2019

Toxic Environmental Risk Factors for Alzheimer's Disease: A Systematic Review

Oluwaseyi Olayinka

Olaniyi O. Olayinka

Brook T. Alemu

Muge Akpinar-Elci
Old Dominion University, makpinar@odu.edu

George T. Grossberg

Original Publication Citation

Olayinka, O., Olayinka, O. O., Alemu, B. T., Akpinar-Elci, M., & Grossberg, G. T. (2019). Toxic environmental risk factors for Alzheimer's disease: A systematic review. *Aging Medicine and Healthcare*, *10*(1), 4-17. https://doi.org/10.33879/AMH.2019.1727

Aging Medicine and Healthcare 2019;10(1):4-17. doi:10.33879/AMH.2019.1727

Aging Medicine and Healthcare
http://www.agingmedhealthc.com

Review Article

Toxic Environmental Risk Factors for Alzheimer's Disease: A Systematic Review

*Oluwaseyi Olayinka[1], Olaniyi O. Olayinka[2], Brook T. Alemu[3], Muge Akpinar-Elci[1,4], George T. Grossberg[5]

[1]Department of Pathology and Laboratory Medicine, Danbury Hospital, Danbury, Connecticut, USA
[2]Department of Psychiatry and Behavioral Sciences, Interfaith Medical Center, New York City, New York, USA
[3]School of Health Sciences, Western Carolina University, Cullowhee, North Carolina, USA
[4]Center for Global Health, College of Health Sciences, Old Dominion University, Norfolk, Virginia, USA
[5]Department of Psychiatry and Behavioral Neuroscience, Saint Louis University School of Medicine, Saint Louis, Missouri, USA

***Correspondence**
Oluwaseyi Olayinka
Department of Pathology and Laboratory Medicine, Danbury Hospital, Danbury, Connecticut, USA
E-mail: seyiolutunfese@gmail.com

Received 15 April 2017
Accepted 2 November 2017

Keywords
Alzheimer's disease, environment, risk factors, review.

ABSTRACT

There is growing evidence of a possible association between toxic environmental factors and Alzheimer's disease (AD), a disabling neurodegenerative condition with no known cause. Previous reviews of toxic environmental factors for AD either focused on occupational exposures or used a non-systematic methodology. The objective of this systematic review is to assess the evidence on the link between AD and exposure to a variety of toxic environmental risk factors beyond the work environment. Structured database search was used to identify relevant studies. Twenty-nine eligible studies examining the effect of various toxic environmental agents including electromagnetic fields, solvents, pesticides, toxic metals, and air pollutants were identified. Six out of 11 cohort studies and only two out of 18 case-control studies were considered high quality. Eight out of 12 studies found electromagnetic fields exposure to be a significant risk factor for AD. Significant evidence was also found for pesticide, aluminum, and solvent exposures. Evidence is now emerging of a possible association between air pollution and AD. However, more research is needed to substantiate this evidence. Key methodological issues especially those relating to the assessment of exposure(s) need to be addressed in future studies to facilitate interpretation and synthesis of study result.

1. INTRODUCTION

Alzheimer's disease (AD) is an irreversible degenerative brain disorder that affects memory, intellectual ability, and other cognitive functions.[1] AD is the most common form of dementia and a leading cause of morbidity and mortality globally. The 2015 World Alzheimer Report showed that approximately 47 million people have AD or related dementias worldwide.[2] As populations continue to age, the number of persons living with dementia, including AD, is expected to rise to over 130 million by 2050 - this increase will particularly affect countries with a fast-growing elderly population.[2] Individuals aged 60 years and above are projected to constitute a fifth of the world population over the next three-four decades, and more than 75% will be living in Asia, Latin America or Africa.[3] Despite the current epidemiology of AD and its economic and public health impacts, the cause of the disease remains unknown.

Several genetic and non-genetic factors have been linked to AD. For instance, genetic factors such as mutations in amyloid precursor protein (APP),

presenilin 1, or presenilin 2 genes have been found to cause early-onset/familial AD while late-onset AD, the more common type, is reported to result from interaction between risk genes (e.g. apolipoprotein E-4) and environmental factors.[4] Furthermore, recent studies suggest epigenetic modifications in the etiology of late-onset AD; that is, modification in chemical compounds that regulate gene expression.[5,6]

Because genetic factors are largely non-modifiable, public health efforts aimed at reducing the global burden of AD are focusing on environmental risk factors. There is especially a growing interest in the role of toxic environmental factors (defined in this article as hazardous substances such as solvents, pesticides, toxic metals, electromagnetic fields (EMF), and air pollutants) in the development of AD.[7-13]

While some studies suggest a link between toxic environmental factors and AD, others have been inconclusive.[7-9] For instance, in a 2007 review assessing the quality of studies on risk factors for AD, significant associations were found between work-related pesticide exposure and AD in high quality studies while less consistent associations were reported for other toxic exposures (such as EMF, solvents, lead, and aluminum).[7] In a 2015 meta-analysis, no significant associations were found for occupational exposures to pesticide, solvent, aluminium, and low frequency EMF.[8] Scientific studies suggesting a possible link between air pollution and neurodegenerative diseases (e.g., AD) are also emerging.[9]

Previous reviews of the environmental risk factors for AD have been conducted; however, most either focused on occupational exposure to a single risk factor or used a non-systematic methodology.[10-13] To fill the aforementioned gap, we conducted this systematic review with the aim to assess the evidence on the link between AD and exposure to a variety of toxic environmental risk factors beyond the work environment. Given that public health actions taken at the global and national levels have been effective in reducing or eliminating human exposure to several hazardous agents, examining the evidence linking toxic environmental agents to the development of AD is imperative.

2. METHODS

We searched PubMed for articles on AD that were published in English. No time-period restriction was used so that all published articles related to AD could be retrieved. The search was conducted on 31 January 2016 and updated on 24 October 2016 using the following keywords: “Alzheimer”, “Alzheimer’s”, “Alzheimer’s disease”, "risk factors", and "risk factor". The MeSH heading “Alzheimer's disease” was also used. Screening for eligible studies was conducted by two reviewers (O.O and O.O). Eligible studies were those that included a representative population of healthy individuals at baseline or persons with AD, cohort or case-control studies that reported the effect of at least one toxic environmental risk factor on AD, and studies that used a standardized definition of AD e.g. based on the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA), the Diagnostic and Statistical Manual for Mental Disorders, (DSM III-R, DSM IV, DSM V), the International Classification of Diseases, 9th and 10th revisions (ICD-9, ICD-10), or histopathologic criteria. Studies in which the diagnostic criteria for AD were not clearly stated were excluded. Where two or more publications reported on the same cohort/study population, the most recent publication was selected. All disagreements regarding the eligibility of any of the studies were resolved by discussion among the reviewers.

Two reviewers (O.O and B.A) extracted relevant data from all eligible articles into a data extraction form designed by the authors using Microsoft Excel. The following study variables were extracted; last name of first author, publication year, study design, study setting/country; characteristics of study population including age at baseline, gender, and follow-up period where applicable; environmental exposure(s) examined and assessment method; method for AD diagnosis and diagnostic criteria; confounding variables; study result and conclusion. The extracted data were quality-checked by M.A (an expert environmental and occupational health physician) and G.T.G (an expert geriatric psychiatrist).

To evaluate the quality of all eligible studies, we adapted a quality assessment tool developed jointly by National Heart, Lung, and Blood Institute and Research Triangle Institute International.[14] The tool included items for assessing potential flaws in study methodology or implementation, including sources of bias, confounding, study power, and other factors. Quality reviewers (O.O and O.O) selected "yes" or "no" in response to each item on the tool. The total score for each study was based on the percentage of “Yes”. A study was classified as “high quality” if the total quality score was ≥80%; “moderate quality” if total score was between 80% and 59%; and “low quality” if it scored below 60%.

3. RESULTS

3.1. Study Selection

Our PubMed search yielded 7,434 articles. Of these, 7,091 were excluded following title and abstract screening. A second review of the remaining 343 articles led to the exclusion of an additional 233 articles. After full-text screening, 27 articles, in

addition to two articles identified from our reference list search, were included in the final analysis (n=29) (Figure 1).

3.2. Study Characteristics

The main characteristics of the 29 eligible studies are shown in Table 1. Seven of the 29 selected studies were published within the last decade.[15-21] We identified 18 case-control[16,22-38] and 11 cohort studies.[15,17-21,39-43] The sample sizes varied across studies; ranging from 134 in a case-control study[24] to approximately 4.8 million in a cohort study of economically active individuals in the Swedish 1980 census.[39] The age of the study participants ranged from 16 years[39] to greater than 75 years.[25,41] Thirteen of 29 studies were conducted in North America, 11 studies were conducted in Europe, three in Asia, and one in Australia. One study, a case-control analysis, examined patients from two locations in Finland and an Alzheimer's Disease Research Center in the United States (U.S.).[34] Most of the studies involved both male and female participant. Four studies[22,30,33,43] examined males only and one study investigated the risk of AD in women who took part in the Epidemiology of Osteoporosis (EPIDOS) study.[25]

The most common toxic environmental risk factors examined by the studies included EMF (n=12), aluminum (n=9), pesticides (n=6), and solvents (n=4). Other risk factors examined include air pollutants (n=2), lead (n=2), mercury (n=1), and atomic bomb radiation (n=1). For most of the studies, exposure to the examined risk factors occurred within the work environment. To diagnose AD, 20 of the 29 selected studies used the NINCDS-ADRDA criteria while in seven studies, diagnosis of AD was based on the ICD criteria. In one study conducted in Canada, AD cases and controls were defined based on strict neuropathologic criteria.[29]

3.3. Quality Assessment

The percentage agreement between raters was 95%. Disagreements were resolved by discussion among reviewers. Overall, the quality scores of the included studies ranged from 58.33% to 88.33%. Six[18-21,39,43] out of 11 cohort studies and only two[26,30] out of 18 case-control studies were considered high quality. The individual item, assessment responses, and quality scores can be found in Tables 2 and 3.

3.4. Key Findings

Twelve of the 29 included articles assessed the effect of exposure to EMF. Of the 12 studies, eight[16,28,31,33-35,39,41] found statistically significant associations between EMF exposure and AD. One of the studies, a community-based cohort study conducted in Sweden, found an increased risk of AD in men following lifetime occupational exposure to EMF levels ≥0.2 microtesla (μT) (adjusted relative risk (RR): 2.3; 95% CI: 1.0-5.1).[41] Another cohort study conducted in Sweden found the same risk increase for AD mortality among men occupationally exposed to EMF ≥0.5 μT (adjusted RR: 2.3; 95% CI: 1.6-3.3).[39] Results from a population-based study of dementia in Swedish Twins found a significant risk of AD among manual worker (adjusted OR: 2.09; 95% CI: 1.04-4.19).[16]

In an analysis of data from three independent clinical series and controls in Finland and the U.S., primary lifetime occupational exposure to medium (2-10 mG) to high (>10 mG), compared to low EMF exposure, was associated with sporadic AD (adjusted odds ratio (OR): 2.9; 95% CI: 1.6-5.4).[34] This finding was replicated in a subsequent case-control study involving individuals from an AD Treatment Center in the U.S. (adjusted OR: 3.93; 95% CI:1.5-10.6).[35] In both studies,[34,35] dressmaker, tailor, and seamstress were among the occupations considered to have medium to high EMF exposure. In an analysis of deaths among men who resided in one of 25 U.S. states, a stronger association was found between AD and specific occupations such as electricians (adjusted OR: 1.4; 95% CI: 1.1-1.7) and power plant operators (adjusted OR: 2.6; 95% CI: 1.3-5.1) when compared to all electrical occupations combined (adjusted OR: 1.2; 95% CI:1.0-1.4).[33] A separate analysis of death certificate data from 22 states in the U.S. showed that 60 hertz EMF exhibited a small but significant exposure-response for AD (Mortality OR: 1.12; 95% CI: 1.05-1.20).[31] In a population based case-control study conducted in Turkey, occupational EMF exposure and use of electricity for residential heating were found to be significant risk factors for AD (OR: 4.02; 95% CI: 1.02-15.78 and OR: 2.77; 95% CI:1.12-6.85 respectively).[28]

Three[17,31,42] out of six studies found statistically significant associations between pesticide exposure and AD. In one of the studies, occupational exposure to fumigants and defoliants was found to increase the risk of AD significantly (RR: 4.35; 95% CI: 1.05-17.90).[42] Three[18,29,37] out of nine studies found aluminum exposure to be a significant risk factor for AD. Two[26,31] out of four studies on solvent exposure reported a link with AD. We identified two recent studies on air pollution and AD risk.[20,21] In one of the studies, a dose-response association was observed for nitrogen oxide (NOx) exposure (adjusted HR per 10 μg/m^3 increase in NOx: 1.05; 95% CI: 0.97-1.15)[20] and in the second study, significant associations were reported for baseline ozone (O_3) exposure (HR per 9.63 ppb increase O_3: 1.06; 95% CI: 1.00-1.12) and changes in exposure to both O_3 and particulate matter ≤2.5 μm in diameter ($PM_{2.5}$) during follow up (HR per increase of 10.91 ppb in O_3: 3.12; 95% CI 2.92-3.33 and HR per increase of 4.34 μg/m^3 in $PM_{2.5}$: 2.38; 95% CI: 2.21-2.56).[21]

Table 1. Study characteristics.

Reference, Design, Country	Study Population	Exposure Assessment	AD: Diagnostic Method, Criteria	Confounding Variables	Main Results
Andel et al. 2010, Case-control, Sweden[16]	9,508 men and women aged 65 years or older from the Study of Dementia in Swedish Twins (HARMONY) with valid occupational and diagnostic data. 141 of 216 with dementia had AD	Exposure to ELF-MF in the participant's main lifetime occupation as determined by JEM (based on the general male Swedish popula¬tion). Exposure categorized into three levels: <0.12, ≥0.12 to <0.20, and ≥0.20 μT	In-person clinical diagnostic evaluation, NINCDS/ADRDA	Age, gender, education, complexity of work with people and things, and coronary artery disease	Among manual workers, exposure to EMF levels in the range ≥0.12 to <0.20μT was associated with increased risk of AD compared with low levels <0.12μT (OR: 2.09; 95% CI: 1.04-4.19)
Feychting et al. 2003, Cohort, Sweden[39]	Economically active individuals (16 to 98 years) in the Swedish 1980 census (4,812,646 men and women) followed for neurodegenerative disease mortality from 1981 through 1995 (from 1987 for AD)	Occupational exposure to EMF as determined by JEM (based on workday measurements of EMF from a sample of the general population of men). Information about occupation was available for 1970 and 1980. Exposure was categorized into four levels: ≤0.11, 0.12-0.19, 0.20-0.29, ≥0.30 μT. EMF levels ≥0.50 μT was also analyzed	Cause of Death Registry, diagnoses coded per ICD-9	Age and socioeconomic status	Individuals who were exposed at both times (1970 and 1980) to EMF levels ≥0.50 μT had the highest risk increase (RR: 2.3; 95% CI: 1.6-3.3)
Forster et al. 1995, Case-control, England[23]	109 cases comprised of men and women under 65 years diagnosed as having dementia by specialist services during the period 1981-89, who were alive at the time of follow up in 1990-92. Cases matched with 109 controls	Historical data (based on local authority districts in the mid to late 1980s) on aluminum levels in drinking water related to the place of residence at which the individual had lived the longest in the 10 years before onset of the symptoms	Hospital case notes, NINCDS/ADRDA	Matched for age and sex	Levels of aluminium in drinking water was not significantly associated with presenile dementia of AD-type (OR: 1.0; 95% CI: 0.41-2.43 for mean aluminum concentration >149 μg/l)
Gauthier et al. 2001, Case-control, Canada[24]	68 cases (men and women) randomly selected in the Saguenay-Lac Saint-Jean region paired with a non-demented control for age and sex	Environmental exposure to pesticides based on residential histories and the agriculture census histories of Statistics Canada (1971-1991) for herbicide and insecticide spraying in the area. Occupational exposure was assessed by an occupational hygienist blinded to subject's status. Cumulative exposure for entire working life was estimated	AD diagnosis established in three steps, DSM IV, ICD-10 and NINCDS-ADRDA for possible or probable cases	Level of education, presence of family cases of AD, and presence of at least one ApoE epsilon4 allele	Results did not show a significant risk of AD with long-term exposure (1971-1991) to herbicides, insecticides, and pesticides. Occupational exposure to pesticides was also not significantly related (p=0.81) to AD
Gillette-Guyonnet et al. 2005, Nested case-control, France[25]	Subset of 1,462 women (volunteers) aged ≥75 years taking part in the Epidemiology of Osteoporosis study followed for ≤7 years	Aluminum in drinking water was assessed by obtaining information on daily water consumption using a questionnaire. Composition of the water supply was determined from information obtained from the water companies of the study area	NINCDS-ADRDA for probable or possible AD	Not clearly stated for aluminum exposure	Results did not show any evidence for aluminum as a risk factor for AD
Graves et al. 1990, Case-control, U.S.[37]	130 male and female AD cases (mean age: 66.2 years) diagnosed between January 1980 and June 1985 at one of two clinics and matched with 130 controls who were friends or non-blood relatives of case, matched by age, sex, and the relationship between the case and his or her surrogate	Aluminium- containing antiperspirant use on a regular basis (at least once a month for one year prior to the reference year)	Clinical diagnosis, NINCDS-ADRDA	Age, family history of AD, and prior episode of head trauma	For aluminum-containing antiperspirants, the overall adjusted OR was 1.6 (95% CI:1.04-2.4) with a trend toward a higher risk with increasing frequency of use (p for trend=0.03)
Graves et al. 1998, Case-control, U.S.[26]	89 men and women (mean age: 76.8) identified from a large health maintenance organisation in Seattle, Washington, matched by age, sex, and type of informant to 89 non-demented controls	Occupational exposure to aluminium & five classes of solvents was rated by an IH using information obtained from spouses of cases and controls (a life calendar mapping the subjects' life events from 1905 - 1992 was developed to guide informants). IH was blinded to case-control status. Intensity & duration of exposures were measured	NINCDS-ADRDA for probable AD	Age and education	Non-significant associations were found between AD and ever having been occupationally exposed to solvents (OR: 1.77; 95% CI: 0.81-3.90) and aluminium (OR: 1.46; 95% CI: 0.62-3.42). An increasing risk was found with increasing number of years of exposure to solvents (p=0.03)
Gun et al. 1997, Case-control, Australia[27]	170 male and female AD patients aged 52- 96 years clinically diagnosed at one of two Sydney hospitals matched by age & sex to 170 medical-practice-based controls	Lifetime occupational exposure to solvents, aluminium, lead, mercury, and other agents assessed by a panel of IH blinded to case or control status, using occupational histories & the JEM of the U.S. NIOSH. Cumulative exposures were estimated	Clinical diagnosis, NINCDS-ADRDA for probable or possible AD	Sex, education, and family history of AD	No statistically significant associations were found between any of the occupational exposures and AD

Table 1. Study characteristics (continued).

Reference, Design, Country	Study Population	Exposure Assessment	AD: Diagnostic Method, Criteria	Confounding Variables	Main Results
Harmanci et al. 2003, Case-control, Turkey[28]	57 male and female AD patients aged ≥70 years with 127 cognitively normal controls selected from same population as cases	Job held for the longest time was recorded and EMF exposure classified by the first author (blinded to the case or control status) according to the ISCO-88. Occupations were blindly regrouped into medium to high EMF exposure	Clinical examination, NINCDS-ADRDA for probable AD	Education, rural or urban residence, medical history, drugs use, alcohol. Other variables not clearly stated	Exposure to occupational EMF had an OR of 4.02 (95% CI: 1.02-15.78). Use of electricity for residential heating also showed elevated risk (OR: 2.77; 95% CI: 1.12-6.85)
Hayden et al. 2010, Cohort, U.S.[17]	3,084 men and women from the agricultural community of Cache County, Utah, aged 65 years and older in 1995 followed for an average of 7.2 years	Pesticides in general and four specific types of pesticides including organophosphates, carbamates, organochlorines (DDT), and methyl bromides. Responses to occupational questionnaire were coded by an occupational health nurse according to the Dictionary of Occupational Titles. Participants were classified as exposed if they endorsed any pesticide exposure. Frequency and duration of use were ascertained	Clinical evaluation, DSM-III-R & NINCDS-ADRDA	Baseline age, sex, education level in years, baseline Modified MMSE score, and *APOE €4* status	Increased risk of AD was found in pesticide-exposed individuals (HR: 1.4; 95% CI: 1.06-1.91). The risk of AD associated with organophosphate exposure (HR: 1.53; 95%CI: 1.05-2.23) was slightly higher than the risk associated with organochlorines (HR:1.49; 95% CI: 0.99-2.24)
Johansen C. 2000, Cohort, Denmark[40]	30,631 men and women aged 18-66 years employed for more than three months in Danish Utility Companies between 1900 and 1993 with an average follow-up of 12.3 years	Occupational EMF exposure assessed using JEM. Average level of exposure of 50-Hz EMF was assigned to each combination of job title and work area. This was in turn was grouped into five categories of exposure: background exposure (<0.09 μT), low exposure (0.1-0.29 μT), medium exposure (0.3-0.99 μT), high exposure (>1.0 μT) and unknown exposure	The National Hospital Discharge Register, ICD-8	Age, calendar period, and duration of employment	The incidence of AD was unrelated to exposure to EMF
Jung et al. 2015, Cohort, Taiwan[21]	95,690 men and women retrieved from the longitudinal health insurance database 2,000, aged 65 or older, followed from 2001-2010	Exposure to Particulate Matter (PM) and Ozone (O_3). Data was obtained from 70 Taiwan Environmental Protection Agency monitoring stations on Taiwan's main island from 2000-2010. PM_{10} data was used to estimate the concentration of $PM_{2.5}$ during 2000-2005	Individuals with at least two consensus diagnosis. Criteria includes ICD-9-CM (Clinical Modification), DSM-IV & NINCDS-ADRDA	Age, gender, income, diabetes mellitus, hypertensive disease, myocardial infarction, stroke, asthma, and COPD	HR of AD per 9.63 ppb increase in baseline O_3=1.06 (95% CI: 1.00-1.12). HR per increase of 10.91 ppb in O_3 during follow-up=3.12 (95% CI 2.92-3.33). HR of AD per 13.21 μg/m^3 increase in baseline $PM_{2.5}$=1.03 (95% CI: 0.95-1.11). HR of AD per increase of 4.34 μg/m^3 in $PM_{2.5}$ during follow-up=2.38 (95% CI: 2.21-2.56)
McLachlan et al. 1996, Case-control, Canada[29]	Brains of 830 decedents with neurodegenerative diseases and healthy controls donated by next of kin from many geographical areas to the CBTB for diagnostic and research purposes between 1981 and 1991	Aluminium in drinking water: measures of the concentrations of residual aluminum in municipal drinking water supplies were based on data provided by the Ontario Ministry of Environment and Energy's DWSP. Residence at the time of death (available from clinical records) & a complete 10-year residential history (obtained from a brief telephone questionnaire) were estimated	Donor brains, histopathologic criteria	Not defined	Comparing all AD cases (A1 + A2) with all non-AD controls (C1 + C2), and using the Aluminum level of public drinking water at last residence before death, the estimated RR associated with Aluminum ≥100 μg/L was 1.7 (95% CI: 1.2-2.5). Aluminum exposure from a 10-year weighted residential history resulted in estimates of relative risk of 2.5 or greater
Noonan et al. 2002, Case-control, U.S.[30]	1,556 cases 60 years or more and 1,556 controls formed from among recorded deaths of males in the state of Colorado for the years 1987 through 1996	Occupational EMF exposure assessed using three methods: electrical versus nonelectrical occupations, three-tiered grouping of potential magnetic field exposure based on a combination of job title and industry, and categories of exposure based on the means of the magnetic fields estimated from a JEM	Death certificate, ICD-9	Age, race, and occupational grouping	No consistent associations with magnetic fields were observed for AD

Table 1. Study characteristics (continued).

Reference, Design, Country	Study Population	Exposure Assessment	AD: Diagnostic Method, Criteria	Confounding Variables	Main Results
Oudin et al. 2016, Cohort, Sweden[20]	1,806 men and women from the population-based Betula Study ≥55 years followed over a 15-year period	Exposure to traffic-related air pollution. A land-use regression (LUR) model for the study area - Umeå was used to estimate the annual average levels of nitrogen oxides (NOx). Baseline exposure was categorized into: 4.8-9, >9-17, >17-26, >26 μg/m^3. HR per 10 μg/m^3 increase in NOx was also estimated	DSM-IV	Education, physical activity, smoking, sex, BMI, WHR, alcohol, age, and ApoE4	Participants in the group with the highest (>26 μg/m^3) versus lowest exposure (4.8-9 μg/m^3) had HR of 1.38 (95% CI: 0.87- 2.19). Third (>17-26 μg/m^3) versus lowest quartile had HR of 1.51 (95% CI: 0.96- 2.37) and second (>9-17μg/m^3) versus lowest quartile had HR of 1.15 (95% CI: 0.72-1.86). HR per 10 μg/m^3 increase in NOx was 1.05 (95% CI: 0.97-1.15)
Park et al. 2005, Case-control, U.S.[31]	Death certificate information for all deaths from 22 participating states in the years 1992-1998 obtained using the National Occupational Mortality Surveillance System. 47,783 deaths in men and women <45 to ≥85 years were caused or contributed to by AD	Occupational exposure to solvents assessed using a JEM validated for cancer studies. Probability and intensity of exposure (classified as: none, low, medium, and high) were estimated. For EMF exposure, occupations were classified on magnetic fields using a JEM developed for cancer epidemiology. Occupations with probable pesticide exposure found to have increased PMRs per a previous study were evaluated	Death certificate, ICD-9	Age, race, gender, region and socioeconomic status	Small but significant linear associations were observed for solvents and AD (MOR: 1.09, evaluated at highest exposure category; 95% CI:1.03-1.15). 60 Hz magnetic fields exhibited significant exposure-response for AD (MOR: 1.12; 95% CI: 1.05-1.20). The association between pesticides and AD was strongest in farmers below 65 (MOR: 1.76; 95% CI: 1.04-2.81)
Qiu et al. 2004, Cohort, Sweden[41]	Study population was derived from the Kungsholmen Project. Included 931 men and women ≥75 years followed for maximum 8.3 years	Occupational EMF assessed by IH with no knowledge of subjects' disease status. Three methods used: JEM, direct measurements, and expert estimation	Medical records and death certificates, NINCDS-ADRDA	Age, education, vascular disease, Apo E genotype), alcohol, smoking, mental activity, and social activity	Among men, EMF exposure ≥0.2 μT in lifetime principal job was related to RR of 2.3 (95% CI: 1.0-5.1) for AD. No association was found in women
Rondeau et al. 2009, Cohort, France[18]	1,925 men and women (from the PAQUID cohort) aged 65 years or over living in 91 civil drinking-water areas in southern France followed for 15 years	Aluminum in drinking water based on geographic and individual exposure (over the previous 10 years), taking into account daily consumption of tap water and bottled water	Assessed by senior neurologist, NINCDS-ADRDA	Age, gender, educational level, wine consumption, and place of residence	Analyses restricted to cases classified as AD (364 cases) suggested a deleterious effect of high aluminum intake. Daily aluminium consumption of >0.1 vs <0.1 mg/day was associated with RR of 2.80 (95% CI: 1.24-6.32)
Salib, E. and V. Hillier 1996, Case-control, UK[32]	198 unmatched cases of AD and control (164 other dementias and 176 non-demenating group). The subjects included all male and female patients referred to and seen by the psychogeriatrician during a 2-year study period	Occupational Aluminium exposure obtained using a questionnaire that contained a broad classification of occupation by industry type	Clinical evaluation, NINCDS-ADRDA for probable or possible AD	Age, sex, age of onset, duration of condition and duration of work and family history of dementia	Aluminium workers reported to have worked in direct contact with aluminium dust and fumes did not appear to be at any greater risk than other workers who were employed at the same factory (OR: 1.19; 95%CI: 0.64-4.18)
Savitz et al. 1998, Case-control, U.S.[33]	Study population comprised deaths in the period 1985-1991 among men 20+ years of age who resided in one of 25 U.S. states. 256 AD cases were matched 1:3 with controls who died from causes excluding leukaemia and brain cancer	Occupational EMF exposure based on specific electrical occupation reported on the death certificate	Death certificate, ICD-9	Age, calendar year, social class, and race	Significant associations were found for electricians and power plant operators (OR: 1.4; 95% CI: 1.1-1.7 and OR:2.6; 95% CI: 1.3-5.1 respectively)
Savitz et al. 1998, Cohort, U.S.[43]	Men at five large U.S. electric utility companies who worked for at least 6 months between 1950 and 1986. Death certificates for 20,068 deceased men were obtained. AD was indicated in 56 deaths. Median age at the time of death was 78 years	Occupational EMF exposure assessed as duration of work in exposed jobs and through an index of cumulative exposure based on magnetic field measurements	Death certificate, ICD-9	Age, calendar year, social class, work status, polychlorinated biphenyl exposure and solvent exposure	AD was weakly associated with duration of employment in jobs associated with elevated magnetic field exposure

Table 1. Study characteristics (continued).

Reference, Design, Country	Study Population	Exposure Assessment	AD: Diagnostic Method, Criteria	Confounding Variables	Main Results
Shalat et al. 1988, Case-control, U.S.[22]	98 male cases obtained from hospitals matched by sex, year of birth, and town of residence with 162 population controls	Occupational exposure to organic solvent and lead obtained through direct questions/questionnaire. Three IHs blinded to study hypothesis assigned likelihood and a semi-quantitative level of exposure	Clinical diagnosis, NINCDS-ADRDA & DSM-III	Years of education	Those with significant workplace exposure to organic solvent and lead had no appreciable excess risk of AD
Sobel et al. 1995, Case-control, Finland and U.S.[34]	Three independent clinical series and controls (Finnish series 1 & 2, USC ADRC series). 53, 198, 136 male and female cases were compared with 70, 299, 136 controls for the three series respectively. Ascertainment periods were 1982-1985, 1977-1978, and 1982-1993 respectively	Lifetime occupational EMF exposure evaluated by an IH from primary occupations. Predominant occupations among medium (2-10 mG or >10 mG intermittently) to high (>10 mG or >100 mG intermittently) exposed cases were seamstress, dressmaker, and tailor	Medical records and clinical examination, NINCDS-ADRDA and criteria of Roth	Age at onset, age at examination, sex, education and social class	The adjusted OR for all cases/controls was 2.9 (95% CI: 1.6-5.4). Adjusted OR was 3.9 (95% CI: 1.7-8.6) for women and 1.9 (95% CI: 0.8-5.0) for men
Sobel et al. 1996, Case-control, U.S.[35]	326 male and female cases from ADDTC at RLAMC who were at least age 65 at the time of their first examination at RLAMC compared with 152 controls who had cognitive impairment/ dementia other than vascular dementia	Occupational EMF exposure measured per previous study (Sobel et al. 1995). Primary occupation was obtained from hospital records	Clinical examination, NINCDS-ADRDA for probable or definite AD	Age at onset, age at diagnosis, sex, and education	EMF was found to be etiologically associated with the occurrence of AD. The adjusted OR for both sexes was 3.93 (95% CI: 1.5-10.6). For males the adjusted OR was 4.90 (95% CI: 1.3-7.91), and for females the adjusted OR was 3.40 (95% CI: 0.8-16.0)
Sorahan et al. 2014, Cohort, UK[19]	73,051 male and female employees of the former Central Electricity Generating Board employed for at least six months. Investigated for the period 1973-2010	Occupational EMF exposure based on lifetime, recent or distant exposure. Methods summarized in an earlier companion article	Death certificate, ICD-9 or 10	Sex, attained age, calendar period (5 year periods) and socio-economic status	No statistically significant trends were shown for risks of AD to increase with estimates of lifetime, recent or distant exposure to EMF
The Canadian Study of Health and Aging 1994, Case-control, Canada[38]	258 male and female cases aged 65 or older with onset of symptoms within 3 years of diagnosis and 535 population controls frequency matched on age group, and residence, confirmed to be cognitively normal	Environmental exposure to multiple agents including pesticides were assessed using risk factor questionnaires	Clinical examination, NINCDS-ADRDA for probable AD	Age, sex, residence in community or institution, and education	Occupational exposure to glues as well as to pesticides and fertilizers appeared to be risk factors for AD; however, when education was controlled for, the strength of association diminished. Association between al-containing antiperspirant use and AD was not significant
Tyas et al. 2001, Cohort, Canada[42]	694 cognitively intact men and women (from the Manitoba Study of Health and Ageing) ≥65 years who completed a risk factor questionnaire in 1991/92 and followed for 5 years. 36 developed AD	Method for assessing occupational exposure to fumigants/defoliants and recreational exposure to other agents not defined	Clinical assessment, NINCDS-ADRDA for possible or probable AD	Age, sex, and education	Occupational exposure to fumigants/ defoliants was a significant risk factor for AD (RR: 4.35; 95% CI: 1.05-17.90). No significant association was found between AD and recreational exposures to pesticides/herbicides, turpentine, paints/stains/lacquers, aerosol or spray paints, paint remover, film developing fluids, dyes, plastic cement/glues, plastic resins, epoxy resins, and fuels/gas/petroleum
Wang et al. 1997, Case-control, Taiwan[36]	98 male and female AD patients aged 55 years and older, regularly followed up during the study period (July, 1994-June, 1996). Cases were age- and sex-matched with 98 genetically unrelated controls	Method for assessing Pesticide exposure not defined. Risk factor questionnaire was administered by trained interviewers	Clinical assessment, NINCDS-ADRDA	Not defined	Pesticide exposure showed no significant association with AD

Table 1. Study characteristics (continued).

Reference, Design, Country	Study Population	Exposure Assessment	AD: Diagnostic Method, Criteria	Confounding Variables	Main Results
Yamada et al. 2009, Cohort, Japan[15]	2,286 male and female subjects (members of the Adult Health Study cohort) who were non-demented and aged ≥60 years at baseline examination and had been exposed at ≥13 years of age to a relatively low dose (≤4 Gy). Mean study period: 5.9 years	Exposure to atomic bomb radiation (individual brain dose based on RERF's Dosimetry System 2002). Radiation dose was estimated as weighted sums of gamma ray and neutron components in Gy, and divided into three categories: <5 mGy (non-exposed), 5-499 mGy, and ≥500 mGy	Clinical evaluation, NINCDS-ADRDA for probable AD and possible AD	Age, sex, education, BMI, smoking, drinking, menopausal age, history of hypertension, diabetes, and stroke	After adjustment for potential risk factors, radiation exposure did not affect the incidence rate of AD

AD, Alzheimer's disease; ELF-MF, extremely low-frequency magnetic fields; EMF, electromagnetic fields; OR, odds ratio; CI, confidence interval; HR, hazard ratio; RR, relative risk; JEM, job-exposure matrix; IH, industrial hygienist; NIOSH, National Institute for Occupational Safety and Health; ISCO, International Standard Classification of Occupations; CBTB, Canadian Brain Tissue Bank; DWSP, Drinking Water Surveillance Program; COPD, Chronic Obstructive Pulmonary Disease; BMI, Body Mass Index; WHR, waist-hip ratio; A1 + A2, decedents with a clinical history of dementia and the histopathologic findings suggestive of AD and decedents with clinical dementia and AD pathology coexisting with some other neuropathologic process; C1 + C2, decedents with no histopathology plus a second group composed of decedents with Huntington's disease, schizophrenia, multiple sclerosis, multiple infarcts, Jakob-Creutzfeldt disease, and other neurodegenerative diseases for which aluminum has never been implicated; PMR, proportionate mortality ratio; PAQUID, Personnes a˜ge´es Quid; USC ADRC, University of Southern California site of the Alzheimer's Disease Research Center of Los Angeles and Orange Counties; ADDTC at RLAMC, Alzheimer Disease Treatment and Diagnostic Center, Rancho Los Amigos Medical Center; RERF, Radiation Effects Research Foundation.

Table 2. Methodological quality of eligible cohort studies.

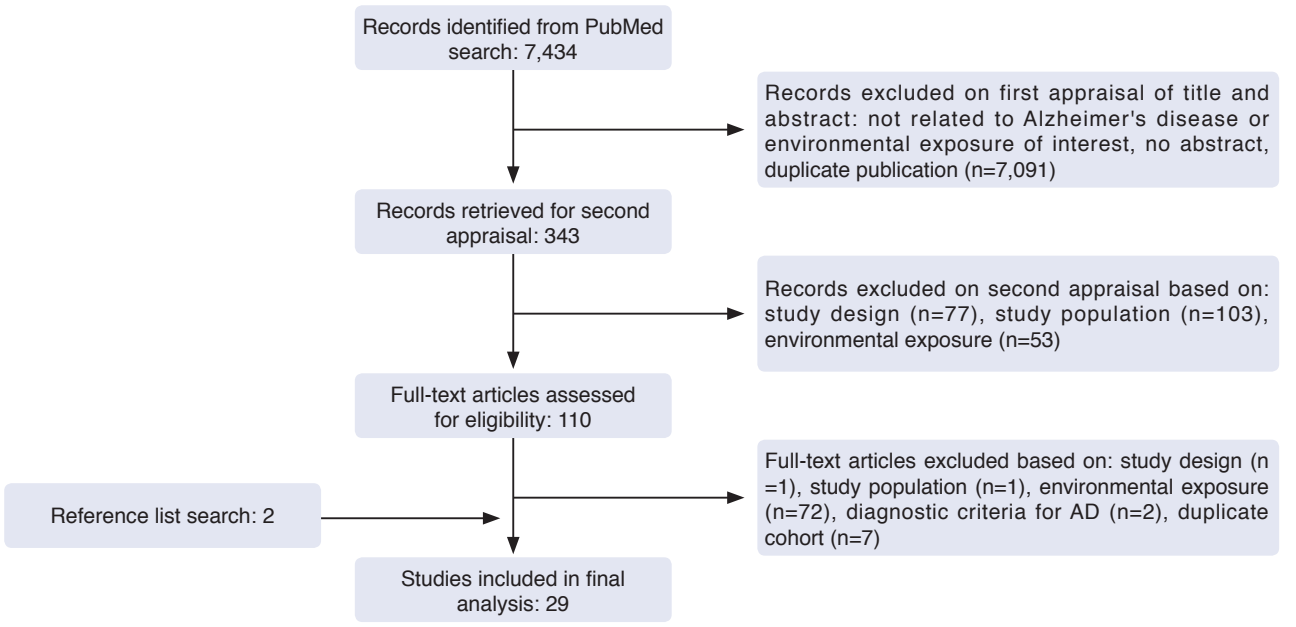
Criteria (Cohort Studies)	Feychting et al. 2003[39]	Hayden et al. 2010[17]	Johansen C. 2000[40]	Jung et al. 2015[21]	Oudin et al. 2016[20]	Qiu et al. 2004[41]	Rondeau et al. 2009[18]	Savitz et al. 1998[43]	Sorahan et al. 2014[19]	Tyas et al. 2001[42]	Yamada et al. 2009[15]
1. Research question clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Study population clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Participation rate at least 50%	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Subjects recruited from same population/ uniform eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Sample size justification	No	No	No	Yes	No	No	No	No	No	No	No
6. Exposure assessed prior to outcome measurement	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Sufficient timeframe to see an effect	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Different levels of the exposure of interest assessed	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
9. Exposure measures and assessment clearly defined	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
10. Repeated exposure assessment	Yes	No	No	Yes	No	No	Yes	Yes	Yes	No	No
11. Outcome measures clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Blinding of outcome assessors	No	No	No	No	Yes	No	No	No	No	No	No
13. Minimal loss to follow-up (20% or less)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14. Adjusted for key potential confounding variables (i.e. age)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Percentage of "Yes" per study (%)	12/14= 85.71	9/14= 64.29	11/14= 78.57	12/14= 85.71	12/14= 85.71	11/14= 78.57	12/14= 85.71	12/14= 85.71	12/14= 85.71	9/14= 64.29	11/14= 78.57

Table 3. Methodological quality of eligible case control studies.

Criteria (Case-Control Studies)	Andel et al. 2010[16]	Forster et al. 1995[23]	Gauthier et al. 2001[24]	Gillette-Guyonnet et al. 2005[25]	Graves et al. 1990[37]	Graves et al. 1998[26]	Gun et al. 1997[27]	Harmanci et al. 2003[28]	McLachlan et al. 1996[29]	Noonan et al. 2002[30]	Park et al. 2005[31]	Salib and Hillier 1996[32]	Savitz et al. 1998[33]	Shalat et al. 1988[22]	Sobel et al. 1995[34]	Sobel et al. 1996[35]	*CSHA 1994[38]	Wang et al. 1997[36]
1. Research question clearly stated	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Study population clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Sample size justification	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	No	Yes	No
4. Groups recruited from the same population	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Eligibility criteria prespecified & applied uniformly	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Cases & controls clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Random selection of study participants	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
8. Use of concurrent controls	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
9. Exposure assessed prior to outcome measurement	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	No
10. Exposure measures and assessment clearly defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Blinding of exposure assessors	No	No	No	Yes	No	Yes	Yes	No	No	No	No	Yes	No	No	Yes	No	No	Yes
12. Adjusted for key potential confounding variables (i.e. age)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Percentage of "Yes" per study (%)	9/12= 75.00	8/12= 66.67	9/12= 75.00	8/12= 66.67	8/12= 66.67	10/12= 83.33	7/12= 58.33	9/12= 75.00	7/12= 58.33	10/12= 83.33	9/12= 75.00	9/12= 75.00	9/12= 75.00	8/12= 66.67	8/12= 66.67	7/12= 58.33	8/12= 66.67	8/12= 66.67

*The Canadian Study of Health and Aging

Figure 1. Flow diagram showing how articles were selected.



No significant associations were found for occupational exposures to lead[22,27] and mercury.[27] Results from a study involving individual from the Adult Health Study Cohort in Hiroshima did not provide any support for a possible relationship between radiation exposure and AD.[15]

4. DISCUSSION

4.1. Summary of Findings

Our review identified a broad group of toxic environmental risk factors for AD reported in 29 studies. Unlike previous reviews and meta-analyses, which either focused on one environmental factor or occupational exposure(s),[44-46] our review explored exposure to several risk factors in and outside the work environment. Of all the risk factors identified, EMF was the most commonly studied. EMF has been reported to affect several processes within the body including calcium homeostasis and melatonin production in the brain but the exact mechanism via which it causes AD is still not known.[47-49] In our review, eight out of 12 studies found EMF to be a significant risk factor for developing AD. The earliest studies investigating the link between EMF and AD were conducted in 1995 and 1996 by Sobel et al.[34,35] Compared to individuals with none to low EMF exposure, the authors found the odds of occupational exposure to medium to high EMF to be two to three times higher among subjects with AD. Similar magnitude of association were reported in subsequent studies.[28,31,33,39,41,43]

Although some of the studies included in this review found slightly higher AD risks in EMF-exposed subjects, the reported strengths of association are generally in keeping with two recent meta-analyses conducted in 2008 and 2013.[44,45] In the 2008 meta-analysis, pooled estimates from nine case-control and five cohort studies showed a stronger association between EMF exposure and AD compared with the meta-analysis conducted in 2013; pooled estimates in the 2013 study were from 13 case-control studies and six cohort studies.

Regarding exposure to metals, aluminum was the most commonly studied. Aluminum is a widely known neurotoxin and has been shown to have toxic effects on the central nervous system; however, its role in the etiology of AD remains unclear. Results from three studies showed that high intake of aluminum from drinking water and frequent use of aluminum containing products such as antiperspirants was associated with an increased risk of AD.[18,29,37] Overall, the low number of studies on other metals (such as lead and mercury) makes definitive conclusions on their impact on AD risk difficult. Exposure to pesticides was found to be a significant risk factor for AD. In one study, the authors found an increased risk of AD that was more evident in persons with occupational exposure to organophosphate pesticides.[17] Another study found a risk of AD that was over four times higher among subjects with occupational exposure to two types of pesticides-fumigants and defoliants.[42] Occupational exposure to other types of pesticides (such as herbicides and insecticides) was not found to increase AD risk. In one of the studies on solvent exposure, an increasing risk of AD was found with increasing number of years

of exposure to solvents.[26] In another study, small but significant linear associations were observed for solvents and AD.[31]

Evidence is now emerging of a possible link between air pollution, second-hand smoke and neurodegenerative conditions, including AD.[46] In various studies, air pollutants have been demonstrated to trigger chronic oxidative stress, a mechanism involved in the pathogenesis of AD.[50] In a study conducted using autopsy brain samples from Mexican subjects, exposure to severe air pollution was found to be associated with brain inflammation and accumulation of amyloid-β 42, known causes of neuronal dysfunction that precede the appearance of neuritic plaques and neurofibrillary tangles which are neuropathological hallmarks of AD.[51] Similarly, Maher et al found magnetite, an airborne nanoparticle, in fresh frozen brain tissues of 38 individuals who lived in two major cities in the United Kingdom and Mexico.[9] Magnetite exposure has been linked to oxidative damage in brain cells especially in the presence of amyloid-β protein.[9,52] We identified two eligible studies on air pollution and AD. Results from one of the studies, a population-based study which used data from 70 Taiwan Environmental Protection Agency (EPA) monitoring station on Taiwan's main island, suggest that long-term exposure to ozone and $PM_{2.5}$ above the current U.S. EPA standards are associated with increased risk of AD.[21] The second study, involving participants from a major city in Sweden, found non-significant associations between traffic air pollution (NOx levels) and AD.[20]

Regarding second-hand smoke (SHS) and AD, studies have suggested a cardiovascular disease-related mechanism similar to that seen with smoking.[53,54] We identified a large population-based cross-sectional study of never-smoked people in China. The result showed a significant risk for AD following exposure to SHS at home and in the workplace.[55] In a US-based study examining the association between self-reported lifetime household SHS exposure and risk of incident dementia, the authors found that subjects with over 25 years of SHS exposure and greater than 25% carotid artery stenosis had a three-fold increase in dementia risk compared with subjects with no to low (i.e., 0-15 years) SHS exposure. Most (64%) of the subjects with dementia had AD. Moderate (16-25 years) and high (>25 years) SHS exposure levels, however, were not independently associated with dementia risk.[56] These findings, if substantiated, have significant public health implications because of the endemicity of SHS as well as the close relationship between air pollution and climate change.

Evidence is also emerging on the role of epigenetic mechanisms in the development of neurodegenerative diseases. Epigenetics involve heritable changes in gene expression that occur without changes in the DNA sequence.[57] Epigenetic modifications especially those related to DNA methylation may explain the link between environmental risk factors and late-onset AD. Several AD-related genes contain methylated CpG sites (sites where cytosine lies next to guanine in the DNA sequence) in their promoter regions.[58] Low levels of methylation at these regions have been implicated in the etiology of AD.[59] For instance, demethylation in the promoter region of the APP gene was found to be associated with amyloid-β deposition in the aged brain.[60] Two post-mortem studies found a significant decrease in DNA methylation in the hippocampus and entorhinal cortex of post-mortem samples with AD.[61,62] Furthermore, recent reviews of the scientific literature have found a correlation between toxic environmental factors and decreased levels of DNA methylation.[63,64] Studies have also suggested that early exposure to metals such as lead could result in epigenetic modifications of AD-related genes and subsequent dysregulated expression later in life.[65]

Despite the emergence of new information on the possible link between specific groups of toxic exposures and AD, research on toxic environmental agents in general and their role in the etiology of AD appears to have declined over the years. In our review for example, only seven out of 29 selected studies were published within the last decade. The level of evidence observed in some of the selected studies appear to be high and should not be ignored. Rather, necessary precautions should be taken in settings where the risk of exposure to implicated toxic environmental agents is high. There is no doubt that more studies are needed to validate the evidence seen.

4.2. Limitations in the Original Studies

We identified key methodological issues that may have resulted in inconsistencies in findings across studies. These issues need to be addressed in future studies to facilitate interpretation of study results and more importantly, to improve the validity of study results.

We found that measurement of exposure levels was a challenge in most studies. The methods used to assess the different exposure levels were fairly inconsistent across studies. For some studies, the degree of exposure was based on assumptions made by the investigators or an expert and in others, the methods used to determine the level of exposure was not clearly stated. For instance, in Sobel et al. (1995), probable exposure to ELF-MF for each occupation was blindly assessed by a certified industrial hygienist and by direct measurement of magnetic fields while in the population-based study of Swedish Twins, occupational exposure to ELF-MF was determined from a job exposure matrix which was based on workday measurements of magnetic fields obtained from a specific population.[16]

Since some study results were based largely on data from specific job classes, exposure levels regarded as medium or high in one study may not be comparable to the same exposure levels in others. Inconsistencies in measurement of exposure pose a significant problem when synthesizing information from different epidemiological studies. In a recent meta-analysis of modifiable risk factors for AD, the lack of evidence for significant associations between AD and four occupational exposures including low frequency EMF, aluminum, pesticide, and solvents was attributed to differences in the measurement approaches used for the exposures.[8] Another review assessing the quality of epidemiological studies on occupational risk factors for AD noted that the lack of a valid assessment of exposure in some of the studies may have impacted evidence conclusion.[7]

In most cases, it was difficult to determine the true impact of the environmental exposure of interest since data on the intensity exposure was scarce. The source of information was another issue that may have underestimated the risks seen in some of the studies. Recall bias is often a problem in case-control studies more so if the information was obtained from the subjects. The use of proxy informants as was the case in some studies is also likely to lead to information bias as it is often difficult to obtain a comprehensive report on exposures from such informants.[17] In one study that did not find consistent associations between occupational exposure to magnetic fields and AD, a major study limitation was the use of death certificates to obtain both exposure and disease data.[30] The use of death certificate information in epidemiological studies often creates errors especially when incomplete as is the case in many parts of the world. There is also the issue of inaccuracies with recording the underlying cause of death particularly for chronic disorders such as AD. In a recent retrospective cohort study, only 53.6% of decedents who were diagnosed clinically with dementia were certified with dementia as a cause of death at the beginning of the observation period.[66] Definition and classification of exposure was also a challenge. In one study[24] exposures were classified in the broad category of "pesticides", "insecticides" or "herbicides" while in another study, specific types of pesticides including organophosphates, organochlorines, carbamates, and methyl bromides were examined.[17]

Based on these observations, we recommend that future research efforts focus on improving and standardizing methods used to assess exposure to toxic environmental agents. An example is the use of well-designed questionnaires to capture indicators that are proxies of actual exposures in different settings. A more objective approach is to directly measure the levels of toxic agents or their metabolites in human biological specimens. However, this approach is often difficult given the inter-individual variability in the toxicokinetics of the different toxic environmental agents and the challenges in obtaining and processing tissue samples especially from a large group of participants. Given that case-control studies are prone to recall bias and do not usually allow the determination of exposure prior to the outcome of interest, we recommend that researchers conduct cohort studies that involve large numbers of individuals followed for adequate periods of time.

4.3. Limitations of Review

Since the literature search was conducted in one electronic database, our search may have missed publications that could significantly impact our findings. Having this in mind, we used a search strategy that will allow us retrieve as many relevant articles as possible from the database. We also supplemented our search with a manual search of the reference lists of eligible articles. Although our original aim was to combine the results from eligible studies in a meta-analysis, this method would not have been appropriate given the variation in the assessment of exposure as described above.

5. CONCLUSION

Our review highlights important evidence on the role of toxic environmental factors in the development of AD. We identified 29 eligible studies which focused on exposure to several toxic environmental factors mostly in the work setting. Of all the risk factors identified, the evidence was mostly significant for exposure to EMF. In light of this evidence, it is important to further explore the relationship between EMF exposure and AD given that humans are exposed to some amounts of EMF on a daily basis. Significant associations were also found for aluminum, pesticides, and solvents exposure. Overall, more work is needed to substantiate existing evidence on the possible role of toxic environmental risk factors in the etiology of AD. Research efforts should focus on designing high quality longitudinal studies that will facilitate appropriate definition and accurate measurement of exposures, ensure adequate follow-up given the long latency period between environmental exposures and development of AD, and limit potential sources of bias at study design level or during analysis of collected data. More epigenetic studies are also needed to determine the pathophysiologic mechanisms by which environmental factors cause AD.

CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

REFERENCES

1. National Institute of Health. Alzheimer's Disease Fact Sheet.

2016. *National Institute on Aging*. Accessed on 1 February 2017 at: https://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet.

2. Alzheimer's Disease International. *World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends*. London, UK: Alzheimer's Disease International; 2015.

3. Duthey B. Background Paper 6.11: Alzheimer Disease and other Dementias. In: Priority Medicines for Europe and the World: A Public Health Approach to Innovation. Geneva, Switzerland: World Health Organization; 2013. Available at: https://www.who.int/medicines/areas/priority_medicines/BP6_11Alzheimer.pdf

4. Bekris LM, Yu CE, Bird TD, Tsuang DW. Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol*. 2010;**23**:213-27.

5. Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, Rogers J. Epigenetic mechanisms in Alzheimer's disease. *Neurobiol Aging*. 2011; **32**:1161-80.

6. Daniilidou M, Koutroumani M, Tsolaki M. Epigenetic mechanisms in Alzheimer's disease. *Curr Med Chem*. 2011;**18**:1751-6.

7. Santibanez M, Bolumar F, Garcia AM. Occupational Risk Factors In Alzheimers Disease: A Review Assessing Quality Of Published Epidemiological Studies. *Occup Environ Med*. 2007;**64**:723-32.

8. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015;**86**:1299-306.

9. Maher BA, Ahmed IA, Karloukovski V, MacLaren DA, Foulds PG, Allsop D, et al. Magnetite pollution nanoparticles in the human brain. *Proc Natl Acad Sci USA*. 2016;**113**:10797-801.

10. Campdelacreu J. Parkinson disease and Alzheimer disease: environmental risk factors. *Neurologia. (English Edition)*. 2014;**29**:541-9.

11. Yegambaram M, Manivannan B, G Beach T, U Halden R. Role of environmental contaminants in the etiology of Alzheimer's disease: a review. *Curr Alzheimer Res*. 2015;**12**:116-46.

12. Brown RC, Lockwood AH, Sonawane BR. Neurodegenerative diseases: an overview of environmental risk factors. *Environ Health Perspect*. 2005;**113**:1250-6.

13. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Front Cell Neurosci*. 2015;**9**:124.

14. National Institute of Health. Study Quality Assessment Tools. 2017. *National Heart Lung and Blood Institute*. Accessed on 14 April 2017 at: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools.

15. Yamada M, Kasagi F, Mimori Y, Miyachi T, Ohshita T, Sasaki H. Incidence of dementia among atomic-bomb survivors--Radiation Effects Research Foundation Adult Health Study. *J Neurol Sci*. 2009; **281**:11-4.

16. Andel R, Crowe M, Feychting M, Pedersen NL, Fratiglioni L, Johansson B, et al. Work-related exposure to extremely low-frequency magnetic fields and dementia: results from the population-based study of dementia in Swedish twins. *J Gerontol A Biol Sci Med Sci*. 2010;**65**:1220-7.

17. Hayden KM, Norton MC, Darcey D, Østbye T, Zandi PP, Breitner JC, et al. Occupational exposure to pesticides increases the risk of incident AD: the Cache County study. *Neurology*. 2010;**74**:1524-30.

18. Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: findings from 15-year follow-up of the PAQUID cohort. *Am J Epidemiol*. 2009;**169**:489-96.

19. Sorahan T, Mohammed N. Neurodegenerative disease and magnetic field exposure in UK electricity supply workers. *Occup Med. (Lond)* 2014;**64**:454-60.

20. Oudin A, Forsberg B, Adolfsson AN, Lind N, Modig L, Nordin M, et al. Traffic-related air pollution and dementia incidence in northern Sweden: a longitudinal study. *Environ Health Perspect*. 2016;**124**:306.

21. Jung CR, Lin YT, Hwang BF. Ozone, particulate matter, and newly diagnosed Alzheimer's disease: A population-based cohort study in Taiwan. *J Alzheimers Dis*. 2015;**44**:573-84.

22. Shalat SL, Seltzer B, Baker Jr. EL. Occupational risk factors and Alzheimer's disease: a case-control study. *J Occup Med*. 1988;**30**:934-6.

23. Forster DP, Newens AJ, Kay DW, Edwardson JA. Risk factors in clinically diagnosed presenile dementia of the Alzheimer type: a case-control study in northern England. *J Epidemiol Community Health*. 1995;**49**:253-8.

24. Gauthier E, Fortier I, Courchesne F, Pepin P, Mortimer J, Gauvreau D. Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study. *Environ Res*. 2001;**86**:37-45.

25. Gillette-Guyonnet S, Andrieu S, Nourhashemi F, de La Guéronnière V, Grandjean H, Vellas B. Cognitive impairment and composition of drinking water in women: findings of the EPIDOS Study. *Am J Clin Nutr*. 2005;**81**:897-902.

26. Graves AB, Rosner D, Echeverria D, Mortimer JA, Larson EB. Occupational exposures to solvents and aluminium and estimated risk of Alzheimer's disease. *Occup Environ Med*. 1998;**55**:627-33.

27. Gun RT, Korten AE, Jorm AF, Henderson AS, Broe GA, Creasey H, et al. Occupational risk factors for Alzheimer disease: a case-control study. *Alzheimer Dis Assoc Disord*. 1997;**11**:21-7.

28. Harmanci H, Emre M, Gurvit H, Bilgic B, Hanagasi H, Gurol E, et al. Risk factors for Alzheimer disease: a population-based case-control study in Istanbul, Turkey. *Alzheimer Dis Assoc Disord*. 2003;**17**:139-45.

29. McLachlan DR, Bergeron C, Smith JE, Boomer D, Rifat SL. Risk for neuropathologically confirmed Alzheimer's disease and residual aluminum in municipal drinking water employing weighted residential histories. *Neurology*. 1996;**46**:401-5.

30. Noonan CW, Reif JS, Yost M, Touchstone J. Occupational exposure to magnetic fields in case-referent studies of neurodegenerative diseases. *Scand J Work Environ Health*. 2002;**28**:42-8.

31. Park RM, Schulte PA, Bowman JD, Walker JT, Bondy SC, Yost MG, et al. Potential occupational risks for neurodegenerative diseases. *Am J Ind Med*. 2005;**48**:63-77.

32. Salib E, Hillier V. A case-control study of Alzheimer's disease and aluminium occupation. *Br J Psychiatry*. 1996;**168**:244-9.

33. Savitz DA, Loomis DP, Tse CK. Electrical occupations and neurodegenerative disease: analysis of U.S. mortality data. *Arch Environ Health*. 1998;**53**:71-4.

34. Sobel E, Davanipour Z, Sulkava R, Erkinjuntti T, Wikstrom J, Henderson VW, et al. Occupations with exposure to electromagnetic fields: a possible risk factor for Alzheimer's

disease. *Am J Epidemiol.* 1995;**142**:515-24.

35. Sobel E, Dunn M, Davanipour Z, Qian Z, Chui HC. Elevated risk of Alzheimer's disease among workers with likely electromagnetic field exposure. *Neurology.* 1996;**47**:1477-81.

36. Wang PN, Wang SJ, Hong CJ, Liu TT, Fuh JL, Chi CW, et al. Risk factors for Alzheimer's disease: a case-control study. *Neuroepidemiology.* 1997;**16**:234-40.

37. Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB. The association between aluminum-containing products and Alzheimer's disease. *J Clin Epidemiol.* 1990;**43**:35-44.

38. The Canadian Study of Health and Aging: risk factors for Alzheimer's disease in Canada. *Neurology.* 1994;**44**:2073-80.

39. Feychting M, Jonsson F, Pedersen NL, Ahlbom A. Occupational magnetic field exposure and neurodegenerative disease. *Epidemiology.* 2003;**14**:413-9; discussion 427-8.

40. Johansen C. Exposure to electromagnetic fields and risk of central nervous system disease in utility workers. *Epidemiology.* 2000;**11**:539-43.

41. Qiu C, Fratiglioni L, Karp A, Winblad B, Bellander T. Occupational exposure to electromagnetic fields and risk of Alzheimer's disease. *Epidemiology.* 2004;**15**:687-94.

42. Tyas SL, Manfreda J, Strain LA, Montgomery PR. Risk factors for Alzheimer's disease: a population-based, longitudinal study in Manitoba, Canada. *Int J Epidemiol.* 2001;**30**:590-7.

43. Savitz DA, Checkoway H, Loomis DP. Magnetic field exposure and neurodegenerative disease mortality among electric utility workers. *Epidemiology.* 1998;**9**:398-404.

44. Garcia AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. *Int J Epidemiol.* 2008;**37**:329-40.

45. Vergara X, Kheifets L, Greenland S, Oksuzyan S, Cho YS, Mezei G. Occupational exposure to extremely low-frequency magnetic fields and neurodegenerative disease: a meta-analysis. *J Occup Environ Med.* 2013;**55**:135-46.

46. Power MC, Adar SD, Yanosky JD, Weuve J. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology.* 2016;**56**:235-53.

47. Davanipour Z, Sobel E. Long-term exposure to magnetic fields and the risks of Alzheimer's disease and breast cancer: Further biological research. *Pathophysiology.* 2009;**16**:149-56.

48. García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. *Int J Epidemiol.* 2008;**37**:329-40.

49. Terzi M, Ozberk B, Deniz OG, Kaplan S. The role of electromagnetic fields in neurological disorders. *J Chem Neuroanat.* 2016;**75**:77-84.

50. Moulton PV, Yang W. Air pollution, oxidative stress, and Alzheimer's disease. *J Environ Public Health.* 2012;2012:472751.

51. Calderón-Garcidueñas L, Reed W, Maronpot RR, Henríquez-Roldán C, Delgado-Chavez R, Calderón-Garcidueñas A, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol.* 2004;**32**:650-8.

52. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci.* 2009;**32**:506-16.

53. McKenzie J, Bhatti L, Tursan d'Espaignet E. World Health Organization Tobacco Knowledge Summaries: Tobacco and dementia. Geneva, Switzerland: World Health Organization; 2014.

54. Zlokovic BV. Neurovascular mechanisms of Alzheimer's neurodegeneration. *Trends Neurosci.* 2005;**28**:202-8.

55. Chen R. Association of environmental tobacco smoke with dementia and Alzheimer's disease among never smokers. *Alzheimers Dement.* 2012;**8**:590-5.

56. Barnes DE, Haight TJ, Mehta KM, Carlson MC, Kuller LH, Tager IB. Secondhand smoke, vascular disease, and dementia incidence: findings from the cardiovascular health cognition study. *Am J Epidemiol.* 2010; **171**:292-302.

57. Wolffe AP, Matzke MA. Epigenetics: regulation through repression. *Science.* 1999;**286**:481-6.

58. Cacabelos R, Torrellas C. Epigenetics of aging and Alzheimer's disease: Implications for pharmacogenomics and drug response. *Int J Mol Sci.* 2015;**16**:30483-543.

59. Wang J, Yu JT, Tan MS, Jiang T, Tan L. Epigenetic mechanisms in Alzheimer's disease: implications for pathogenesis and therapy. *Ageing Res Rev.* 2013;**12**:1024-41.

60. Tohgi H, Utsugisawa K, Nagane Y, Yoshimura M, Genda Y, Ukitsu M. Reduction with age in methylcytosine in the promoter region-224-101 of the amyloid precursor protein gene in autopsy human cortex. *Mol Brain Res.* 1999;**70**:288-92.
61. Mastroeni D, Grover A, Delvaux E, Whiteside C, Coleman PD, Rogers J. Epigenetic changes in Alzheimer's disease: decrements in DNA methylation. *Neurobiol Aging.* 2010;**31**:2025-37.

62. Chouliaras L, Mastroeni D, Delvaux E, Grover A, Kenis G, Hof PR, et al. Consistent decrease in global DNA methylation and hydroxymethylation in the hippocampus of Alzheimer's disease patients. *Neurobiol Aging.* 2013;**34**:2091-9.

63. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr.* 2009;**21**:243-51.

64. Hou L, Zhang X, Wang D, Baccarelli A. Environmental chemical exposures and human epigenetics. *Int J Epidemiol.* 2011;**41**:79-105.

65. Coppedè F, Teresa Zitarosa M, Migheli F, Lo Gerfo A, Bagnoli S, Dardano A, et al. DNMT3B promoter polymorphisms and risk of late onset Alzheimer's disease. *Curr Alzheimer Res.* 2012;**9**:550-4.

66. Perera G, Stewart R, Higginson IJ, Sleeman KE. Reporting of clinically diagnosed dementia on death certificates: retrospective cohort study. *Age and ageing.* 2016;**45**:668-73.