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Air pollution: a latent key driving force of dementia

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Abstract

Many researchers have studied the role of air pollutants on cognitive function, changes in brain structure, and occurrence of dementia. Due to the wide range of studies and often contradictory results, the present systematic review was conducted to try and clarify the relationship between air pollutants and dementia. To identify studies for this review, a systematic search was conducted in Scopus, PubMed, and Web of Science databases (without historical restrictions) until May 22, 2023. The PECO statement was created to clarify the research question, and articles that did not meet the criteria of this statement were excluded. In this review, animal studies, laboratory studies, books, review articles, conference papers and letters to the editors were avoided. Also, studies focused on the effect of air pollutants on cellular and biochemical changes (without investigating dementia) were also excluded. A quality assessment was done according to the type of design of each article, using the checklist developed by the Joanna Briggs Institute (JBI). Finally, selected studies were reviewed and discussed in terms of Alzheimer's dementia and non-Alzheimer's dementia. We identified 14,924 articles through a systematic search in databases, and after comprehensive reviews, 53 articles were found to be eligible for inclusion in the current systematic review. The results showed that chronic exposure to higher levels of air pollutants was associated with adverse effects on cognitive abilities and the presence of dementia. Studies strongly supported the negative effects of $PM_{2.5}$ and then NO_2 on the brain and the development of neurodegenerative disorders in old age. Because the onset of brain structural changes due to dementia begins decades before the onset of disease symptoms, and that exposure to air pollution is considered a modifiable risk factor, taking preventive measures to reduce air pollution and introducing behavioral interventions to reduce people's exposure to pollutants is advisable.

Keywords Vascular dementia, Non-Alzheimer dementia, Air pollution, Dementia, Elderly, Alzheimer

Introduction

Technological development and the rapid expansion of mechanization during the last few decades have led to an increase in life expectancy in various societies, especially in developed countries [1]. An increase in the life expectancy can lead to the growth of neurological disorders [2]. According to statistics published worldwide, neurological disorders, including Parkinson's (PD), cognitive dysfunction, Alzheimer's (AD) and dementia, are a leading cause of disability and death [3, 4]. Cognitive function also diminishes with age [5] and therefore, elderly people are disproportionately affected by cognitive disorders and, finally, dementia [6, 7] which imposes

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a significant burden on health care systems. According to statistics published by the World Health Organization (WHO), approximately 55 million people worldwide suffered from dementia in 2019, which is estimated to more than double in 2050 [8]. Dementia is the cause of 2.4 million deaths and 28.8 million disability-adjusted life years (DALYs) in 2016 and is known as the third cause of neurological DALYs [3, 9].

Various factors are involved in dementia, including anthropometric parameters (for example, body mass index), the APOE Ɛ4 allele [10], lack of weight [11], inactivity [12], non-Mediterranean diet [13], and the lack of specific micronutrients and macronutrients [14]. In addition, many epidemiological studies have shown that exposure to air pollution can also contribute to neuropathology through oxidative stress, hyperactivation of microglia, disruption of the blood–brain barrier (BBB) and neuroinflammation [15, 16] and cause adverse effects on the brain, accelerate cognitive aging and even increase the occurrence of AD and other forms of dementia [17–19]. The 2020 Lancet Commission on dementia prevention, intervention and care, considered air pollution as a new modifiable risk factor for dementia, accounting for about 2% of cases worldwide [20]. Studies conducted in the United Kingdom showed that an increase of 1 $\mu g/m^3$ $PM_{2.5}$ (particles with a diameter of 2.5 µm or less) increases the risk of dementia by 6% and the risk of AD by 10% [21]. Mortamais et al. (2021) found that an increase of 5$\mu g/m^3$ in $PM_{2.5}$ level, increases 20% the risk for all-cause dementia, 20% for AD and 33% for Vascular Dementia (VaD) in elderly people over 70 years [22]. However, the adverse effects of air pollution on cognitive function are not limited to old age. Recent epidemiological studies support the hypothesis that public exposure to air pollutants can cause structural and functional changes in children's brains [23, 24] and by causing negative effects on neuropsychological development, make them susceptible to neurological disorders in middle and old age [25, 26].

Therefore, prevention of exposure to air pollution is a potentially correctable risk factor in the occurrence of cognitive decline and dementia in the elderly. The present systematic review was conducted to critically examine the published scientific literature related to the impact of exposure to air pollution on dementia. Specifically, the objectives were: (1) to evaluate the type and concentration of air pollutants including PM_{10} (particles with a diameter of 10 µm or less), $PM_{2.5}$, NO_2, O_3, black carbon (BC), polycyclic aromatic hydrocarbons (PAHs), benzene, toluene, ethylbenzene and xylenes (BTEX), formaldehyde (FA) in geographic areas and (2) to assess the risk of dementia in adults with chronic respiratory exposure to the mentioned pollutants.

Methods

Protocol

This systematic review was guided by the PRISMA statement (Preferred Reporting Items for Systematic Review and Meta-analyses) and fully complied with the protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023413916).

PECO statement

In this study, the PECO (population, exposure, comparator, and outcome) [27] statement was used to develop the research question, search terms, and inclusion and exclusion criteria of the systematic review. Table 1 shows the PECO statement for understanding the adverse effects of respiratory exposure to pollutants PM_{10}, $PM_{2.5}$, NO_2, O_3, BC, PAHs, BTEX, and FA on dementia.

Search strategy and selection of studies

According to our knowledge, this is the first systematic review that investigated the effect of respiratory exposure to pollutants i.e. PM_{10}, $PM_{2.5}$, NO_2, O_3, BC, PAHs, BTEX, and FA on dementia. To obtain all published studies in this field, a systematic search was conducted in Scopus, PubMed, and Web of Science databases, without a date limit until May 22, 2023. The keywords used in this study include the following (the details of the search strategy used for the systematic search in the databases are shown in Appendix A1):

Table 1 PECO (Population, Exposure, Comparator, and Outcome) Statement

PECO	Evidence
Population	All adults who have suffered from dementia due to chronic exposure to air pollutants
Exposure	Chronic respiratory exposure to PM_{10}, $PM_{2.5}$, NO_2, O_3, BC, PAHs, BTEX, and FA
Comparator	Comparison of the adverse effects caused by the chronic exposure of adults to different levels of pollutants on the occurrence and type of dementia
Outcome	Occurrence and progress of types of dementia caused by chronic respiratory exposure to air pollutants

- Exposure to pollutants: "air pollution", "PM_{10}", "$PM_{2.5}$", "nitrogen dioxide", "ozone", "black carbon", "diesel", "diesel exhaust", "PAH*", "BTEX", "toluene", "ethylbenzene", "xylene", "benzene", "formaldehyde", "formal", "formalin", "methanol", "methylene oxide"
- Outcomes of exposure: "Alzheimer's disease", "Neuromarker", "Neuroinflammation", "Dementia", "Vascular dementia", "Frontotemporal dementia", "Frontotemporal lobar degeneration", "Lewy body disease", "Lewy body dementia"

The mentioned keywords were extracted by (M.M and A.H.Kh) and systematically searched by (A.H.Kh) in Title/Abstract and Mesh (if any). After merging the studies in EndNote X20 software, all duplicates were removed and the data were independently screened and extracted by two researchers (M.M and A.H.Kh). More contradictions and ambiguities were resolved with the intervention of the third author (J.G). In addition, to obtain additional studies that meet the inclusion criteria, additional to the hand searching, the reference list of selected studies was also systematically searched in parallel.

Criteria of entering and extracting studies

In this review, we excluded studies focused on the effects of exposure to air pollutants on neurological and biochemical changes (without examining dementia) and studies that investigated exposure to air pollutants as a dependent variable. Animal studies, laboratory studies, books, review articles, conference papers, and letters to the editors were also excluded. In this systematic review, only original peer-reviewed articles in English were reviewed.

Finally, the following information was extracted from the selected articles:

Authors, the year of publication, study design, country, the number of sample people, the age range of people, gender, the type of pollutant, the mean concentration of pollutant, diagnosis tool, and the type of dementia.

Quality control

The quality of the selected studies was checked by two researchers (M.M and A.H.Kh) using the Joanna Briggs Institute (JBI) checklist for cohort studies, case–control studies and analytical cross-sectional studies, independently. This checklist evaluates the risk of bias in studies by asking 2 questions from each of the sample areas including selection criteria, exposure assessment, confounding factors and results and appropriate statistical analysis. The defined answers for each question can be one of the options (yes, no, unclear, or not applicable). According to the total selection percentage of each of the 4 mentioned answers, the quality of articles is determined in the following 3 levels:

- High-quality level and low risk of bias (Q1) (Yes ≥ 50–75%).
- Moderate quality level and unclear risk of bias (Q2) (unclear ≥ 50–75%).
- Low-quality and high risk of bias (Q3) (No ≥ 50–75%) [28].

All the articles that were of adequate quality were included in the study.

Result synthesis

Due to heterogeneity in study design, exposure (occupational/environmental) and the age of subjects, quantitative synthesis of studies in the form of meta-analysis was not possible. Therefore, the results obtained from the selected studies, which included the type of dementia, the age of the subjects, gender, the type of air pollutants, mean concentration, the instrument for detecting pollutants, and the diagnosis of dementia, and the outcome of exposure (Appendix A2), were narratively combined. This synthesis was done in two steps. The first stage included the initial synthesis using the general grouping of studies based on Alzheimer's and non-Alzheimer's dementia; therefore, the results of articles were carefully studied, and considered which of the types of Alzheimer's dementia (AD) (Appendix A2) and non-Alzheimer's dementia (VaD, FTD and PD) (Appendix A3) have been investigated. In the second step, the relationship between the type and concentration of each pollutant in dementia was investigated.

Figure 1 shows the process of conducting the present systematic review by the members of the research team, which includes six general steps:

Topic selection, systematic search, screening and data extraction, quality control, resolving contradictions and ambiguities, and synthesis of results.

Results and Discussion

Selection process and characteristics of articles

In this review, 14,924 articles were obtained through a systematic search in databases, of which 4532 studies were retrieved from PubMed, 5878 from Scopus, and 4514 from Web of Science. After entering the articles into EndNote X20 software, 6546 duplicates were removed and 8378 studies were screened for title and abstract. At this stage, 8289 articles were excluded and the entry and exit criteria and quality assessment were done for 88 full texts. Finally, after conducting additional reviews, 36 studies were excluded for the following reasons:

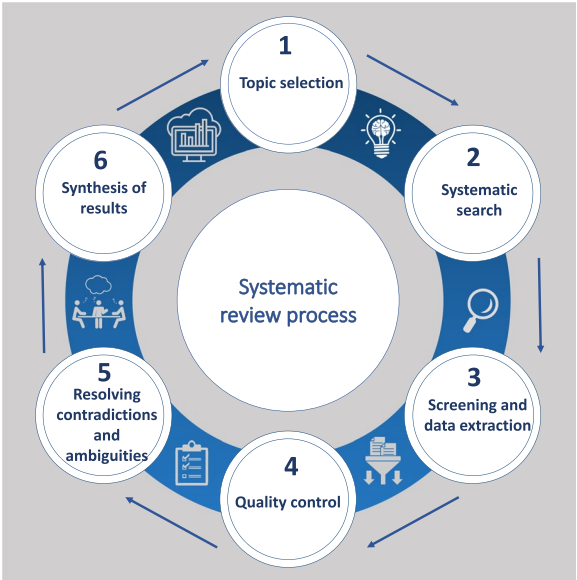

Fig. 1 Visualization of the systematic review guiding process comprising eight distinct stages

Nine studies were review articles, two studies only investigated brain volume, in twelve articles the type of air pollutant was not specified, five studies investigated the effect of other pollutants on dementia, five studies were excluded due to the high risk of bias and access to three full texts was not possible.

In addition, hand searching and systematic search of the selected articles' reference lists were also conducted to identify additional studies eligible for inclusion, which led to the identification of two studies through reference checking. Therefore, the total number of studies included in this systematic review increased to 53 articles (Fig. 2).

The studies in this systematic review included 6 case–control [29–34], 7 cross-sectional [19, 35–40], and 40 cohort studies [1, 2, 18, 21, 22, 41–75]. Specifically, selected studies have been conducted in 17 countries around the world:

19 in the United States of America, 7 in Sweden, 7 in Taiwan, 4 in Canada, 3 in France, 2 in Australia, 2 in Germany, 2 in Hong Kong, 2 in Mexico, 2 in the United Kingdom, 1 in each country of Netherlands, Spain, China, Denmark, England, Italy, and the Republic of Korea.

In total, 173,698,774 subjects were contained in the studies examined in this systematic review. The characteristics of the reviewed studies are shown in Table 2.

Diagnostic methods in the types of dementia

When we examined the 53 selected studies, 39 diagnostic tools and methods for AD and other types of dementia had been used (Appendix A2 and A3); of these, 21 diagnostic tools were used for Alzheimer's dementia and 28 methods for non-Alzheimer's dementia. According to the investigations carried out in studies related to Alzheimer's dementia, the methods of medical records ($N=11$) and Mini-Mental Status Examination (MMSE) ($N=8$) were the most prevalent. Five studies also used medical imaging (such as MRI and CT scan) to investigate the changes made in brain structures, which indicate the onset of Alzheimer's disease. In addition, the most common diagnostic tools for non-Alzheimer's dementia were included medical reports ($N=4$), MMSE ($N=10$), Medical imaging ($N=4$), Clinical Dementia Rating Sum of Box (CDR-SB) ($N=4$), and the Montreal Cognitive Assessment (MoCA) ($N=3$).

MMSE and MoCA are among the most important reliable screening tools that are widely used for clinical and research purposes [76, 77]. These tools have received a lot of attention due to the need for little training, ease of implementation, and the ability to differentiate dementia patients from healthy people [78–80]. MMSE is also widely used to describe a wide range of cognitive functions, including attention, memory, verbal ability, and visual-spatial cognitive function [81], and its total score is related to disease progression [82]. However, it has been found that the MMSE may be less reliable than the MoCA in the diagnosis of mild cognitive impairment (MCI) because this instrument had lower sensitivity among multiple study settings [83–87]. In addition, the MoCA can show differences in the cognitive profile of people diagnosed with MMSE in the normal range, which makes the MoCA a powerful, concise, and useful tool [77, 88, 89].

Although the use of questionnaire methods is a standard requirement for dementia researchers, the importance of medical imaging methods in diagnosing dementia types with high certainty should not be neglected to investigate the changes made in the brain structure and the speed of disease progression. Among the most important diagnostic imaging tools for dementia are PET imaging with 2-deoxy-positron emission tomography (PiB-PET), 2 [18F] fluoro-D-glucose tracer (FDG-PET) and Structural and Functional Magnetic Resonance Imaging (MRI) [90]. The first PET technique used to diagnose neurodegenerative disorders was 18F-fluorodeoxyglucose (18F-FDG) metabolic imaging, which is a measure of neuronal or synaptic integrity [91, 92]. More recent advances using PET includes the detection of specific neural ligands, such as specific ligands for fibrillar Aβ [93], paired-helical filament tau [94, 95], and synaptic vesicle protein 2A [96]. The PET technique, however, is only available in specialized centers due to its high cost.

In our systematic review, the main neuroimaging technique used was MRI. This tool can measure brain

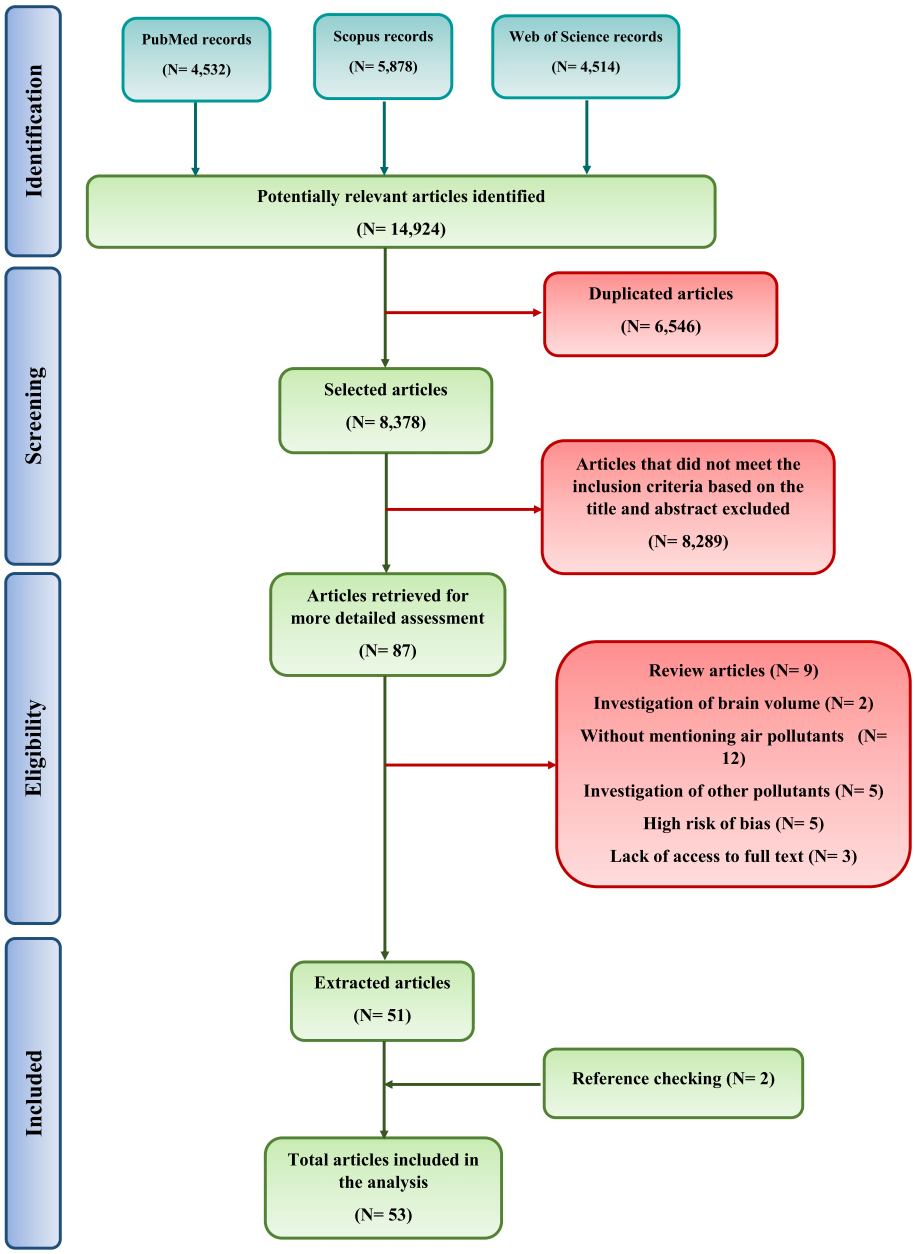

Fig. 2 PRISMA flow diagram of the literature search

atrophy, especially in the mesial-temporal structures, and detect it even before appearing the first clinical symptoms [97, 98]. This method is included in both the diagnostic criteria presented by Dubois [99] and NIA-AA [100] and has been used as a reliable diagnostic tool by many researchers [101–103]. The sensitivity of this method as an AD marker has been reported to be more than 85% [97], which is more than PiB-PET (70%) [104] and FDG-PET (80%) [105, 106].

Atrophy in the medial temporal lobe, especially the hippocampus, and a decrease in the thickness of the cerebral cortex in vulnerable areas of AD are among the first signs detectable by MRI in the early stages of the disease [107–109]. This tool can show hippocampal volume reduction 2 to 3 years before the onset of dementia in asymptomatic carriers of APP mutations [110] and in elderly people up to 6 years before that [103, 107]. In addition, entorhinal cortex volume reduction, which

Table 2 Characteristics of selected studies

First Author	Title	study design	Country (city)	N
Walter A. Kukull (1995) [29]	Solvent Exposure as a Risk Factor for Alzheimer's Disease: A Case Control Study	Case–Control	USA (Seattle)	Case: 193 Control: 243 Total: 436
Ulrich Ranft (2009) [41]	Long-term exposure to traffic-related particulate matter impairs cognitive function in the elderly	Cohort	Germany (Ruhr)	402
Kuang-Hsi Chang (2014) [42]	Increased Risk of Dementia in Patients Exposed to Nitrogen Dioxide and Carbon Monoxide: A Population-Based Retrospective Cohort Study	Cohort	Taiwan (Taichung)	29,547
Yun-Chun Wu (2015) [30]	Association between air pollutants and dementia risk in the elderly	Case–control	Taiwan (Taipei)	Case: 374 Control: 497 Total: 871
Chau-Ren Jung (2015) [43]	Ozone, Particulate Matter, and Newly Diagnosed Alzheimer's Disease: A Population-Based Cohort Study in Taiwan	Cohort	Taiwan (National)	95,690
Anna Oudin (2016) [44]	Traffic-Related Air Pollution and Dementia Incidence in Northern Sweden: A Longitudinal Study	Cohort	Sweden (Umeå)	1,806
Hong Chen (2017) [45]	Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study	Cohort	Canada (Ontario)	2,066,639
Dante Roger Culqui (2017) [46]	Association between environmental factors and emergency hospital admissions due to Alzheimer's disease in Madrid	Cohort	Spain (Madrid)	3,287
Jiu-Chiuan Chen (2017) [47]	Particulate Air Pollutants, Brain Structure, and Neurocognitive Disorders in Older Women	Cohort	USA (National)	1,403
John Andersson (2018) [48]	Road traffic noise, air pollution, and risk of dementia – results from the Betula project	Cohort	Sweden (Umeå)	1,721
Anna Oudin (2018) [49]	Association between air pollution from residential wood burning and dementia incidence in a longitudinal study in Northern Sweden	Cohort	Sweden (Umeå)	1,806
Iain M Carey (2018) [21]	Are noise and air pollution related to the incidence of dementia? A cohort study in London, England	Cohort	England (London)	130,978
Chung-Yi Li (2019) [31]	Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan	Case–control	Taiwan (National)	Case: 831 Control: 3,324 Total: 4,155
Hyewon Lee (2019) [50]	Exposure to ambient fine particles and neuropsychiatric symptoms in cognitive disorder: A repeated measure analysis from the CREDOS (Clinical Research Center for Dementia of South Korea) study	Cohort	Republic of Korea (Seoul)	645
Ruo-Ling Li (2019) [51]	Influence of $PM_{2.5}$ Exposure Level on the Association between Alzheimer's Disease and Allergic Rhinitis: A National Population-Based Cohort Study	Cohort	Taiwan (National)	2,384
Francesco Cerza (2019) [52]	Long-term exposure to air pollution and hospitalization for dementia in the Rome longitudinal study	Cohort	Italy (Rome)	350,844
Anna Oudin (2019) [53]	Traffic-Related Air Pollution as a Risk Factor for Dementia: No Clear Modifying Effects of APOE 4 in the Betula Cohort	Cohort	Sweden (Umea)	1,567
Han-Wei Zhang (2019) [54]	Long-Term Exposure to Ambient Hydrocarbons Increases Dementia Risk in People Aged 50 Years and above in Taiwan	Cohort	Taiwan (National)	178,085

Table 2 (continued)

First Author	Title	study design	Country (city)	N
Marta Crous-Bou (2020) [1]	Impact of urban environmental exposures on cognitive performance and brain structure of healthy individuals at risk for Alzheimer's dementia	Cohort	Spain (Barcelona)	958
Liuhua Shi (2020) [2]	Long-term effects of $PM_{2.5}$ on neurological disorders in the American Medicare population: a longitudinal cohort study	Cohort	USA (National)	63,038,019
Audrey Smargiassi (2020) [55]	Exposure to ambient air pollutants and the onset of dementia in Quebec, Canada	Cohort	Canada (Quebec)	1,807,133
Sindana D Ilango (2020) [56]	The role of cardiovascular disease in the relationship between air pollution and incident dementia: a population-based cohort study	Cohort	Canada (Ontario)	34,391
Kimberly C. Paul (2020) [57]	Traffic-Related Air Pollution and Incident Dementia: Direct and Indirect Pathways Through Metabolic Dysfunction	Cohort	USA (National)	1,564
Weiran Yuchi (2020) [32]	Road proximity, air pollution, noise, green space and neurologic disease incidence: a population-based cohort study	Case–control	Canada (Metro Vancouver)	678,000
Marion Mortamais (2021) [22]	Long-term exposure to ambient air pollution and risk of dementia: Results of the prospective Three-City Study	Cohort	France (Dijon, Bordeaux, and Montpellier)	7,066
Jiping Tan (2021) [35]	Associations of particulate matter with dementia and mild cognitive impairment in China: A multicenter cross-sectional study	Cross-sectional	China (National)	7,040
Jinjun Ran (2021) [58]	Long-term exposure to fine particulate matter and dementia incidence: A cohort study in Hong Kong	Cohort	Hong Kong	59,349
Andrew J. Petkus (2021) [36]	Associations Between Air Pollution Exposure and Empirically Derived Profiles of Cognitive Performance in Older Women	Cross-sectional	USA	2,142
Rachel M.Shaffer (2021) [59]	Fine Particulate Matte rand Dementia Incidence in the Adult Changes in Thought Study	Cohort	USA (Seattle)	4,166
Sung Han Rhew (2021) [33]	Exposure to low-dose ambient fine particulate matter $PM_{2.5}$ and Alzheimer's disease, non-Alzheimer's dementia, and Parkinson's disease in North Carolina	Case–control	USA (North Carolina)	Case: 1,665,073 Control: 357,574 Total: 2,022,647
Diana Younan (2021) [60]	$PM_{2.5}$ Associated With Gray Matter Atrophy Reflecting Increased Alzheimer Risk in Older Women	Cohort	USA (48 states)	1,365
Maayan Yitshak-Sade (2021) [61]	$PM_{2.5}$ and Hospital Admissions Among Medicare Enrollees with Chronic Debilitating Brain Disorders	Cohort	USA (National)	30,079,287
Rachel M. Shaffer (2021) [62]	Fine Particulate Matter and Markers of Alzheimer's Disease Neuropathology at Autopsy in a Community-Based Cohort	Cohort	USA (National)	5,546
Kevin J Sullivan (2021) [63]	Ambient Fine Particulate Matter ($PM_{2.5}$) Exposure and Incident Mild Cognitive Impairment and Dementia	Cohort	USA (National)	2,735
Hedi Katre Kriit (2021) [64]	Annual dementia incidence and monetary burden attributable to fine particulate matter ($PM_{2.5}$) exposure in Sweden	Cohort	Sweden (National)	820

Table 2 (continued)

First Author	Title	study design	Country (city)	N
Liuhua Shi (2021) [65]	A national cohort study (2000–2018) of long-term air pollution exposure and incident dementia in older adults in the United States	Cohort	USA (National)	24,689,818
Feng Cheng Lin (2021) [34]	Air Pollution Is Associated with Cognitive Deterioration of Alzheimer's Disease	Case–control	Taiwan (Kaohsiung,Pingtung)	704
Jing Wu (2022) [66]	Air pollution as a risk factor for Cognitive Impairment no Dementia (CIND) and its progression to dementia: A longitudinal study	Cohort	Sweden (Stockholm)	1,987
Zorana J. Andersen (2022) [67]	Long-term exposure to air pollution and mortality from dementia, psychiatric disorders, and suicide in a large pooled European cohort: ELAPSE study	Cohort	Sweden, Denmark, France, Netherlands, Germany, Austria	271,720
ErinO. Semmens (2022) [37]	Air pollution and dementia in older adults in the Ginkgo Evaluation of Memory Study	Cross-sectional	USA (Winston, Hagerstown, Sacramento, Pittsburgh)	2,564
Lilian Calderón-Garcidueñas (2022) [38]	Metals, Nanoparticles, Particulate Matter, and Cognitive Decline	Cross-sectional	Mexico (Mexico City)	336
Diana Younan (2022) [68]	Racial/Ethnic Disparities in Alzheimer's Disease Risk: Role of Exposure to Ambient Fine Particles	Cohort	USA (24 states)	6485
Fan He (2022) [69]	Impact of air pollution exposure on the risk of Alzheimer's disease in China: A community-based cohort study	Cohort	China (Changshan, Haishu, Jingning, Tongxiang, Yuecheng, Yuhuan)	6,115
Dylan Wood (2022) [70]	Exposure to Ambient Air Pollution and the Incidence of Dementia in the Elderly of England: The ELSA Cohort	Cohort	UK (National)	8,525
Lilian Calderón-Garcidueñas (2022) [39]	Hemispheric Cortical, Cerebellar and Caudate Atrophy Associated to Cognitive Impairment in Metropolitan Mexico City Young Adults Exposed to Fine Particulate Matter Air Pollution	Cross-sectional	Mexico (Mexico City)	302
Cheng Chen (2022) [71]	B vitamin intakes modify the association between particulate air pollutants and incidence of all-cause dementia: Findings from the Women's Health Initiative Memory Study	Cohort	USA (National)	7,183
Noémie Letellier (2022) [72]	Air quality improvement and incident dementia: Effects of observed and hypothetical reductions in air pollutant using parametric g computation	Cohort	France (Bordeaux, Dijon, and Montpellier)	7,051
Zhenjiang Li (2022) [19]	Neighborhood characteristics as confounders and effect modifiers for the association between air pollution exposure and subjective cognitive functioning	Cross-sectional	USA (Atlanta)	12,058
Kimberly L. Parra (2022) [73]	Exposure to air pollution and risk of incident dementia in the UK Biobank	Cohort	UK (National)	187,194
Michelle L. Trevenen (2022) [74]	Ambient air pollution and risk of incident dementia in older men living in a region with relatively low concentrations of pollutants: The Health in Men Study	Cohort	Australia (Perth)	11,243
Daniel Mork (2023) [18]	Time-lagged relationships between a decade of air pollution exposure and first hospitalization with Alzheimer's disease and related dementias	Cohort	USA (National)	8,507,437

Table 2 (continued)

First Author	Title	study design	Country (city)	N
Liuhua Shi (2023) [75]	Incident dementia and long-term exposure to constituents of fine particle air pollution: A national cohort study in the United States	Cohort	USA (National)	37.7 million
Haisu Zhang (2023) [40]	Short-term associations between ambient air pollution and emergency department visits for Alzheimer's disease and related dementias	Cross-sectional	USA (California, Missouri, North Carolina, New Jersey, and New York)	1,595,783

progresses up to four years before cognitive decline, can be detected by MRI up to 90% [107].

Alzheimer's dementia

The characteristics and results extracted from the articles related to Alzheimer's dementia are shown in Appendix A2. Thirty-one studies investigated the effect of pollutants i.e. PM_{10}, $PM_{2.5}$, NO_2, O_3, BC, PAHs, BTEX, and FA on the occurrence of Alzheimer's dementia. These studies were published from 1995–2023, and most were since 2018, indicating the novelty of the subject under discussion. More than 80% of the studies investigated the incidence of Alzheimer's in people over 60 years old, but some studies included younger people, comprising Haisu Zhang (2023) [40], Lilian Calderón-Garcidueñas (2022) [38, 39], Marta Crous-Bou (2020) [1], Anna Oudin (2019 and 2016) [44, 53], and Ruo-Ling Li (2019) [51].

The results showed that chronic exposure to air pollutants, especially particulate matter (PMs), increases the number of hospitalizations due to the exacerbation of neurocognitive disorders caused by Alzheimer's dementia or related diseases. This finding is compatible with previous studies on the role of exposure to air pollutants on the development of this neurological disorder [18, 74, 75]. Results from human and animal studies have shown that air pollution is associated with atherosclerosis, increased blood inflammatory biomarkers, and oxidative stress, which may accelerate hospitalization for several neurological diseases [111, 112]. In the United Kingdom, the results of a population-based cohort study showed that the risk of AD was associated with exposure to $PM_{2.5}$ (adjusted hazard ratio—HR 1.10, 95% CI 1.02–1.18) and NO_2 (1.23, 1.07–1.43) increases significantly so that an increase of 1 $\mu g/m^3$ $PM_{2.5}$ is associated with a 10% increase in the risk of AD. Exposure to O_3 reduced this risk [21]. Also Cerza et al. (2019) in a cohort study in Italy concluded that a positive association between exposure to O_3 and NO_x and dementia hospitalizations, (O_3: HR = 1.06; 95% CI: 1.04–1.09 per 10 $\mu g/m^3$; NO_x: HR = 1.01; 95% CI: 1.00–1.02 per 20 $\mu g/m^3$) [52]. This study showed that exposure to NO_x, NO_2, $PM_{2.5}$, and PM_{10}, except for O_3, has a significant negative relationship with AD [52].

He et al. (2022) also demonstrated in a population-based cohort study in China that exposure to $PM_{2.5}$, PM_{10}, and CO pollutants was significantly associated with an increased risk of AD, but there is no significant relationship between exposure to NO and SO_2 with the occurrence of this disorder. This study also showed an inverse relationship between O_3 exposure and AD [69]. Meanwhile, Jung et al. (2015) concluded that for an increase of 9.63 ppb in O_3 concentration, the risk of AD increases 1.06 times in the elderly ≥ 65 years (adjusted HR 1.06, 1.00–1.12) [43]. The difference between the results of these studies can be caused by different characteristics in the study population, study design, sample size, setting, and different measurements of exposure to air pollutants.

In addition, the researchers found evidence of the adverse effect of exposure to air pollutants on episodic memory. Several animal studies showed that exposure to inhaled $PM_{2.5}$ can impair neural systems that underlie episodic memory processes [113–115]. So far, limited longitudinal epidemiological studies have been conducted about $PM_{2.5}$ and episodic memory in humans [116–118]. The results of a prospective study on 998 elderly women aged 73 to 87 years old in the US showed that chronic exposure to $PM_{2.5}$ in residential environments was associated with a rapid decline in episodic memory, especially in measures of immediate recall and learning of new material [68]. A decrease in verbal episodic memory (such as the ability to remember details, with context, from daily and distant experiences) is prominent in AD and can be detected in the preclinical stage [119, 120]. For example, impaired episodic memory is one of the main criteria for the classic diagnosis of AD by Dubois et al. (2007), which appears early in the course of the disease [99]. Studies have proven that the rapid decline of this memory is somewhat associated with an increase in the Alzheimer's disease pattern similarity (AD-PS) score [68]. AD-PS is a brain MRI-based structural biomarker that reflects high-dimensional gray matter atrophies in brain regions vulnerable to AD

neuropathology [68]. In addition to exposure to environmental factors, natural aging can also lead to a decrease in episodic memory, which is related to the decrease in the volume of the hippocampus and other structures of the medial temporal lobe [121]. The medial temporal lobe and its structural components, especially the hippocampus, play an important role in encoding (learning, recalling) and retrieving (recalling) the details of events that make up episodic memories [121].

Zhao et al. (2019) showed in a human imaging study that atrophy in hippocampal subfields can impose a wide range of effects on measures of episodic memory (immediate recalls, delayed-recalls, and recognition) [122]. Although so far the relative roles of hippocampal subfields (e.g. cornu ammonis (CA, CA2-3), CA4-denate gyrus, presubiculum, subiculum) have not been determined in the processes related to encoding and retrieval, animal studies have proven the adverse effects of PMs on the morphology and functional changes in hippocampal subfields. Also, we can mention the decrease in apical dendritic spine density and dendritic branches in the CA1 and CA3 regions [123], decrease in synaptic function in CA1 neurons [114, 124], decrease in basic protein in white matter, and increase in atrophy of neurites in the CA1 region [125]. Based on the studies, encoding is done by CA2, CA3, and dentate gyrus, while CA1 and subiculum are involved in retrieval [126]. According to the results obtained by Younan et al. (2020), it seems that the significant reduction of episodic memory processes (immediate recall/new learning) caused by exposure to $PM_{2.5}$ is more due to the adverse effects of this pollutant on hippocampal subfields associated with encoding, such as CA2, CA3, and dentate gyrus [68]. These neurotoxicological results indicate that some hippocampal subfields may be more sensitive to the adverse effects of particulate matter than other subfields.

So far, many studies have proven the existence of an inverse relationship between exposure to air pollutants and white matter volume, gray matter volume, and cerebral cortex thickness in brain areas affected by AD [127–130]. Wilker et al. (2015) showed in a study that with increasing $PM_{2.5}$ concentration, brain volume decreases by 0.32% [131], which was consistent with the results obtained by Chen et al. (2015) regarding the reduction of white matter volume and the volume of the whole brain due to exposure to high concentrations of this pollutant [128]. The results of the study by Crous-Bou et al. (2020) showed that chronic exposure to air pollutants, especially NO_2 and PM_{10}, is associated with a decrease in the thickness of the cerebral cortex in brain areas affected by AD [1], which is consistent with the results of study done by Casanova et al. (2016) [127]. In a voxel-based morphometry study, they examined the local brain structure related to PMs in elderly women and concluded that exposure to $PM_{2.5}$ has an inverse relationship with the reduction of the frontal cortex [127]. Furthermore, Cho et al. (2023) showed that a 10 $\mu g/m^3$ increase in ($\beta = -1.13$; 95% CI, −1.73 to −0.53) PM_{10} and a 10 ppb increase in ($\beta = -1.09$; 95% CI, −1.40 to −0.78) NO_2 are significantly associated with decreasing MoCA score. Also, these two pollutants were significantly associated with an increase in AD-like cortical atrophy scores and a decrease in the thickness of the cerebral cortex [129].

PET ligand studies indicate that gray matter atrophy of the brain can be caused by tau neuropathological processes, which can lead to cognitive decline in patients [132–134]. Several plausible biological mechanisms explain the rapid development or onset of neurological diseases caused by exposure to air pollution. After inhalation, air pollutants can pass through the BBB and enter the brain through the olfactory bulb or systemic circulation [135] causing oxidative stress and systemic inflammatory responses, disruption of the blood–brain barrier, deposition of peptides beta-amyloid (Aβ) and activation of microglia and as a result may exacerbate the disease progression of AD [136, 137]. In addition, it has been reported that NO_2 is associated with inflammatory responses and markers such as increased serum concentration of systemic interleukin IL-6 [138]. Recent studies have shown that exposure to air pollutants can be effective in causing neurological and cognitive disorders by contributing to AD pathologies such as brain Aβ and tau burden [139, 140]. Researchers use the levels of Aβ, total tau (t-tau) and phospho-tau (p-tau) in CSF as specific biomarkers for the clinical diagnosis of probable AD [99]. Some studies have proven that CSF Aβ, as the first marker of AD, shows abnormal levels several years before the appearance of impaired memory [141, 142]. Diagnosis of early AD in patients with mild cognitive impairment (MCI) can be done by detecting low levels of Aβ and high levels of p-tau and t-tau in CSF [143].

Reports show that living in areas with high air pollution can lead to the accumulation of Aβ in neurons and astrocytes [144]. Also, the results obtained from the study of Fu et al. (2022) indicate that the increase in the concentration of each unit of ln-transformed Σ-OH PAHs in the urine of coke oven workers was associated with an increase of 9.416 units of P-Tau231 in plasma and a decrease of 0.281 in visuospatial/executive function [145]. Tau is a microtubule-associated protein that contributes to the stability of axonal microtubules in the brain [146]. The presence of hyperphosphorylated tau leads to the formation of neurofibrillary tangles, which is considered a pathological characteristic of AD [147]. Some researchers have reported changes in the concentration of phosphorylated tau as a possible sign of the

progression of some neurological diseases [148, 149]. This is consistent with the results of Nie et al.'s (2013) study, which showed that benzo[a]pyrene (B[a]P) leads to tau 231 hyperphosphorylation [150].

Non-Alzheimer's dementia

Among the 53 selected articles, 41 studies investigated the effect of air pollutants on the incidence of non-Alzheimer's dementia (Appendix A3), which were published during the years 2014–2023. Except for the studies of Anna Oudin (2016) [44], Anna Oudin (2018) [49], Iain M Carey (2018) [21], Anna Oudin (2019) [53], Han-Wei Zhang (2019) [54], Zorana J. Andersen (2022) [67], Lilian Calderón-Garcidueñas (2022) [38, 39], and Haisu Zhang (2023) [40], the rest of the articles included people over the age of 60 years old.

Non-Alzheimer's dementia accounts for almost half of dementia cases [151]. The most common non-Alzheimer's neurological disorders include vascular dementia (VaD) [152, 153], Parkinson's disease (PD) [154], Fronto-Temporal Dementia (FTD) [155] and Dementia with Lewy Bodies (DLB) [92], which are characterized by the accumulation of natural proteins in the CNS, as proteinopathies [156].

Vascular Dementia

The present study showed that exposure to air pollutants may have a direct effect on the incidence and progression of VaD. In a longitudinal study, Oudin et al. (2016) concluded that the probability of VaD diagnosis, with HR = 1.43, was higher among citizens with the highest exposure to traffic-related air pollution than those with low exposure [44]. These results were consistent with the study conducted by Cerza et al. (2019) [52]. In a longitudinal study on elderly men and women in Italy, they reported that chronic exposure to NO_x, NO_2, PM_{10} and $PM_{2.5}$ has a positive relationship with VaD. In addition, a direct relationship between exposure to O_3 and NO_x with dementia hospitalization was also observed (O_3: HR = 1.06 per 10 μg/m^3; NO_x: HR = 1.01; per 20 μg/m^3) [52].

According to the studies, chronic exposure to air pollutants can cause vascular damage caused by large vessel atherosclerosis and small vessel arteriosclerosis and cause cortical and subcortical infarcts, sub-infarct ischemic lesions, and large and small cerebral hemorrhages [153, 157]. Researchers identify these factors as responsible for the initiation of VaD [153]. Moreover, dysfunction and degeneration of the neurovascular unit, which consists of a network of pericytes, myocytes, astrocytes, neurons, oligodendrocytes, endothelial cells and cerebral microvessels, aggravate the pathogenesis of VaD by disrupting the BBB [158]; which require hospital care to treat and prevent further side effects.

Also, the results obtained from a case–control study in Taiwan indicate that exposure to high levels of NO_2 significantly increases the risk of developing VaD [31]. According to the studies, some researchers showed that for an increase of 5 μg/m^3 NO_2, the risk of VaD increases by 1.62 [74]. However, some studies have reached contradictory results. A cohort study conducted in England estimated the prevalence of VaD among men and women aged 50–79 years old at 29%, but found little evidence of the effect of air pollution on this neurological disorder [21]. Differences in results could be due to differences in instruments used, study design, and sample population characteristics.

VaD is a pathological condition in the elderly characterized by progressive cognitive dysfunction and is the second most common form of dementia, after AD [159]. This disorder is manifested by the loss of rationality, judgment skills, and especially cognitive functions and memory, and patients usually survive only 5–7 years after its onset [160]. Multifactorial etiopathology, diverse clinical manifestations, and numerous clinical subgroups are among the characteristics of VaD [152]. Chronic reduction in cerebral blood flow is one of the main characteristics of this neurological disorder [161], which results in the departure of brain blood vessels from regulation. This causes functional damage to capillaries, arteries and venules and damage to myelinated axons, and by creating a lesion in the white matter, it starts the pathophysiological process of VaD [162]. Small vessel disease (leukoaraiosis and lacunar infarcts), microinfarcts, microhemorrhages, cerebral amyloid angiopathy, and mixed vascular lesions are among the most important debilitating lesions of VaD [163, 164]. In addition, chronic cerebral hypoperfusion (CCH) has been reported as the main cause of this type of dementia [163, 165]. The results obtained from the studies indicate that CCH is associated with both neurodegeneration and dementia [166, 167]. Studies have shown that exposure to PMs can increase CCH-induced white matter neurotoxicity by enhancing pathophysiology [168, 169]. In a recent epidemiological study, Chen et al. (2015) showed that exposure to $PM_{2.5}$ was associated with a decrease in regional white matter volume in the corpus callosum and frontal/temporal lobes of elderly women [128], which is consistent with the results of the study by Erickson et al. (2020) was matched [170]. In addition, experimental data obtained from animal studies showed that exposure to air pollutants, especially PMs, causes changes in myelin in the CA1 area of the hippocampus in rodents [171], which can increase the risk of developing neurological disorders and types of dementia.

Dementia due to Parkinson's disease

The results of the studies retrieved in this systematic review showed that dementia due to PD, a dementia that begins 1 year or more after well-established Parkinson's disease [92], can be considered as one of the adverse effects of exposure to air pollutants, especially PMs. Shi et al. (2020) in a national cohort study in the USA showed that for an annual increase of 5 $\mu g/m^3$ $PM_{2.5}$, the probability of the first hospital admission due to PD and other related dementias will increase by 1.13 times for the American Medicare population (HR = 1.13) [75]. In this regard, Yuchi et al. (2020) also obtained similar results [32]. In a population-based cohort study in Canada, they proved that exposure to air pollutants increases the risk of PD (HR for PMs = 1.09, HR for BC = 1.03, HR for NO_2 = 1.12), but no relationship was observed on the occurrence of AD [32]. These results were consistent with those obtained from the studies of Rhew et al. (2021) [33], Yitshak-Sade et al. (2021) [61] and Calderón-Garcidueñas et al. [39].

The studies have demonstrated that over 80% of individuals with Parkinson's disease develop dementia [172]. Generally, the point prevalence of dementia in patients with Parkinson's has been determined to be approximately 25%, which has a higher prevalence in men than in women [173]. Researchers have proven that the risk of dementia increased as the duration of the disease increased, so that this probability reached 50% 10 years after the diagnosis of Parkinson's [91]. Research indicates that dementia occurs in patients who survive for more than 10 years [93].

PD, containing Lewy bodies and Lewy neurites, is one of the common brain disorders associated with aging and is characterized by the accumulation of α-synuclein in intracellular inclusions [154]. The main pathological characteristic of PD is the progressive loss of nigrostriatal dopaminergic neurons in the substantia nigra pars compacta, which causes Parkinsonism in PD patients [174]. Parkinsonism is a clinical syndrome characterized by rest tremor, rigidity, bradykinesia and gait dysfunction with postural instability [174]. Neurological disorders such as progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), or FTD may overlap in their symptoms with PD [156]. Reports show that a significant number of people with PD suffer from cognitive impairment and PD dementia during their disease [172, 175]. In some cases, co-existing pathology of TDP-43 can also be detected in PD patients [176]. TDP-43 is a protein biomarker whose accumulation can diagnose and classify neurological disorders [177]. The available evidence indicates that exposure to air pollutants plays a role in the accumulation of this protein [178]. Neuropathological examination of 44 children (average age 12.89 ± 4.9 years old) and 159 young adults (average age 29.2 ± 6.8 years old) living in Mexico City showed that exposure to $PM_{2.5}$ and O_3 pollutants can cause AD and PD in 23% of people. Furthermore, it causes TDP-43 pathology in 18.7% of cases [179, 180], which is in line with the results of the present systematic review.

Fronto-Temporal Dementia

FTD is a group of neurodegenerative disorders and although clinically and pathologically heterogeneous, they mainly affect the frontal and/or temporal lobes of the brain [156, 181]. This type of dementia is usually characterized by predominant frontal or temporal atrophy, and atrophy in the fronto-polar region is considered a special symptom of FTD [182]. The main clinical manifestations of FTD include two types of behavioral variant (bvFTD) and primary progressive aphasia (PPA). BvFTD mainly leads to personality changes and behavioral problems; While PPA causes gradual deterioration in speech/language and has a lower prevalence than bvFTD [183]. Primary Parkinsonism is observed in more than 20% of patients with FTD, mostly in bvFTD patients, and then non-fluent variant primary progressive aphasia occurs [184]. Each of the mentioned stages can have an effective role in reducing people's lives and increasing the economic burden for health systems by creating FTD.

In the current review, only two studies investigated FTD. Parra et al. (2022) concluded in a national cohort in the UK that there was a strong association between exposure to $PM_{2.5}$, NO_2, and NO_x with the incidence of AD and VaD but not with FTD [73]. Meanwhile, Calderón-Garcidueñas et al. (2022) obtained completely contradictory results in the study of neurological disorders caused by exposure to $PM_{2.5}$ in young adults living in the metropolis of Mexico City [39]. They showed that chronic exposure to $PM_{2.5}$ higher than the values recommended by US-EPA causes a significant reduction of gray matter in higher-order cortical areas, which is usually associated with AD, PD and FTD in educated Mexicans [39]. The discrepancy in the results of these two studies can be explained by the difference in the number of cases, the age range of the cases, and the country under study.

Strengths and limitations of the study

Although several review studies related to exposure to air pollutants and the incidence of dementia have been published in recent years [135, 185–187], the present systematic review has several notable strengths that distinguish our study from other review studies. First, this study is the most up-to-date systematic review published related to the role of chronic exposure to air pollutants on dementia (Alzheimer's/Non-Alzheimer's).

Second, unlike other studies, we did not impose any restrictions on publication time [135], study design [185–187], and geographic scope [185] in the systematic search, which allowed us to find more studies and more comprehensive results. In addition, we tried to perform a systematic search in the largest and the most reliable databases to ensure the inclusion of all eligible studies. This resulted in the extraction of 53 related studies that met the inclusion criteria for the present review. However, our investigations showed that none of the recent review articles discussed the current number of studies [135, 185–187].

Third, due to the inclusion of an acceptable number of articles in the present systematic review, the results obtained from examining a substantial population of subjects, 173,698,774 people, were presented, which indicates the comprehensiveness and generalizability of the results of the present study.

Fourth, our study included types of dementia, such as Alzheimer's and non-Alzheimer's, and related dementias. This will help researchers to understand the impact of air pollution on each type of dementia and the action mechanism of pollutants in creating structural changes in the brain.

Fifth, in this study, in addition to criterion pollutants, other common and dangerous air pollutants, including FA, BTEX, and PAHs, were also investigated; these pollutants were not investigated in any of the published reviews.

However, the lack of access to the full texts of some studies and the examination of a limited number of pollutants were among the inevitable limitations of this systematic review.

Gaps and Recommendations

An in-depth review of published studies indicates the existence of some gaps in this important health field, including the lack of sufficient studies related to the role of air pollutants on FTD. As mentioned earlier, we could find only two studies related to the effect of exposure to $PM_{2.5}$, PM_{10}, NO_2, and NO_x on FTD [39, 73], which makes it impossible to compare the results with each other. Therefore, it is recommended that more researchers investigate the impact of exposure to different pollutants in diverse populations on FTD, to cover this important gap.

Moreover, the presence of various confounding factors can also be effective in achieving contradictory results in studies. Researchers believe that factors such as aging, early retirement, smoking, body mass index (BMI), alcohol consumption, and physical inactivity are among the confounding factors that can accelerate the process of dementia [66]. Also, studies have proven that co-morbidities, such as cardiovascular diseases, cerebrovascular disease, diabetes and mental health, environmental tobacco smoke (ETS), chronic exposure to noise, insufficient sleep, and unhealthy diet can also play an effective role in occurring or developing dementia at an older age [188]. Research has identified several potential socioeconomic factors that can influence the relationship between air pollution exposure and neurological outcomes at the individual and regional levels. Based on this, living in deprived neighborhoods and on the outskirts of cities increases the possibility of exposure to high levels of air pollution [189]. Studies have also shown that lower levels of education, and poor access to socioeconomic benefits, such as health care, are associated with an increased risk of dementia in the future [190, 191]. Therefore, it is necessary to consider strategies to control the impact of confounding factors to achieve more accurate results.

Also, due to the limited number of studies related to occupational exposure to pollutants in dementia, it is recommended to conduct more research to investigate occupational exposure in workers of different occupations and compare and analyze their results.

Since it has been proven that prenatal exposure is effective in the occurrence of some diseases in the future; therefore, it is recommended that cohort studies be designed and implemented to investigate the role of prenatal exposure to air pollutants and dementia at older ages.

Conclusion

The results of this systematic review showed that chronic exposure to air pollutants, especially $PM_{2.5}$ and NO_2, could have a potential role in the development and progression of AD and non-Alzheimer's dementia in old age. The review of selected studies indicates that the relationship between exposure to $PM_{2.5}$ and then NO_2 and O_3 and suffering from dementia has been the focus of researchers in the last 5 years. No study was found that investigated the effect of FA on dementia and met the inclusion criteria for this study. In addition, BTEX and PAHs have been neglected by researchers, which is surprising due to the widespread presence of these pollutants in the environment and industries. Therefore, conducting more studies on the impact of other air pollutants, including FA, BTEX and PAHs, on the incidence of dementia and cognitive disorders is highly recommended. We believe that the identification and prevention of modifiable risk factors, such as exposure to toxic air in conjunction with behavioral interventions, can help prevent or delay the progression of neurodegenerative disorders and significantly reduce the burden of those disorders on society.

Abbreviations

AD	Alzheimer's dementia
BBB	Blood-brain barrier
BC	Black carbon
BTEX	Benzene, Toluene, Ethylbenzene, and Xylenes
CCH	Chronic cerebral hypoperfusion
DLB	Dementia with Lewy Bodies
DALYs	Disability-adjusted life years
FA	Formaldehyde
FTD	Fronto-Temporal Dementia
PD	Parkinson Disease
PM	Particulate Matter
PM_{10}	Particles with a diameter of 10 µm or less
$PM_{2.5}$	Particles with a diameter of 2.5 µm or less
PAH	Polycyclic Aromatic Hydrocarbons
MoCA	The Montreal Cognitive Assessment
VaD	Vascular Dementia
WHO	World Health Organization

Supplementary Information

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Additional file 1: Appendix A1. Supplementary material online: Search Queries.

Additional file 2: Appendix A2. Air pollution and Alzheimer's dementia.

Additional file 3: Appendix A3. Air pollution and non-Alzheimer's dementia.

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M.M and A.H. Kh conceptualized the study and were involved in screening and data extraction. All authors were involved in the interpretation of the findings. M.M wrote the first draft. All authors were involved in the scientific processes leading up to the writing of the manuscript and contributed to the interpretation of the findings and the critical evaluation of the final version of the manuscript.

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