollutants were considered, including fine particulate matter (PM2.5), nitrogen dioxide, ozone, and several other particulate components such as soot, nitrates, sulfates, and sea salt. The results of this observation indicated a 7-month longer survival associated with a decrease in annual PM2.5 concentration by 2.1 $\mu g/m^3$ [27].

In a 2021 prospective cohort study, blood levels of arsenic, cadmium, copper, lead, manganese, mercury, selenium, and zinc were analyzed. The study included 1,007 participants. It was shown that cadmium and lead were associated with an increased risk of ALS, whereas zinc was associated with a reduced risk of developing ALS [28].

A case-control study published in 2025, involving 454 individuals with ALS and 294 controls, also analyzed metal concentrations in plasma and urine samples. Higher levels of copper, selenium, and zinc were associated with an increased risk of ALS and were also linked to shorter survival after disease onset. The study highlighted the importance of combined exposure to multiple metals in ALS development and demonstrated that the effect of metals is independent of genetic factors [29].

Smoking and exposure to tobacco smoke are risk factors for the development of ALS. Based on a publication including data from 28 case-control studies and 4 cohort studies, the odds ratio was 1.14, indicating a modestly increased risk of developing ALS. Smoking is therefore considered a modifiable risk factor that should be eliminated [30].

Epidemiological studies also indicate an association between pesticide exposure and the risk of ALS. Chlorinated pesticides are a group of synthetic chemical compounds mainly used in agriculture. They have the ability to accumulate in the adipose tissue of living organisms. The pesticide cis-chlordane has been shown to damage motor neurons. It is a substance that impairs mitochondrial function in nerve cells, contributing to the formation of reactive oxygen species. Chlordane acts as an antagonist of GABA chloride channels, thereby disrupting gamma-aminobutyric acid neurotransmission. Although this compound has now been

withdrawn from use, its half-life ranges from 10 to 20 years, allowing it to persist in soil and organisms and potentially exert long-term effects [31].

A study conducted in the United States confirmed the neurotoxic effects of herbicides such as 2,4-D, glyphosate, and the insecticide carbaryl [32].

A case-control study based on the National ALS Registry showed that serum levels of organochlorine pesticides are a risk factor for ALS. Survey data from this study also indicated that occupational exposure to lead and agricultural work, including professional gardening, are associated with an increased risk of ALS [33].

3.4.2 Physical activity

A cohort study of football players (6,007 players and 56,168 controls) from Sweden showed that the risk of neurodegenerative disease was higher among football players compared with the control group; however, no significant differences were observed between the groups in terms of motor neuron disease [34].

Another study reported that the incidence and mortality of ALS are four times higher among National Football League players compared with men in the general U.S. population [35].

Italian professional football players were also investigated, and a relationship was found between the duration of professional football activity and the risk of ALS [36].

Based on 10 cohort studies and 26 observational studies, researchers concluded that risk factors for ALS include pesticide exposure (OR = 1.96), military service (OR = 1.34), head injuries (OR = 1.26), and physical activity (OR = 1.06) [37]. This study suggests that contact sports associated with repeated head trauma may represent a risk factor for ALS development.

A Norwegian study including 373,696 participants, among whom 504 developed ALS, indicated that physical activity may have a protective effect. Overall sports participation reduced the risk of ALS by 29%. In men, moderate physical activity (at least 4 hours of walking or cycling) was associated with a 29% reduction in risk, while high levels of activity were associated with a 41% reduction. A lower resting heart rate was associated with a 32% reduced risk of ALS [38].

MRI-based studies have also demonstrated a potential association between ALS and sports activity. Physical exertion may contribute to motor neuron damage in individuals with genetic susceptibility to ALS. Exercise has been shown to activate the expression of G4C2 repeats in the C9orf72 gene, potentially predisposing individuals to ALS development [3].

3.5 Pharmacology and new therapies in ALS

Amyotrophic lateral sclerosis is an incurable disease. Treatment is divided into disease-modifying therapy and symptomatic therapy. The aim of therapy is to improve the patient's quality of life as much as possible.

The only approved drug for the treatment of ALS is riluzole. This drug inhibits the presynaptic release of excitatory amino acids, such as aspartate and glutamate, as well as γ-aminobutyric acid (GABA) and glycine. It also inhibits neuronal uptake of dopamine, GABA, and glutamate, and has relaxing and sedative effects. Riluzole delays the need for mechanical ventilation. Recent studies indicate a 30% reduction in the risk of death with riluzole therapy. A multicenter study demonstrated that patients treated with riluzole had a median survival extended by approximately 7 months, particularly in patients with rapidly progressing disease [39].

Edaravone is used as a disease-modifying treatment. It inhibits inflammatory reactions in microglia, scavenges free radicals, and exerts neuroprotective effects. Treatment with edaravone has been associated with slower disease progression and a reduced number of deaths within the first two years of the disease [40].

Sodium phenylbutyrate and taurursodiol (PB and TURSO) reduce endoplasmic reticulum stress and mitochondrial dysfunction. These agents decrease the risk of death by 52% [41].

Tofersen is a drug designed for patients with the SOD1 mutation. It is an antisense oligonucleotide that binds to SOD1 gene mRNA, reducing the production of the SOD1 protein. The VALOR study included 108 participants with ALS carrying the SOD1 mutation and showed that earlier initiation of treatment leads to better therapeutic outcomes. Earlier pharmacotherapy was associated with slower disease progression, improved respiratory function and muscle strength, as well as longer survival [42].

Methylcobalamin (vitamin B12) supports the normal functioning of the nervous system. In very high doses, methylcobalamin may contribute to slowing functional decline in patients with early-stage ALS. The safety of high-dose vitamin B12 administration was confirmed over a 16-week treatment period [43].

Stem cells are still the subject of extensive research in the context of ALS treatment. They demonstrate neuroprotective effects, and clinical studies suggest potential therapeutic benefits [44]. In turn, transplantation of neural stem/progenitor cells has shown improvements in muscle function and a slowing of the negative effects of progressive tissue degeneration [45].

Gene therapy research also offers significant promise. Approximately 10% of ALS cases are genetically confirmed. The development of gene therapies focuses on gene silencing in gain-of-function mutations, gene replacement in loss-of-function mutations, as well as gene addition and genome editing.

These approaches often utilize antisense oligonucleotides, which bind to abnormal genetic sequences and lead to their silencing. In loss-of-function mutations, viral vectors are used to deliver functional genetic material. The most effective therapeutic responses have been observed in ALS cases associated with SOD1 and C9orf72 mutations [46].

CRISPR/Cas9, known as the Clustered Regularly Interspaced Short Palindromic Repeats system, is a gene-editing technique that has enabled the silencing of SOD1 mutations in mouse models. Research on this type of therapy is highly important, as these approaches could potentially allow for causal treatment by preventing the formation of toxic proteins [47].

4. Summary and conclusions

The aim of this study was to review the most recent information on the impact of environmental factors and physical activity on the development of ALS, as well as to present available pharmacological treatments and the development of new therapeutic approaches.

The conducted analysis showed that chlorinated pesticides, as well as cadmium and lead, increase the risk of developing ALS. In contrast, studies investigating the potential association between air pollution and ALS have yielded inconclusive results. Exposure to tobacco smoke and active cigarette smoking are factors that increase the likelihood of disease occurrence. Based on these findings, it can be concluded that individuals exposed to pesticides, cadmium, and lead constitute a high-risk group. Contact with these substances should therefore be minimized as much as possible.

Based on studies conducted among football players, physical activity cannot be unequivocally classified as a risk factor. Although an increased risk of ALS has been observed among NFL players, it cannot be stated that this is directly related to physical exertion itself. Moreover, large population-based studies have shown that physical activity may reduce the risk of developing ALS. At present, findings regarding physical activity as a risk factor for ALS remain inconclusive, and further research in this area is required.

ALS remains an incurable disease despite the availability of several disease-modifying therapies. Therefore, further research into new therapeutic options is necessary, with particular emphasis on developing treatments that target the underlying cause of the disease.

Disclosure

The authors report no disclosures.

Author's contribution

Conceptualization: Natalia Zięba
Methodology: Natalia Zięba, Olgierd Czapiński, Anna Brodowska, Ewa Tomicka, Justyna Kuś
Software: Not applicable
Check: Patrycja Białowąs, Justyna Kuś, Maciej Ciesielski, Ewa Tomicka
Formal analysis: Olgierd Czapiński, Maciej Ciesielski, Mateusz Pysiewicz
Investigation: Justyna Kuś, Mateusz Pysiewicz
Resources: Ewa Tomicka, Olga Stadnicka, Patrycja Białowąs, Natalia Zięba
Data curation: Natalia Zięba, Olga Stadnicka, Anna Brodowska
Writing-rough preparation: Maciej Ciesielski, Natalia Zięba, Mateusz Czech
Writing review and editing: Olgierd Czapiński, Anna Knapik
Visualization: Olga Stadnicka
Supervision: Natalia Zięba
Project administration: Natalia Zięba, Mateusz Pysiewicz, Anna Knapik
Receiving funding: Not applicable.

All authors have read and agreed to the published version of the manuscript.

Funding Statement:

This research received no external funding.

Institutional Review Board Statement:

Not applicable.

Informed Consent Statement:

Not applicable.

Data Availability Statement:

Not applicable.

Acknowledgments:

Not applicable.

Conflict of Interest Statement:

The authors declare no conflict of interest.

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