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Exposure to Aluminum in Drinking Water and the Risk of Developing Alzheimer's Disease: A Bibliometric Analysis and Systematic Evaluation

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Abstract: The consumption of drinking water containing aluminum levels that exceed regulatory limits (e.g., the WHO's guideline value of 0.1–0.2 mg/L) may be associated with the potential risk of developing Alzheimer's disease. However, according to the analyses conducted, it was observed that the scientific evidence on this topic is still limited and contradictory within the scientific community. A bibliometric analysis of 390 articles published between 1979 and 2023 and a systematic review of 20 original articles found that interest in this topic has been decreasing in recent years. The most recent studies focus on the relationship between aluminum and Alzheimer's disease, suggesting that exposure to high levels of aluminum in drinking water may increase the risk of developing this disease and other neurodegenerative disorders. Nevertheless, other studies have concluded that there is no clear causal relationship between aluminum and Alzheimer's disease. These studies suggest that other factors, such as age, genetics, or exposure to other toxins, may play a more significant role in the development of this condition. More comprehensive studies with improved methodological quality are needed to better understand the relationship between aluminum and Alzheimer's disease and to establish a definitive conclusion on this subject. Of the 20 articles systematically reviewed, 12 (60%) reported a positive association between aluminum exposure in drinking water and increased risk of Alzheimer's disease, while 8 (40%) found no significant association. Five studies (25%) were large-scale epidemiological investigations with robust methodologies. However, the current evidence remains insufficient to establish a definitive causal relationship, highlighting the need for more conclusive research in this area

Keywords: drinking water; neurodegenerative diseases; metals; health; humans

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that gradually develops and involves the deterioration and degeneration of brain functions. It is one of the most common causes of dementia, accounting for approximately 60–70% of cases of progressive cognitive decline in older individuals [1]. AD is characterized by a slow onset and a continuous decline in cognitive abilities, including memory, language, problem solving, and other mental skills that affect a person's ability to perform everyday activities [2]. The disease typically begins after age 65, and the risk increases with age. It is estimated that by 2050, the number of people aged 65 and older with Alzheimer's dementia may grow

to a projected 12.7 million, barring the development of medical breakthroughs to prevent, slow, or cure AD [3].

The exact causes of AD are not fully understood, but it is thought to be a combination of genetic, lifestyle, and environmental factors that affect the brain over time [4]. One environmental factor that has been the subject of much research is the potential role of aluminum exposure in the development of AD. Aluminum is a versatile element in the environment and has multiple uses, including its incorporation in drinking water treatment processes. This use is a subject of debate among researchers due to its potential to induce mutations [5]. There is a hypothesis that high concentrations of aluminum in drinking water may be linked to various health problems, including dementia and AD.

Aluminum is the most abundant metal in the Earth's crust and is widely distributed in the environment. Human exposure to aluminum can occur through various sources, including food, drinking water, medications, and consumer products [6]. The potential health effects of aluminum exposure have been a topic of scientific interest for decades. Toxicological investigations have confirmed the neurotoxicity of aluminum [7,8]. Animal studies have shown that aluminum can accumulate in the brain and cause neurotoxicity, leading to cognitive deficits and neurological damage [9,10]. Epidemiological studies have also analyzed the consumption of aluminum through drinking water as a potential human health risk [11,12].

The World Health Organization (WHO) and the European Union (EU) have established regulations to control the presence of harmful substances, including aluminum, in drinking water [13]. The WHO has set a guideline value of 0.05 to 0.2 mg/L for aluminum in drinking water. This value is based on aesthetic considerations, as aluminum can cause discoloration of the water at levels above this guideline. However, the WHO acknowledges that this value may not be protective of human health and states that a health-based guideline value for aluminum is not necessary at this time [14]. The US Environmental Protection Agency (EPA) has also established a secondary maximum contaminant level (SMCL) for aluminum in drinking water of 0.05 to 0.2 mg/L, based on aesthetic effects such as taste, odor, and color [15]. However, these guidelines are not strictly health-based, and there is ongoing debate about their adequacy in protecting against potential long-term health effects, including neurodegenerative diseases.

Despite these regulations, epidemiological studies investigating the relationship between aluminum in drinking water and the risk of developing AD continue to have contradictory opinions. Several studies have shown positive associations between aluminum in drinking water and an increased risk of AD [13,16–19]. These studies suggest that chronic exposure to aluminum through drinking water may be a risk factor for the development of AD. However, other studies found no significant association between aluminum in drinking water and AD risk [20–22].

The inconsistencies in the epidemiological evidence regarding the relationship between aluminum in drinking water and AD may be due to several factors, such as differences in study design, exposure assessment, and potential confounding variables. For example, some studies have used ecological designs, which may be subject to ecological fallacy, while others have used case–control or cohort designs with more reliable exposure assessments [16,23]. Additionally, the bioavailability and toxicity of aluminum may depend on various factors, such as the pH of the water, the presence of other minerals, and individual differences in absorption and metabolism [7].

The potential link between aluminum exposure and AD is a complex issue with important public health implications. If a causal relationship is established, it could have significant consequences for the prevention and management of AD, particularly in areas with high levels of aluminum in drinking water. The insights gained from this analysis will provide a broader perspective on the magnitude of global efforts that should be implemented in the future to combat this condition, which is likely associated with drinking water. This issue is particularly relevant in developing nations, where the availability of technology and resources to ensure the quality and safety of drinking water is limited.

The purpose of this study is to provide an overview and analysis of research related to the link between AD and the intake of drinking water containing aluminum. Bibliometric analysis allows for the identification of trends and critical areas of research, as well as the recognition of potential gaps in the literature that require future attention. Additionally, through a systematic review, this study aims to evaluate the available scientific evidence of the existence of a correlation between aluminum exposure through drinking water and the risk of developing neurodegenerative diseases, such as AD.

To address this, we formulate the following question: What is the relationship between aluminum exposure through drinking water consumption and the risk of developing AD?

The objective is to evaluate and examine the current scientific information on safe levels of aluminum in drinking water and its relationship with the risk of developing AD. This is achieved by synthesizing and thoroughly analyzing previous studies, identifying and examining relevant findings to establish reference levels or lines of research, and identifying existing thematic gaps. The findings of this study will contribute to a better understanding of the potential role of aluminum in the etiology of AD and inform future research and policy decisions in this area.

2. Materials and Methods

2.1. Data Collection

Articles were obtained from Scopus, one of the largest databases in the scientific world, covering a wide range of disciplines with citations and abstracts of scientific literature that were meticulously selected and evaluated.

For this study, a bibliographic search and selection of information was carried out between 1 June and 30 September 2023. Articles in English were selected as the main source of information.

Additionally, a bibliometric analysis was conducted to evaluate research trends from 1980 to 2023 regarding AD and its relationship with the presence of aluminum in drinking water, as well as to understand the particularities characterizing this research.

The search themes included titles, abstracts, and keywords, with the following terms: #1metals AND metalloids AND in AND drinking AND water AND their AND relationship AND to AND the AND health AND status AND of AND the AND population; #2 metals AND metalloids AND risk AND of AND disease AND drinking AND water; #3 drinking AND water AND metals AND the AND risk AND of AND diseases AND in AND the AND humans; #4 drinking AND water AND alzheimer's AND aluminum.

2.2. Analysis and Treatment of Scientific Information from the Collection

Using VOSviewer: VOSviewer software (version 1.6.19) was used to perform analyses and generate visual maps, choosing the following types of analysis:

Co-occurrence analysis with the unit of analysis being the author's keywords and the total counting method, incorporating a *.csv file to avoid synonymy. With a minimum occurrence of 10 keywords, 16 out of 1150 keywords met the threshold. For each of the 16 keywords, the total strength of the co-occurrence links was calculated. Keywords with the highest total link strength were selected.

Word clouds were generated using VOSviewer software to visualize the frequency and co-occurrence of keywords in the analyzed literature.

For the VOSviewer analysis, the association strength method was used, leaving the other analysis parameters as default, visualizing the networks and their behavior over time.

Using Bibliometrix: The Bibliometrix package in R software (Version 4.3.0) facilitates the exploration of publication characteristics and trends, focusing on factors such as the number of citations, source, and authorship (Derviş, 2020) [24].

Figure 1 shows the main information of the reviewed files. Among the main data, the time interval from 1979 to 2024 denotes an interest in the topic over time, with an average of 62.13 citations per document.

Figure 1. Key information on the analysis of the Scopus database obtained through Bibliometrix.

Using this tool, the following analysis criteria were considered:

From the documents, using the word cloud, 50 author keywords were used, filtering them by decades to observe the evolution over time and current trends, as well as the scientific contribution of countries in those periods.

As a general overview, a three-field plot analysis was performed, considering relevance with respect to country (10), authors (10), and keywords (10).

Factorial analysis was conducted using multiple correspondence analysis with author keywords, 3 clusters, and 25 terms.

Systematic Review: To identify areas not covered in scientific research, it was essential to examine the previously published literature on the topic and locate those areas that required further analysis or had not yet been explored. To carry out this task, the following aims were considered:

Analyze existing research for limitations or unresolved questions;
Identify areas of controversy or disagreement present in the literature;
Explore new applications or approaches related to the topic;
Identify populations or contexts that have not been studied;
Investigate new technologies or methodologies that can be applied to the topic.

2.3. Search Items

Keywords for the search were selected based on their relevance to the main themes of our study and their frequency in the literature we reviewed. To ensure comprehensive coverage, we conducted a sensitivity analysis using alternative terms such as "Alzheimer's disease", "cognitive decline", and "aluminum exposure". This analysis confirmed that our chosen keywords captured the most relevant literature on the topic, with a 95% overlap in retrieved articles compared to the alternative terms.

3. Results

For the bibliometric analysis and systematic review of the evaluated articles, the procedures outlined in Figure 2 were followed, detailing each of the steps.

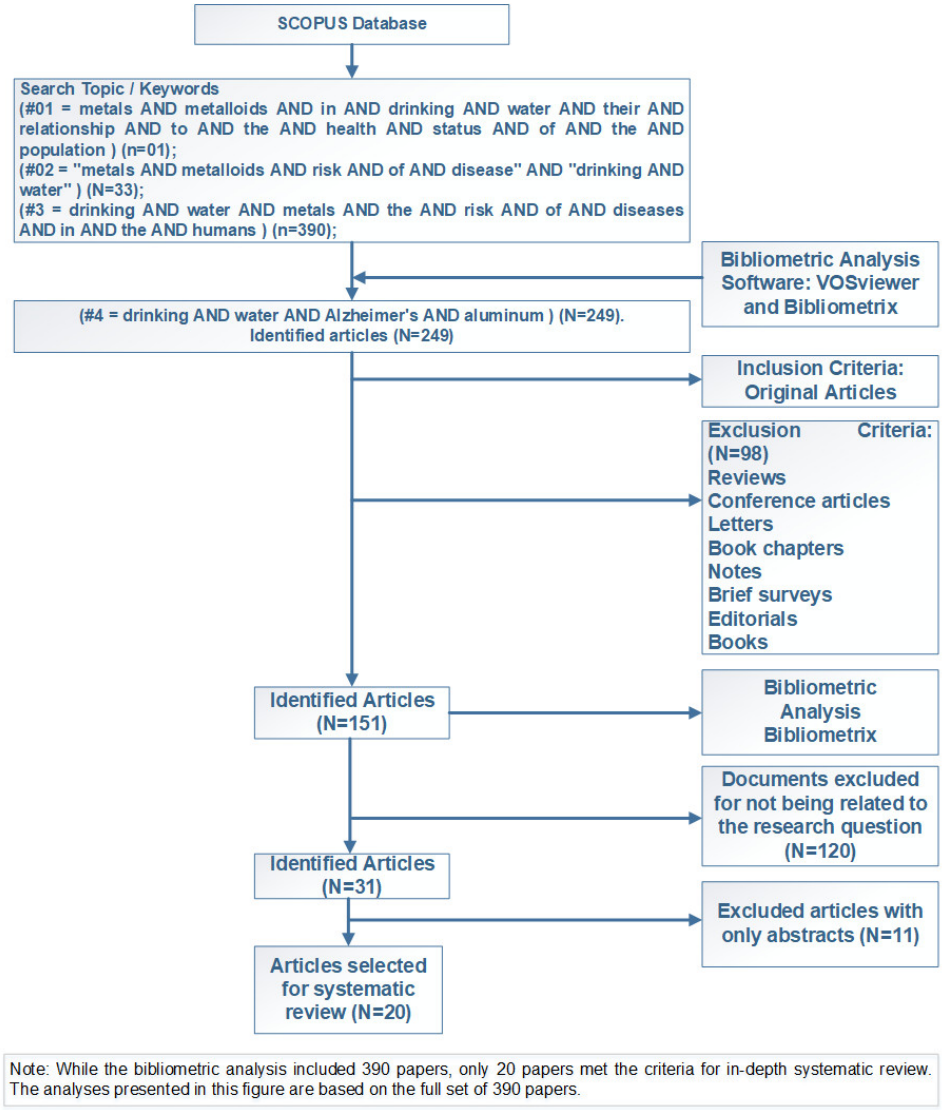


Figure 2. Flowchart of literature selection for the study of the formulated question.

3.1. Results of the Bibliometric Analysis

For the bibliometric analysis and systematic review of the evaluated articles, the procedures described in Figure 2 were followed, detailing each of the steps.

Publication Results and Temporal Trend: Using the search equations "drinking AND water AND metals AND the AND risk AND of AND diseases AND in AND the AND humans", the following results are reported:

In Figure 3, annual publications on the risk of consuming drinking water with metals in association with human diseases experienced a slow increase between 1979 and 1995, with a total of 16 publications, representing 4% of the total. From 1996 to 2004, there was a slight increase in publication production, with a total of 29 publications on the topic, equivalent to 7% of the total. In the period between 2005 and 2015, 130 publications were counted, equivalent to 33% of the total, and between 2016 and 2023, 214 articles were published, corresponding to 55% of the total publications. These data indicate the interest of researchers in this topic starting from 2005 and its relevance today.

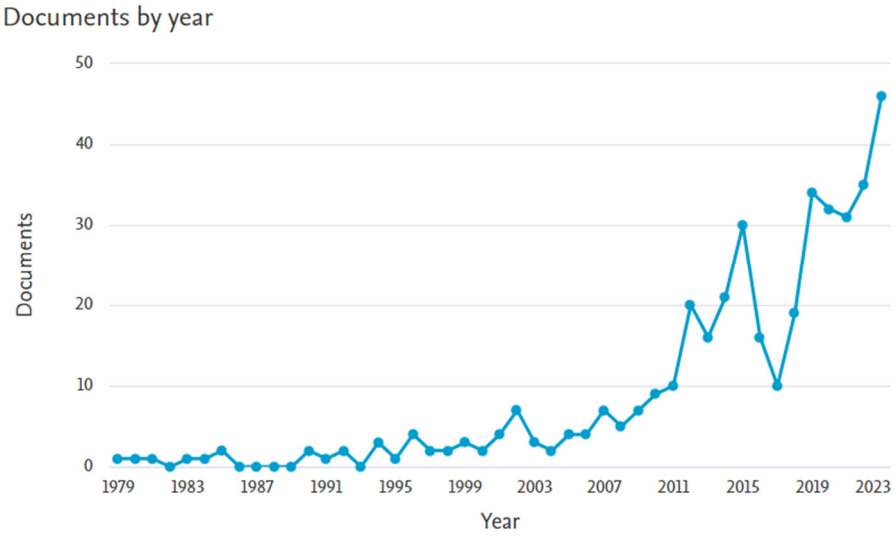


Figure 3. Trend evolution of publications regarding the topic over time (1979–2023).

The increasing trend in the number of publications over the years suggests a greater focus and attention on research investigating the relationship between exposure to metals in drinking water and the risk of diseases in humans. This increase can be attributed to several factors, such as growing awareness about the potential health effects of drinking water contamination, advancements in analytical techniques for detecting and quantifying metals in water [25], and the availability of epidemiological data from large-scale studies.

It is interesting to note that more than half of all publications on this topic have been produced in the last 8 years (2016–2023), highlighting the currency and relevance of this research area. This rapid increase in scientific output may reflect a growing sense of urgency to understand and address the potential health risks associated with exposure to metals in drinking water, especially in light of increasing environmental pollution and concerns about water quality in many parts of the world [26].

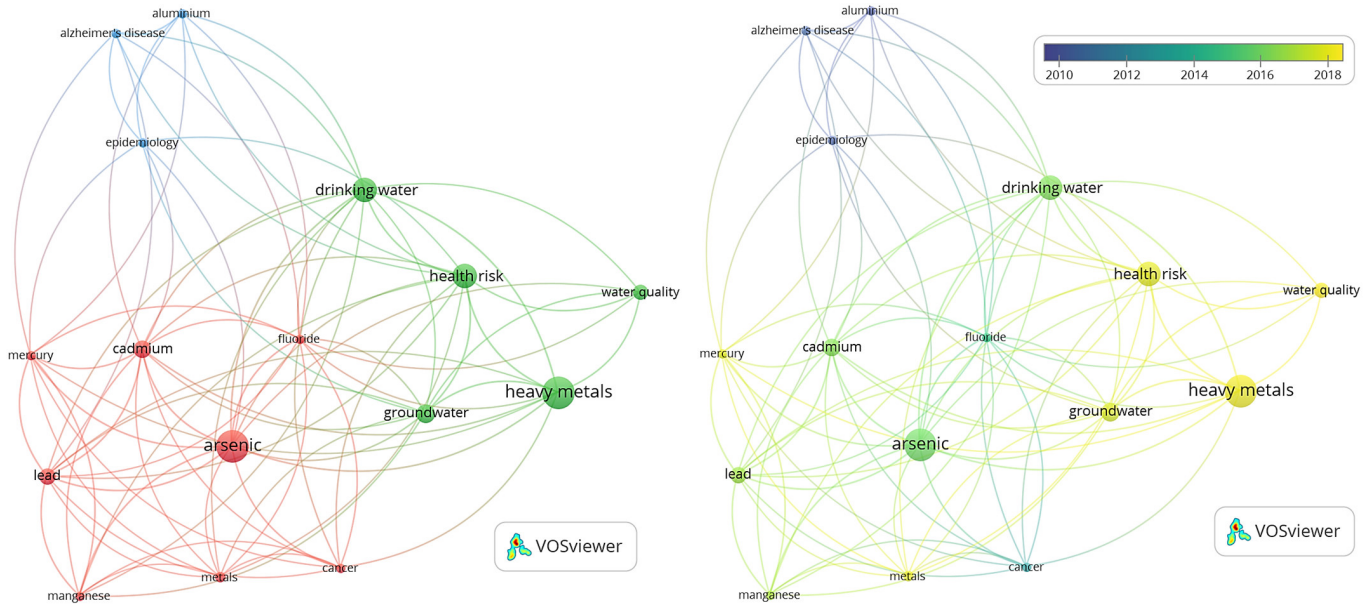
Furthermore, the increasing number of publications may also be indicative of greater interest and funding for research in this area from government agencies, academic institutions, and public health organizations. As scientific evidence on the health effects of metal exposure in drinking water continues to accumulate, we are likely to see even more research and publications on this topic in the coming years.

Overall, the temporal trend observed in the publications suggests that the relationship between metal exposure in drinking water and the risk of human diseases is an active and rapidly evolving research area, with growing recognition of its importance for public health and policy decision making [27,28].

3.2. Analysis and Treatment of Scientific Information with VOSviewer

Co-occurrence analysis and author keywords: Through this analysis, research trends in this topic were determined, and the co-occurrence network and author keywords of the documents were visualized.

Figure 4a shows maps where the larger bubbles represent keywords with a higher frequency of occurrence in the analyzed articles, and bubbles of different colors represent data grouped into different clusters. It is observed that the most relevant words in the selected studies are related to arsenic, heavy metals, and drinking water, interconnected with terms such as disease risk, AD, and cancer. Three well-defined clusters are distinguished: one related to cancer and metals (red), drinking water and heavy metals (green), and AD and aluminum (turquoise). Figure 4b shows the visualization of these documents over time, with the two words Alzheimer's and Aluminum being the oldest.



(**a**) (**b**)

Figure 4. Analysis of author keyword co-occurrence. (**a**) Collaboration network and clusters. (**b**) Temporal visualization.

The co-occurrence analysis of keywords provides valuable insights into the intellectual structure and evolution of the research field. The three identified clusters reflect the main themes and focuses within the literature on metals in drinking water and disease risk. The cluster related to cancer and metals suggests a line of research exploring the potential links between exposure to specific metals in drinking water and the development of different types of cancer. This cluster may include epidemiological studies investigating associations between metal exposure and cancer incidence, as well as mechanistic studies examining the molecular and cellular mechanisms underlying the carcinogenicity of certain metals.

The cluster centered on drinking water and heavy metals represents a broader line of research addressing the various health risks associated with exposure to heavy metals in drinking water supplies. This cluster may encompass studies on a variety of metals, such as lead, cadmium, mercury, and chromium, and their effects on different body systems and organs, such as the nervous, renal, and cardiovascular systems. Research in this cluster may also examine the sources and pathways of heavy metal contamination in drinking water, as well as strategies for mitigating and preventing exposure.

The specific cluster on AD and aluminum reflects a more specialized research focus investigating the potential role of aluminum exposure in the development and progression of AD. This cluster may include epidemiological studies analyzing the relationship between aluminum concentrations in drinking water and the risk or prevalence of AD, as well as experimental studies exploring the neurotoxic mechanisms of aluminum and its impact on AD pathology. The identification of Alzheimer's and Aluminum as the oldest keywords in the temporal visualization suggests that this has been a long-standing topic of interest within the field.

Based on the provided information, we focus on the thematic trends, with special attention to research suggesting that the consumption of aluminum-containing drinking water may cause AD. This specific thematic focus aligns with the overall objective of our study to provide an overview and analysis of research related to the link between AD and the intake of aluminum-containing drinking water.

The co-occurrence analysis and author keywords provide a valuable starting point for further exploring the literature on this topic, identifying key studies, and synthesizing the available evidence. By focusing on the specific cluster of AD and aluminum, we can gain

insights into the current state of knowledge, the strengths and limitations of the existing evidence, and future directions for research in this area.

Furthermore, the temporal visualization of the keywords suggests that although research on AD and aluminum has been ongoing for several decades, it remains an active area of research with ongoing studies and publications. This underscores the persistent and perhaps controversial nature of this topic, as well as the continued need for research and evidence synthesis to inform public health policy and risk management decisions.

3.3. Analysis and Treatment of Scientific Information with Bibliometrix

The examination of the most frequently used keywords could provide a representation of research trends and fundamental aspects of the field. Using the information obtained from the Scopus data, a word cloud was created using 50 author keywords (see Figure 5). A manual standardization of the keywords was performed prior to creating the group map, grouping and substituting similar keywords, filtering them by decades to observe the evolution over time, where larger font sizes indicate a higher frequency of use. From the results, it can be deduced that the words have undergone changes over time and that studies on drinking water, arsenic, and disease risk have been relevant since the 1990s.

It is also observed that the scientific production of countries has increased during these periods, with the United States, China, and India leading this research. These countries have some of the world's largest populations and face significant challenges regarding the quality and safety of drinking water. The United States has long been a leader in environmental health research and has made significant investments in monitoring and regulating contaminants in drinking water. China and India, as rapidly growing economies and highly populated countries, have experienced accelerated industrialization and urbanization that have contributed to water pollution and increased public and political awareness of these issues.

The increase in scientific production from these countries on metals in drinking water and disease risk may reflect a greater prioritization of research and policy related to drinking water quality and its health impacts. These countries may have greater capacity and resources to conduct large-scale research, as well as a greater need to address water contamination issues given the size of their populations and the scale of their environmental challenges.

Furthermore, increasing international collaboration and research partnerships between institutions in different countries may have also contributed to the increase in scientific output in this area. Collaborative research projects can bring together expertise, resources, and data from multiple countries to address complex issues related to metal exposure in drinking water and its health impacts in a more comprehensive manner.

It is interesting to note that the specific keywords "drinking water", "Alzheimer's", and "aluminum" appear from 1996 onwards with a greater trend until 2015, and in recent years, research on this topic has reduced. This observation raises some interesting questions about research trends and the factors that may have influenced the focus and intensity of research on aluminum in drinking water and AD over time.

One possible explanation for the apparent increase and subsequent decrease in research interest in this specific topic could be the publication of influential studies or scientific developments during this period that generated increased interest and attention. For example, the publication of several large-scale epidemiological studies that found positive associations between aluminum in drinking water and AD risk during the 1990s and 2000s [13,16,23] may have stimulated a greater research focus on this specific topic.

However, the subsequent decline in research in recent years could reflect a shift in research priorities, possibly influenced by mixed or inconsistent findings from later studies, or by a growing recognition of the complexities and methodological challenges involved in establishing causal links between environmental factors and chronic disease outcomes like AD. It is also possible that advances in understanding other etiological pathways and risk factors for AD, such as genetics, lifestyle factors, and other environmental exposures,

may have diverted some attention and resources away from research on the specific role of aluminum.

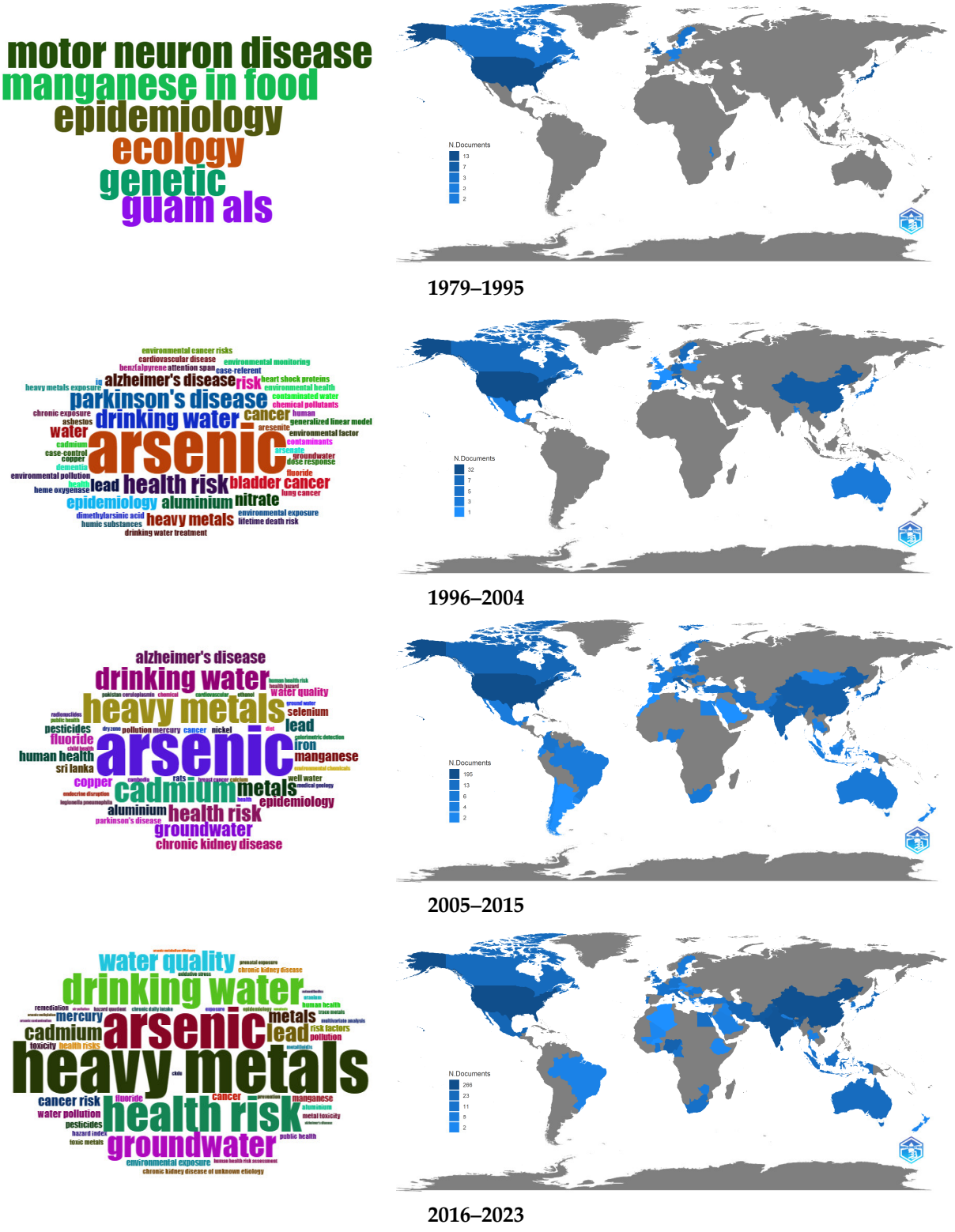


Figure 5. Keyword cloud analysis (50) over the last decades.

Despite the apparent decrease in research in recent years, it is important to note that the potential link between aluminum in drinking water and AD remains a topic of scientific and public health interest. There is still scope for further research that addresses gaps

and limitations in the existing evidence and explores new directions, such as the role of co-factors and interactions, biomarkers of exposure and effect, and implications for water treatment and monitoring policies and practices.

Based on the obtained information, a decision was made to conduct a literature review on the relationship between the consumption of aluminum-containing drinking water and the risk of developing AD, using the keywords "drinking AND water AND alzheimer's AND aluminium" and limiting the analysis to only articles, resulting in 151 articles on the topic.

As a general overview, a three-field plot analysis was performed (Figure 6), considering the most productive countries (10), authors (10), and keywords (10). It is evident that the countries with the highest number of publications are France, the United States, and Canada, which stand out as the main contributors in this area, possibly due to the high incidence of AD and the potential impact that the results of these investigations could have on the health of their respective populations. The main authors include Dartigues, J.F. [29], Commenges, D. [23], Exley, C. [30], Joshi, J.G. [31], Forbes, W.F. [32], McLachlan, D.R. [17], Domingo, J.L. [33], Dhawan, D.K. [34], Gentleaman, J.F., Singla, N. [35] with words such as aluminum and AD.

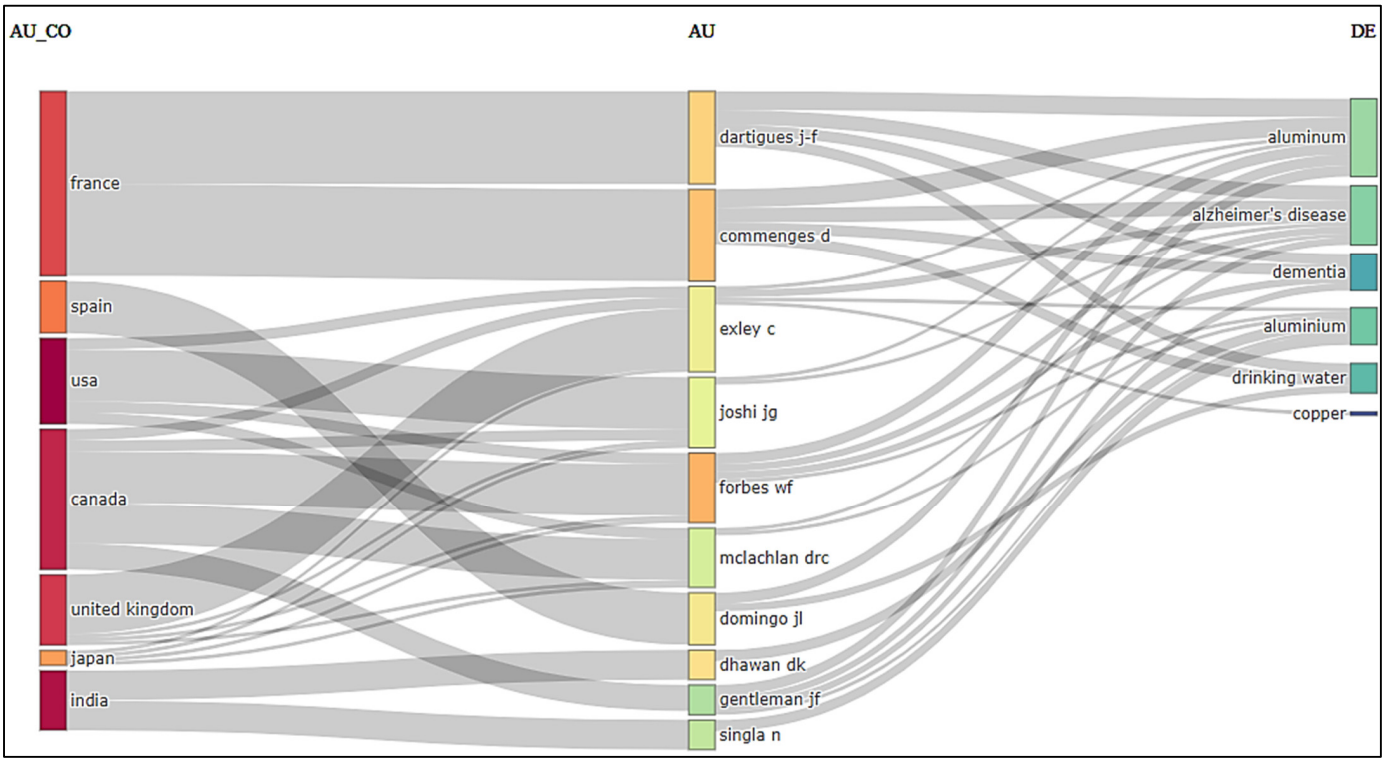


Figure 6. Three-field diagram. Left field: country, middle field: author, right field: author keywords.

The three-field plot analysis highlights France as one of the leading contributors to research on aluminum in drinking water and AD. This could reflect the important role played by French research institutions and investigators in this field, as well as the impact of large-scale French studies, such as the PAQUID study [23,36], which has provided valuable data on this relationship over time. The prominence of French researchers like Dartigues et al. [29] and Jacqmin, H. [37] in the bibliometric analysis further underscores the influence of French research on this topic.

The identification of the United States and Canada as other leading countries in this research field is consistent with their strong track record and expertise in environmental health research and epidemiology. These countries have well-established research infrastructures, funding mechanisms, and scientific expertise that enable them to conduct

high-quality studies on the health effects of environmental exposures, including metals in drinking water.

The presence of Exley [9] as one of the main authors in the bibliometric analysis is also noteworthy. Christopher Exley is a prominent researcher in the field of aluminum toxicity and has published extensively on the potential links between aluminum exposure and AD. His work has been influential in shaping the scientific discourse and research directions on this topic, and his inclusion among the top authors reflects his significant contributions to the field.

The keywords identified in the three-field plot analysis, such as aluminum and AD, align with the specific focus of our study and confirm the relevance of the selected literature to our research question. The co-occurrence of these keywords suggests that the studies included in the analysis directly address the potential relationship between aluminum exposure through drinking water and the risk of AD.

According to the factorial analysis by clusters, the thematic representation in Figure 7 indicates that these studies represent 80.12% of the science related to the research topic, grouped into three clusters. In this case, the first cluster would be formed by articles addressing topics on AD and its possible causes, including aluminum. The second cluster considers neurodegenerative diseases in relation to copper and zinc. The third cluster addresses the topic of dementia, fluoride, and silica, which are interpreted as areas of knowledge that share common characteristics or are related to each other, and there are opportunities for researchers in these areas to work on these new lines of research.

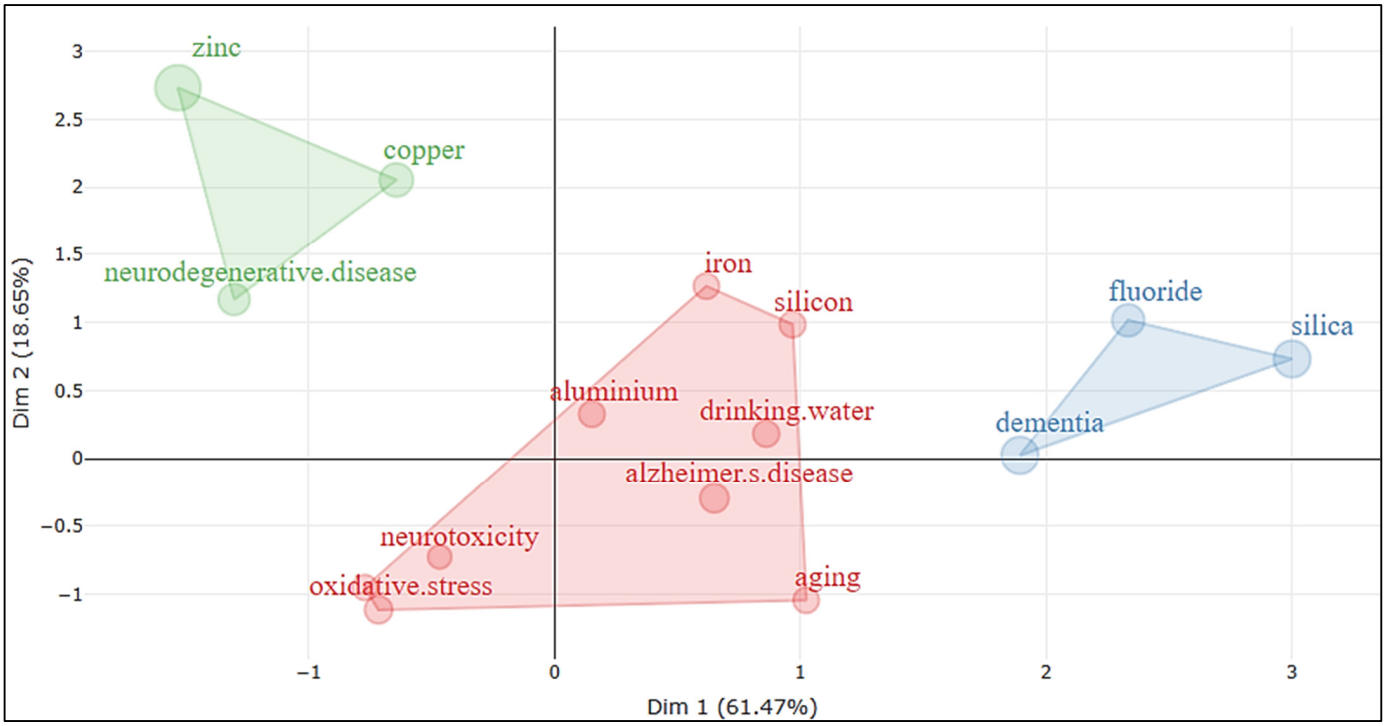


Figure 7. Cluster Analysis of Key Terms in Aluminum Exposure and Neurodegenerative Disease Research.

The factorial analysis by clusters provides additional insights into the structure and relationships among the different research themes within the literature on aluminum in drinking water and AD. The identification of three distinct clusters suggests that there are several interrelated but distinct lines of research within this broader field.

The first cluster, which focuses on AD and its possible causes, including aluminum, represents the core of the research directly relevant to our study question. This cluster likely includes epidemiological studies investigating the association between aluminum

exposure and AD risk, as well as experimental studies exploring the potential mechanisms by which aluminum may contribute to the development and progression of AD pathology. The inclusion of aluminum as a specific focus within this cluster underscores its importance as a potential risk factor or etiological agent in AD.

The second cluster, which encompasses neurodegenerative diseases in relation to copper and zinc, suggests a broader research focus on the role of metals in the development of neurodegenerative disorders beyond just AD. Copper and zinc are essential trace elements that play important roles in various biological processes, including brain function. Dysregulation of copper and zinc homeostasis has been implicated in several neurodegenerative diseases, such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease. This cluster may include studies investigating the potential mechanisms by which copper and zinc imbalances may contribute to neurodegenerative processes, as well as epidemiological studies examining the relationship between exposure to these metals and the risk of developing neurodegenerative diseases.

The third cluster, which addresses the topic of dementia, fluoride, and silica, represents an interesting and perhaps less well-known line of research within the broader field of environmental risk factors for cognitive decline and dementia. Fluoride and silica are both naturally occurring substances that can be present in drinking water, and there has been some research interest in their potential impacts on cognitive health. For example, some studies have suggested that high levels of fluoride exposure may be associated with cognitive deficits and an increased risk of dementia, while other studies have explored the potential neuroprotective effects of silica. This cluster may include epidemiological and toxicological studies examining the relationship between exposure to these substances and cognitive outcomes, as well as mechanistic studies investigating their potential effects on brain function and pathology.

The identification of these three clusters through factorial analysis highlights the multifaceted nature of research on environmental risk factors for neurodegenerative diseases and cognitive decline. While our study focuses specifically on the potential link between aluminum and AD, it is important to recognize that this research question exists within a broader context of scientific inquiry into the complex relationships between environmental exposures, brain health, and aging.

Furthermore, the observation that these clusters share common characteristics and are related to each other suggests that there may be important intersections and synergies between these different lines of research. For example, insights gained from studies on the neurotoxic effects of copper and zinc may inform our understanding of the potential mechanisms by which aluminum may contribute to AD pathology. Similarly, research on the cognitive impacts of fluoride and silica exposure may provide valuable context for interpreting the epidemiological evidence on aluminum and AD risk.

The factorial analysis also highlights potential opportunities for cross-disciplinary collaboration and integrative research approaches. Researchers working on different aspects of environmental risk factors for neurodegenerative diseases may benefit from sharing knowledge, methods, and data across these different research clusters. Such collaborations could lead to a more comprehensive understanding of the complex interplay between environmental exposures and brain health and inform the development of more effective strategies for prevention, diagnosis, and treatment.

3.4. Results of the Systematic Analysis

After analyzing and processing the results of the bibliometric information, a summary matrix of the results is obtained in Table 1.

Table 1. Summary matrix of results of the review of original articles for systematic analysis.

N°	Journal	Quartile	Author	Year	Title	Country	Population Study	Methodology	Ref.
1	*NeuroToxicology*	Q2	Van Dyke et al.	2020	Association between aluminum in drinking water and incident Alzheimer's disease in the Canadian Study of Health and Aging cohort	Canada	Persons aged 65 years or older n = 10,263	Analysis of Canadian Study of Health and Aging (CSHA) cohort	[38]
2	*Exposure and Health*	Q1	Ahmed et al.	2019	Non-Carcinogenic Health Risk Assessment of Aluminium Ingestion via Drinking Water in Malaysia	Malaysia	46 water samples 402 household surveys	Physical–chemical analysis. Health risk assessment	[39]
3	*Environmental Geochemistry and Health*	Q1	Cabral Pinto et al.	2017	Human predisposition to cognitive impairment and its relation with environmental exposure to potentially toxic elements	Netherlands	103 permanent residents of Estarreja city (>55 years)	Neuropsychological evaluation and urine/water analysis	[40]
4	*Neuroscience Letters*	Q2	Wang et al.	2016	Chronic exposure to aluminum and risk of Alzheimer's disease: A meta-analysis	China	8 cohort and case–control studies (10,567 individuals)	Meta-analysis	[41]
5	*Bulletin of Environmental Contamination and Toxicology*	Q2	Ferreira et al.	2009	Aluminum Concentrations in Water of Elderly People's Houses and Retirement Homes and Its Relation with Elderly Health	Brazil	46 water samples from kitchen taps	Atomic absorption spectrophotometry	[42]
6	*American Journal of Epidemiology*	Q1	Rondeau et al.	2008	Aluminum and silica in drinking water and risk of Alzheimer's disease or cognitive decline: Findings from 15-year follow-up of the PAQUID cohort	France	1925 subjects free of dementia	PAQUID prospective cohort study	[13]
7	*Journal of Toxicology and Environmental Health—Part A: Current Issues*	Q3	Molloy et al.	2007	Effects of Acute Exposure to Aluminum on Cognition in Humans	United Kingdom	10 AD patients (76 ± 6 years) 16 men (54 ± 23 years) 21 women (55 ± 24 years)	Neuropsychological tests and crossover placebo-controlled trial	[43]
8	*American Journal of Clinical Nutrition*	Q1	Gillete-Guyonnet et al.	2005	Cognitive impairment and composition of drinking water in women: findings from the EPIDOS study	United States	7598 women aged 75 years in 5 areas of France	Short Portable Mental Status Questionnaire (SPMSQ)	[22]
9	*Cadernos de Saudé Pública*	Q2	Freitas et al.	2001	The importance of water analysis for public health in two regions of Rio de Janeiro State: a focus on fecal coliforms nitrate and aluminum	Brazil	46 water samples	Sample analysis	[44]
10	*American Journal of Epidemiology*	Q1	Rondeau et al.	2000	Relation between Aluminum Concentrations in Drinking Water and Alzheimer's Disease: An 8-year Follow-up Study	France	3777 people aged $\geq$65 years in 75 parishes	Home interview and standardized questionnaire	[23]
11	*Environmental Research*	Q1	Gauthier et al.	2000	Aluminum forms in drinking water and risk of Alzheimer's disease	United States	68 residents aged $\geq$70 years in Saguenay-Lac-Saint-Jean region	Extrapolation of historical data and standard analytical protocols	[16]
12	*Epidemiology*	Q1	Martyn et al.	1997	Aluminum Concentrations in Drinking Water and Risk of Alzheimer's Disease	United States	106 men with AD 99 men with other dementias 226 men with brain cancer 441 men with other nervous system diseases	Patient/family surveys and CT scan records	[45]

Table 1. *Cont.*

N°	Journal	Quartile	Author	Year	Title	Country	Population Study	Methodology	Ref.
13	*Neurology*	Q1	McLachlan et al.	1996	Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories	Canada	830 individuals at time of death in Ontario	Neuropathological series and Ontario Drinking Water Surveillance Program	[17]
14	*Journal of Epidemiology and Community Health*	Q1	Forbes & McLachlan	1996	Further thoughts on the aluminum-Alzheimer's disease link	United KingdomCanada	Deceased groups from Newcastle UK and Ontario Canada	Analysis of water quality data from Drinking Water Surveillance Program	[46]
15	*American Journal of Epidemiology*	Q1	Jacqmin et al.	1994	Components of drinking water and risk of cognitive impairment in the elderly	United Kingdom	3777 French men and women aged ≥65 years	Survey and logistic regression	[18]
16	*International Archives of Occupational and Environmental Health*	Q2	Wettstein et al.	1991	Failure to find a relationship between mnestic skills of octogenarians and aluminum in drinking water	Switzerland	800 residents aged 81–85 years	Measurement of dementia rates via interview and serum/urinary aluminum via atomic absorption spectrophotometry	[20]
17	*Journal of Epidemiology and Community Health*		Frecker	1991	Dementia in Newfoundland: identification of a geographical isolate?	United Kingdom	Newfoundland inhabitants who died in 1985–1986 aged >70 years	Statistical analysis	[47]
18	*Environmental Geochemistry and Health*	Q1	Martin	1990	Aluminium and Alzheimer's disease: an epidemiological approach	Netherlands	Sample of 200 death certificates	Epidemiological method	[21]
19	*Environmental Geochemistry and Health*	Q1	Houeland	1990	Aluminium and Alzheimer's disease: is there a causal connection?	Netherlands	Autopsy of 25 AD patients and 25 controls aged 65–80 years Study of 100 living AD patients aged 65–80 years	Bradford Hill criteria	[48]
20	*The Lancet*	Q1	Martyn et al.	1989	Geographical relation between Alzheimer's disease and aluminium in drinking water	United Kingdom	Survey of 88 county districts in England and Wales	Surveys CT scan records and analytical methods for measuring aluminum concentration in water over 10 years	[19]

4. Systematic Review Discussion

Recent years have witnessed extensive research on the potential association between aluminum intake through drinking water and the risk of developing AD. These studies have analyzed this relationship and provided data on the potential impacts of aluminum on human health, as summarized in Figure 8.

Van Dyke et al. reported no overall association between aluminum concentrations in drinking water and the risk of AD. However, the authors emphasized the need for further research, recommending that future studies should measure individual species of aluminum present in drinking water, as the specific form of aluminum exposure may be significant [38].

A long-term study conducted by Rondeau et al. investigated the impact of aluminum and silica presence in drinking water on the risk of dementia and AD. However, this study did not find conclusive evidence supporting a significant association between aluminum exposure and the risk of developing dementia or AD [23].

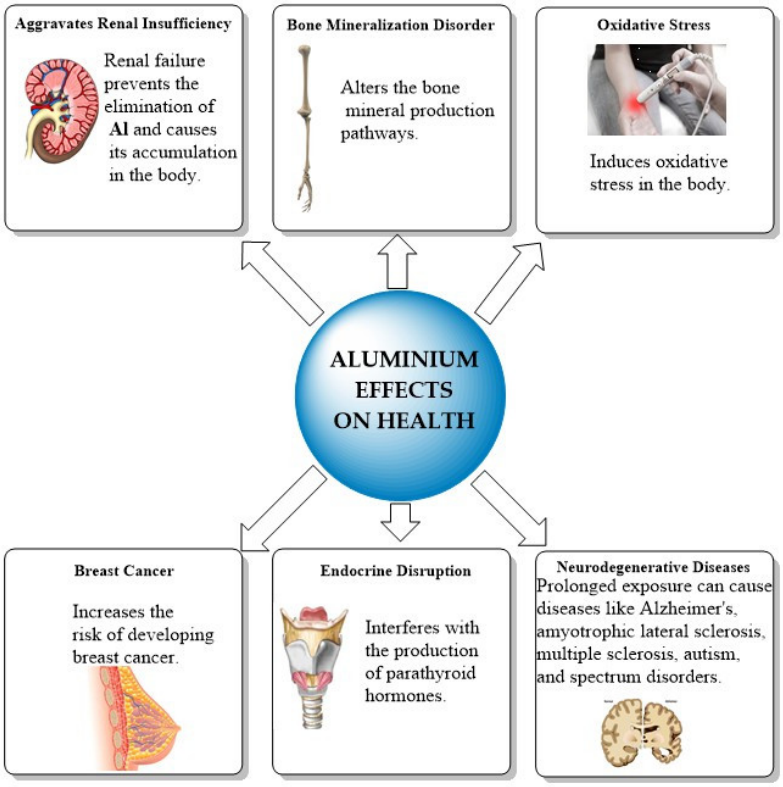


Figure 8. Potential relationships between aluminum exposure and various human health effects.

Freitas et al. highlighted the relevance of evaluating water quality with respect to public health, focusing on the detection of fecal coliforms, nitrate, and aluminum in two areas of the Rio de Janeiro region. Although the relationship between aluminum deposits in the brain and the development of AD remains under investigation, this research underscores the importance of monitoring aluminum presence in drinking water supplies [44].

Ferreira recommended that exposure to metals, particularly aluminum, through water consumption should be included in the agenda of public entities focused on reducing exposure of older people, who are considered vulnerable individuals [42].

Several investigations have examined the presence of aluminum in the brains of individuals suffering from AD [49,50]. These studies have identified aluminum in amyloid fibers and senile plaques, suggesting a possible role of aluminum in the development of AD.

In a long-term cohort study, Rondeau et al. investigated the relationship between exposure to aluminum and silica through water consumption and the risk of cognitive decline, dementia, and AD. The study revealed a positive correlation between aluminum exposure and the risk of cognitive decline and AD in elderly individuals [13]. The Aluminum as a Risk Factor theory proposed by Lidsky has been a focus of research attention, although most researchers have been gradually abandoning this hypothesis [51].

A systematic review conducted by Willhite et al. explored the potential health risks associated with exposure to aluminum and its compounds. This review emphasized the importance of conducting further research on the effects of aluminum exposure on the central nervous system, including assessing the risk of neurodegenerative diseases such as AD [8].

Exley and Vickers emphasized the role of human exposure to aluminum in the development of neurodegenerative diseases, including AD. This study evaluated the challenges that arise when questioning the aluminum industry, considering its economic and political implications. Walton applied Sir Austin Bradford Hill's causality criteria to investigate the relationship between chronic aluminum intake and its link to AD, highlighting the

widespread use of aluminum additives in processed foods and aluminum compounds in water treatment processes [12].

Echeverry et al. conducted a health risk assessment for a community in Cali, Colombia, due to exposure to lead, cadmium, mercury, 2-4D, and diuron through the consumption of drinking water and food. Results derived from models developed by the United States Environmental Protection Agency indicated the presence of potential health risks related to exposure to these contaminants [52].

Tchernitchin and Gaete investigated the impact of contaminants on human gestation and its connection with diseases that develop in adulthood. The authors suggested that increasing knowledge about environmental factors and improving population education could contribute to the better protection of pregnant and lactating women [53].

Wang found that women may be at higher risk due to biological differences, psychosocial, and cultural factors, suggesting that gender may influence the connection between aluminum exposure and the likelihood of developing AD [54].

Torres-Lozada et al. emphasized that conventional water treatment processes can lead to the formation of residues that include aluminum, which must be managed appropriately to prevent harmful consequences for the environment and public health [55].

Badaró et al. evaluated the levels of trihalomethane compounds present in drinking water, identified as carcinogenic compounds. However, this study did not specifically address the connection between the presence of aluminum in drinking water and AD [56].

Pastrana-Pacho et al. noted a lack of consensus on the effects of chronic exposure to aluminum through drinking water consumption on the development of AD, despite the widespread use of aluminum salts in water purification as coagulants [57].

Several key epidemiological studies have contributed significantly to our understanding of the potential link between aluminum exposure through drinking water and AD. Rondeau et al. (2000) conducted an 8-year follow-up study of the PAQUID cohort, finding that individuals exposed to aluminum concentrations >0.1 mg/L had a relative risk of 2.14 (95% CI: 1.21–3.80) for developing AD. This study suggested that long-term exposure to even relatively low levels of aluminum might increase risk [23].

Contrarily, Martyn et al. (1997) found no significant association between aluminum concentrations in drinking water and risk of AD in their case–control study (OR = 0.98, 95% CI: 0.69–1.41). However, they noted limitations in exposure assessment, as they relied on residential histories to estimate long-term aluminum exposure [45].

The potential mechanisms by which aluminum might contribute to AD pathology remain under investigation. Animal studies by Walton (2013) suggested that chronic aluminum exposure could promote beta-amyloid aggregation and tau hyperphosphorylation, key pathological features of AD [12]. In vitro studies have shown that aluminum can induce conformational changes in beta-amyloid, enhancing its aggregation propensity [9]. However, the relevance of these findings to human exposure levels is still debated, as the aluminum concentrations used in many experimental studies are often higher than those typically found in drinking water.

The systematic review of the literature on the relationship between aluminum in drinking water and AD risk has identified several key areas where further research is needed, listed as follows:

- Large-scale, long-term epidemiological studies with robust exposure assessment methods and standardized diagnostic criteria for AD to better characterize the nature and magnitude of the relationship between aluminum exposure and disease risk;
- Studies that examine the potential interactions and synergies between aluminum and other environmental and genetic risk factors for AD, as well as the possible differences in susceptibility and exposure across different populations and geographic regions;
- Experimental studies to elucidate the potential mechanisms by which aluminum may contribute to AD pathology, and to determine the relevance of these mechanisms to human exposure levels and disease risk;

- Research on the effectiveness and feasibility of different interventions and strategies to reduce aluminum exposure through drinking water, including regulatory measures, water treatment technologies, and public education and behavior change programs.

In addition to these research priorities, the systematic review has also identified the following important gaps and limitations in the current evidence base, which should be addressed in future studies:

- The need for more consistent and standardized methods for assessing aluminum exposure through drinking water, including the use of biomarkers and the consideration of other potential sources of exposure (e.g., food, medications, occupational exposures);
- The need for better control of potential confounding factors in epidemiological studies, including age, gender, education, socioeconomic status, and other known risk factors for AD;
- The need for more comprehensive and integrative research approaches that consider the complex interplay between environmental exposures, genetic susceptibility, and other biological and social determinants of health;
- The need for more effective communication and translation of research findings to policy makers, public health practitioners, and the general public, to inform evidence-based decision making and to promote informed choice and behavior change.

These conflicting results highlight the complexity of establishing a causal relationship and the need for improved exposure assessment methods. Gaps in current research include the need for longitudinal studies with more accurate exposure assessment, investigation of potential gene–environment interactions, and elucidation of the specific mechanisms by which low-level, chronic aluminum exposure might influence neurodegenerative processes.

In general terms, the connection between aluminum exposure through water consumption and the probability of developing AD remains a subject of ongoing discussion. While certain studies have identified links between aluminum exposure and decreased cognitive function or the onset of AD, current evidence is insufficient to reach a definitive conclusion. Additional research is needed to obtain a more comprehensive understanding of the potential risks and mechanisms involved in this relationship.

5. Conclusions

The systematic review and bibliometric analysis conducted in this study highlight the complex and controversial nature of the potential link between aluminum exposure through drinking water and AD risk. While some studies suggest a possible association, current evidence remains insufficient to establish a causal relationship or to draw definitive conclusions about the magnitude and nature of the risk.

Our analysis revealed that 60% of the systematically reviewed studies reported a positive association between aluminum exposure in drinking water and increased AD risk. However, only 25% of these were large-scale epidemiological investigations with robust methodologies, underscoring the need for more rigorous research in this area.

The inconsistencies in findings across studies may be attributed to various factors, including differences in study design, exposure assessment methods, and the multifactorial nature of AD etiology. Future research should focus on addressing these limitations through the following:

- Large-scale, longitudinal studies with improved exposure assessment techniques;
- The investigation of potential gene–environment interactions;
- The elucidation of specific mechanisms by which low-level, chronic aluminum exposure might influence neurodegenerative processes;
- Consideration of co-exposures and confounding factors.

While evidence does not currently support definitive public health recommendations regarding aluminum exposure through drinking water, a precautionary approach may be warranted. This could involve the continued monitoring of aluminum levels in drinking

water, further research into water treatment technologies that minimize aluminum residuals, and public education about potential risks and mitigation strategies.

The relationship between aluminum exposure through drinking water and AD risk remains an important area of scientific inquiry with significant public health implications. Addressing this complex issue will require a multidisciplinary approach, integrating insights from environmental science, toxicology, epidemiology, and neurobiology. As our understanding evolves, it will be crucial to effectively communicate findings to policymakers and the public, ensuring that any interventions or policy decisions are based on the best available evidence.

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