Review

Geospatial Analysis of Environmental Atmospheric Risk Factors in Neurodegenerative Diseases: A Systematic Review

Mariana Oliveira [1,2,*], **André Padrão** [3], **André Ramalho** [1,2], **Mariana Lobo** [1,2], **Ana Cláudia Teodoro** [4,5], **Hernâni Gonçalves** [1,2] and **Alberto Freitas** [1,2]

1   CINTESIS—Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Rua Doutor Plácido da Costa, s/n, 4200-450 Porto, Portugal; andrelcramalho@gmail.com (A.R.); nanalobo@gmail.com (M.L.); hernanigoncalves@med.up.pt (H.G.); alberto@med.up.pt (A.F.)
2   Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Rua Doutor Plácido da Costa, s/n, 4200-450 Porto, Portugal
3   Faculty of Arts and Humanities, University of Porto, Via Panorâmica, s/n, 4150-564 Porto, Portugal; andre27.f@hotmail.com
4   Department of Geosciences, Environment and Land Planning, Faculty of Sciences, University of Porto, Rua do Campo Alegre 687, 4169-007 Porto, Portugal; amteodor@fc.up.pt
5   Earth Sciences Institute (ICT), Pole of the FCUP, University of Porto, 4169-007 Porto, Portugal
*   Correspondence: mariana_ramos_oliveira@hotmail.com

check for updates

Abstract: Despite the vast evidence on the environmental influence in neurodegenerative diseases, those considering a geospatial approach are scarce. We conducted a systematic review to identify studies concerning environmental atmospheric risk factors for neurodegenerative diseases that have used geospatial analysis/tools. PubMed, Web of Science, and Scopus were searched for all scientific studies that included a neurodegenerative disease, an environmental atmospheric factor, and a geographical analysis. Of the 34 included papers, approximately 60% were related to multiple sclerosis (MS), hence being the most studied neurodegenerative disease in the context of this study. Sun exposure ($n = 13$) followed by the most common exhaustion gases ($n = 10$ for nitrogen dioxide (NO_2) and $n = 5$ for carbon monoxide (CO)) were the most studied atmospheric factors. Only one study used a geospatial interpolation model, although 13 studies used remote sensing data to compute atmospheric factors. In 20% of papers, we found an inverse correlation between sun exposure and multiple sclerosis. No consensus was reached in the analysis of nitrogen dioxide and Parkinson's disease, but it was related to dementia and amyotrophic lateral sclerosis. This systematic review (number CRD42020196188 in PROSPERO's database) provides an insight into the available evidence regarding the geospatial influence of environmental factors on neurodegenerative diseases.

Keywords: neurodegenerative; environment; geospatial; epidemiology; systematic review

1. Introduction

The human brain suffers pathological changes in the process of ageing, leading to a range of neurodegenerative disorders [1]. Until 2050, the world's population over 60 years old is expected to nearly double compared to 2015, reaching 22% [2]. The ageing of the population raises concerns about the future of neurodegenerative diseases [3] and urges the development of better health systems with long-term care tailored to meet the needs of the elderly population [2]. These diseases are characterised by progressive damage or loss of neuronal cells, leading to compromised functioning of the brain, with either motor or cognitive roles being endangered [4]. Alzheimer's disease (AD) is the most

prevalent neurodegenerative disease worldwide [5], and the most common cause of dementia and it is a progressive disease that can be characterised by extensive cognitive damage, commonly affecting the functional competency to perform quotidian actions [6]. Following AD in prevalence, Parkinson's disease (PD) is defined by the dopaminergic neuronal loss, which presents as a Lewy Bodies (LB) disease that during the course of the disease spreads to different regions of the brain, leading to motor and non-motor symptoms [7]. The third most prevalent neurodegenerative disease is multiple sclerosis (MS), affecting around 2.5 million people worldwide, which is an inflammatory demyelination disorder of the brain, frequently of autoimmune origin [5].

Apart from ageing, the most common risk factors in the development of neurodegenerative diseases include gender, clinical history of hypertension, diabetes, cranial injury, tumours, and infections, as well as smoking and drinking habits [8]. However, the knowledge on the development of most of these diseases remains incomplete, including the influence that environmental factors might have in this context [8]. This review focuses on atmospheric pollution due to its significant impact worldwide, with 91% of the world's population living under air pollution levels exceeding the established limits by the World Health Organisation (WHO) [9]. Atmospheric pollutants are all "substances, laid by the human activities with enough concentration to cause detrimental influences to health (. . .)" [10], but some authors also consider natural sources of pollutants [11].

Recent studies point out that atmospheric pollution can trigger mechanisms responsible for neurodegenerative diseases, especially particulate matter with a diameter under 2.5 μm ($PM_{2.5}$) due to its capacity to reach the brain [12]. Four main pathways have been identified to air pollution reaching the brain [13]: systemic inflammation (in which the pollutant penetrates peripheral organs such as the lungs, provoking a systemic response that transfers the inflammation to the brain) [13–17], nasal olfactory (inhaled ultrafine and fine particles that penetrate the lungs reaching the systemic circulation, the trigeminal nerve, the brainstem, the hippocampus, and the frontal lobe) [18–23], adsorbed compounds (particulate matter from air pollution encloses various toxic compounds that may be adsorbed independently of the particle) [24–26] and inhaled oxidation (reactive oxygen agents such as ozone, which interact with proteins and lipids in the lungs altering them into toxic compounds that provoke oxidative stress, leading to various brain damages) [27–31]. $PM_{2.5}$ is associated with AD, PD, dementia, autism, and stroke [32]. Other pollutants such as ozone (O_3), particulate matter with a diameter under 10 μm (PM_{10}), nitrogen dioxide (NO_2), carbon monoxide (CO), and sulphur dioxide (SO_2) are also toxic to the central nervous system (CNS) [33]. Despite the abundance of studies on neurodegenerative diseases and the environmental influence on the CNS, studies considering a geospatial approach are scarce, and many of them only consider the geographic area as a clustering factor [34–36], not proceeding to further analysis.

One of the tools for environmental data extraction and analysis is remote sensing. It has been broadly used in epidemiological studies, increasing the number of publications featuring remote sensing applied to health from 5.6% in 2007 to 13.3% in 2016 [37]. Apart from remote sensing, GIS (geographic information systems), clustering, and spatial models are other tools that can be used to analyse environmental data. Geospatial analysis is a broad concept that combines both exposure assessment methods and posterior statistical analysis, allowing us to integrate information on health and disease of specific regions with environmental data as well as other spatially distributed relevant data such as socio-economic information. Understanding the strengths and limitations of previous studies that used geospatial approach could inform us on how to better delineate future research, thereby maximising the gains regarding the understanding of the geospatial distribution of environmental risk factors associated with neurodegenerative diseases. This type of knowledge is important to establish to aid in planning future policies that mitigate environmental factors, which may be critical in the prevention and progression of neurodegenerative diseases.

It is important to frame the issue of neurodegenerative diseases in the new coronavirus pandemic caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome Corona Virus-2). This virus can penetrate the CNS mainly through two pathways: by retrograde axonal transport via the cribriform plate,

and by the systemic circulatory system [38]. This last pathway is similar to one of the atmospheric pollutants reaching the CNS, raising the hypothesis that this virus may pose a higher potential for neuroinflammation and neurodegeneration [39]. The concept of Neuro-COVID-19 is, thus, being increasingly used in current research [40].

In this systematic review, we aim to identify studies concerning neurodegenerative diseases and their environmental atmospheric risk factors, which have used geographical analysis/tools as part of their work. The methods used to conduct this systematic review are presented in Section 2 (Materials and Methods), including the query used, the inclusion and exclusion criteria, and the study characteristics gathered by the reviewers. In Section 3 (Results), there are two subsections, the first one being identification, screening, and assessment (which explains the main numbers retrieved by the systematic review, from the total number of studies screened to the included papers and their characteristics) and the second being qualitative synthesis (in which the main relations retrieved between the environmental and neurodegenerative diseases are shown). The results from the systematic review are discussed and compared to those in the literature in Section 4 (Discussion), and study limitations are explored. To finalise, a small conclusion is presented in Section 5.

2. Materials and Methods

We searched PubMed, Web of Science, and Scopus databases from inception to the 4th February 2020, date in which the last search was run. The oldest study retrieved was from 1951 [41]. All studies with at least one neurodegenerative disease, one atmospheric pollutant or factor, and some geographic approach were included for screening, with a total of 4655 abstracts screened. No papers were excluded due to language restrictions. For the literature review, we screened the databases using the following keywords: [((alzheimer*) OR (ataxia*) OR (Chorea Minor) OR (creutzfeldt*) OR (dementia*) OR (Frontotemporal) OR (Guillian-barre syndrome) OR (Huntington*) OR (kennedy* disease) OR (Lewy*) OR (motor neuron*) OR (Myotonic dystrophy) OR (neurodegen*) OR (parkinson*) OR (pick's) OR (Prion) OR (progressive AND palsy) OR (progressive muscular atrophy) OR (sclerosis*) OR (*senile) OR (spinal atrophy)) AND ((atmospher*) OR (carbon) OR (environment*) OR (humidity) OR (meteorologic*) OR (nitrogen) OR (ozone) OR (particulate*) OR (PM2*) OR (pollut*) OR (sulphur*) OR (surface pressure) OR (temperature)) AND ((drone) OR (geograph*) OR (imagery) OR (landsat) OR (map) OR (mapping) OR (modis) OR (remote sens*) OR (satellite) OR (sentinel) OR (spatial) OR (topologic*))]. This query was a result of the sensitivity analysis of terms that could be relevant for this review, keywords that added no papers to the results were excluded from the query. These included the terms: geospatial, spatio*, and cartograph*. This review was submitted to PROSPERO under the registration number CRD42020196188.

All studies with at least one neurodegenerative disease, one atmospheric pollutant or factor, and some geographic approach were included for screening. The inclusion criteria were the following: (1) Studying a neurodegenerative disease; (2) Accounting for atmospheric environmental factors or pollutants; (3) Using geospatial analysis or tools; (4) All the previous criteria in the same study. Studies were excluded if: no evidence of geographic analysis was found (stating a geographic area without further analysing it or comparing it to other areas was an exclusion motive), no atmospheric pollutants or factors referred (soil and water pollutants were excluded from this revision) and no focus on neurodegenerative diseases (studies about the mechanisms and biospecimen behind the disease were discarded). Full papers were independently read by the same researchers to apply the inclusion and exclusion criteria further. Unavailable full texts were requested to the authors individually. Those studies that remained unavailable were excluded.

For the included full papers data extraction and analysis, structured forms were created and used by the reviewers. The forms included free writing inputs such as the title, year, country, authors, DOI (digital object identifier), participants, aims, and key findings. Additionally, multiple-choice inputs were available for study type, statistical methods, outcome measurements, study limitations, neurodegenerative disease, environmental risk factors, geographic approach, and type of geographical

approach. A level of simplification was applied to categorise the study limitations, to better fit most studies on the main biases and issues encountered. Both reviewers filled these forms independently and discussed the extracted information at the end of the process. Nonetheless, the reviewers had the option to input free text if they considered necessary to complement any of the inputs mentioned. Risk of bias from individual studies was assessed by fitting the study limitations into one or more of the pre-defined form options: none given by the authors; conflict of interests (any conflict of interests stated by the authors); confounding factors (unassessed confounding factors); ecological bias (extrapolation of a conclusion from a population to a patient); exposure assessment (issues with assessing the patient's exposure to the environmental factor); interpolation (issues with spatially interpolating the environmental factor); recall bias (data collection relying on patient's memory); migration of patients (patients moving from one residence to another); referral bias (studies relying on the doctor's referring similar cases); sampling issues (under sampling; over sampling or non-representative sampling); statistical issues (lacking of more relevant statistical methods); study design issues (studies acknowledging inappropriate study design); survival bias (relying on a patient being alive over a period of time); time related issues (inability to assess the amount of time a patient was exposed to the environmental factor); unassessed patients (patients outside the databases not being considered).

3. Results

3.1. Identification, Screening, and Assessment

Of the 4655 articles initially screened, only 34 were included in the final study. The selection process is summarised using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [42] presented by a flow diagram (Figure 1). In the diagram of Figure 1, it is possible to identify that 4655 records were screened in this systematic review, most of which did not relate simultaneously to neurodegenerative diseases, atmospheric factors, and geographical factors (*n* = 3239). After screening, 90 full papers were assessed for eligibility, from which nearly half (*n* = 44) did not tackle any atmospheric pollutants or factors. By the end of the selection process, 34 articles were included. The discrepancy in the total number of excluded studies and the sum of the exclusion reasons categories is due to the overlapping of exclusion reasons.
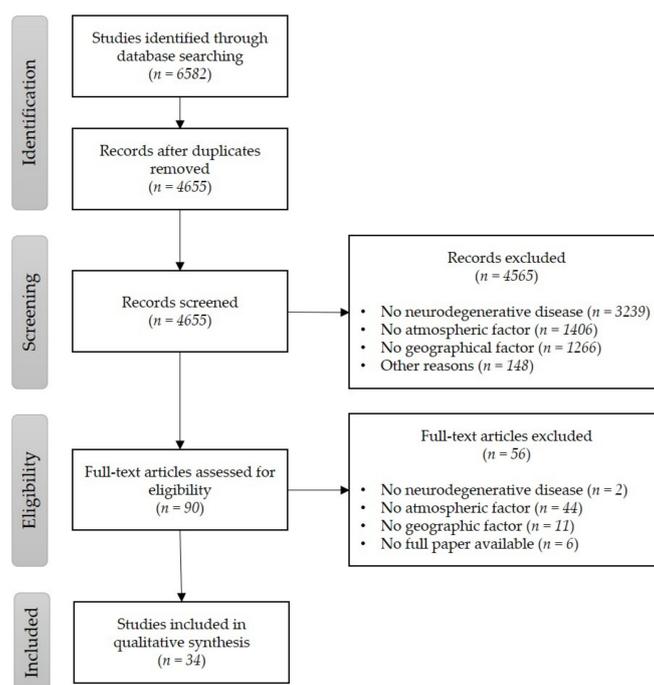

Figure 1. Systematic review PRISMA flowchart.

The number of times each disease, environmental factor, and geographical approach was retrieved are detailed in Table 1. The sum of the categories' absolute frequencies for environmental and geographic factors exceeds the number of studies because they are not mutually exclusive. Most papers focused on (MS) (56%), of which 63% studied sun exposure as the main environmental factor, mostly using remote sensing data (58%), always combined with another geographic factor. Administrative divisions were the most used geographical approach when considering all diseases (47%).

Table 1. The number of studies addressing each subtopic of the domains, retrieved from the included studies: neurodegenerative diseases, environmental pollutants/factors, and geographic factors.

	Number of Studies	Percentage of Total Entries
Neurodegenerative Disease		
Amyotrophic lateral sclerosis	2	5.9
Dementia (includes Alzheimer's disease)	3	8.8
Motor neuron disease	1	2.9
Multiple sclerosis	19	55.9
Paediatric multiple sclerosis	2	5.9
Parkinson's disease	7	20.6
Environmental Pollutant/Factor		
Arsenic (As)	1	1.2
Benzopyrene (C_2OH_{12})	1	1.2
Benzene (C_6H_6)	1	1.2
Cadmium (Cd)	1	1.2
Carbon monoxide (CO)	5	6.1
Cooper (Cu)	2	2.4
Hydrogen sulphide (H_2S)	1	1.2
Humidity	3	3.7
Index	2	2.4
Magnesium (Mg)	2	2.4
Manganese (Mn)	1	1.2
Nickel (Ni)	1	1.2
Nitrogen dioxide (NO_X)	10	12.2
Ozone (O_3)	4	4.9
Lead (Pb)	5	6.1
PM_{10}	6	7.3
PM_{25}	8	9.8
Precipitation	6	7.3
Pressure	5	6.1
Radon (Rn)	1	1.2
Sulphur dioxide (SO_2)	6	7.3
Sun exposure	13	15.9
Temperature	8	9.8
Geographic Factors		
Administrative division	16	24.2
Clustering	2	3.0
GIS	14	21.2
Latitude	5	7.6
Longitude	1	1.5
Remote sensing	13	19.7
Residence	14	21.2
Spatial interpolation	1	1.5

The main characteristics of the studies—study design, outcomes, statistical methods, and study limitations—are summarised in Table 2. Most of the studies are cross-sectional ($n = 12$) and correlation was the most reported effect measure ($n = 19$) and statistical method ($n = 22$) used. The most common study limitations found were related to exposure assessment ($n = 18$) and confounding

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

6 of 25

factors *n* = 15). The full characteristics of the studies can be found in Table 3. This table contains all the characteristics retrieved by the reviewers for each included study: country of origin, year of publication, neurodegenerative disease, environmental factor, geographic factor, study design, study limitations, statistical methods, and outcome. A list of excluded studies [1,7,43–96] is also available in Table A1, Appendix A.

Table 2. Study characteristics summary: study design, study limitations, statistical methods, and effect measures.

	Number of Studies	Percentage of Total Entries
Study Design		
Case-control	9	26.5
Cohort	4	11.8
Cross-sectional	12	35.3
Ecological	6	17.6
Methodological	2	5.9
Review	1	2.9
Study Limitations		
Conflict of interests	1	1.1
Confounding	15	16.1
Ecological bias	3	3.2
Exposure assessment	18	19.4
Interpolation	3	3.2
Recall bias	3	3.2
Migration	4	4.3
None is given by the author	5	5.4
Referral bias	2	2.2
Sampling	7	7.5
Statistics	13	14.0
Study design	3	3.2
Survival bias	1	1.1
Time-related	9	9.7
Unassessed patients	6	6.5
Statistical Methods		
ANOVA	2	2.6
Chi-squared	5	6.5
Clustering	2	2.6
Correlation	22	28.6
Cox regression	4	5.2
Linear regression	11	14.3
Logistic regression	10	13.0
None	2	2.6
Poisson regression	3	3.9
Sensitivity analysis	10	13.0
Spatial autoregressive model	1	1.3
T-test	5	6.5
Effect Measures		
Coefficients	14	24.1
Correlation	19	32.8
Hazard ratio	3	5.2
None	3	5.2
Odds ratio	11	19.0
Prevalence	4	6.9
Relative risk	4	6.9

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

7 of 25

Table 3. Study characteristics of the 34 included papers [97].

Ref	Country (year)	Neurodege-Generative Disease	Environmental Factor	Geographic Factor	Study Design	Study Limitations	Statistical Methods	Outcome
[97]	Canada (2012)	Multiple sclerosis	Sun exposure	GIS, Remote Sensing	Methodological	Exposure assessment	None	None
[98]	Israel (1971)	Multiple sclerosis	Sun exposure, Temperature, Precipitation, Humidity	Residence	Review	None given by the authors	None	None
[99]	Bulgaria (1987)	Multiple sclerosis	Sun exposure, Temperature, Precipitation	Administrative division, Latitude	Cross-sectional	Unassessed patients	Correlation, Chi-squared, Linear regression	Correlation, Coefficients
[100]	Australia (2001)	Multiple sclerosis	Sun exposure, Temperature, Precipitation	Administrative division, Latitude, Remote Sensing	Ecological	Confounding, Exposure assessment	Correlation, Poisson regression	Prevalence, Correlation
[101]	Canada (2011)	Multiple sclerosis	Sun exposure	Latitude, Longitude, Remote Sensing	Cross-sectional	None given by the authors	Correlation, Linear regression	Correlation
[102]	England (2011)	Multiple sclerosis	Sun exposure	GIS, Remote Sensing	Cross-sectional	Confounding, Sampling, Statistics	Correlation, Linear regression	Correlation, Coefficients
[103]	USA (2017)	Multiple sclerosis	Sun exposure, Temperature	Administrative division, GIS, Remote Sensing	Cross-sectional	Confounding, Statistics	Correlation, Linear regression	Correlation, Coefficients
[104]	USA (2018)	Multiple sclerosis	Sun exposure	Residence, Remote Sensing	Cohort	Confounding, Exposure assessment, Interpolation, Recall bias, Migration, Survival bias, Time related	Cox regression	Relative risk, Hazard ratio
[105]	USA (1983)	Multiple sclerosis	Sun exposure, Temperature, Precipitation, Humidity	Latitude	Case-control	None given by the authors	Logistic regression	Relative risk

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

8 of 25

Table 3. *Cont.*

Ref	Country (year)	Neurodege-Generative Disease	Environmental Factor	Geographic Factor	Study Design	Study Limitations	Statistical Methods	Outcome
[106]	Italy (2016)	Multiple sclerosis	Sun exposure	Administrative division, GIS	Cross-sectional	Confounding, Ecological bias, Time related	Correlation, Linear regression	Correlation, Odds ratio
[107]	Canada (2018)	Multiple sclerosis	Sun exposure	Residence, Remote Sensing	Cohort	Confounding, Exposure assessment, Time related	Linear regression	Coefficients
[108]	Norway (2010)	Multiple sclerosis	Sun exposure, Temperature, Precipitation	Administrative division	Cross-sectional	Migration, Statistics	ANOVA, Poisson regression	Prevalence
[109]	Italy (2018)	Multiple sclerosis	$PM_{2.5}$	Residence, Remote Sensing	Cross-sectional	Conflict of interests, Confounding, Study design	Correlation, Chi-squared	Correlation, Coefficients
[110]	USA (2008)	Multiple sclerosis	PM_{10}, $PM_{2.5}$, NO_X, SO_2, CO	Administrative division	Cross-sectional	None given by the authors	Correlation, T-test, Linear regression	Correlation, Coefficients
[111]	Italy (2005)	Multiple sclerosis	SO_2	Administrative division, Latitude	Cross-sectional	Exposure assessment, Interpolation	Correlation, Linear regression	Correlation, Coefficients
[112]	Iran (2014)	Multiple sclerosis	PM_{10}, NO_X, SO_2	Clustering, GIS	Cross-sectional	Confounding, Statistics, Study design	Correlation, Clustering	Correlation, Coefficients
[113]	Iran (2018)	Multiple sclerosis	Index	Administrative division, GIS, Residence	Cross-sectional	Exposure assessment, Statistics	Correlation, Logistic regression	Odds ratio, Coefficients
[114]	Norway (1997)	Multiple sclerosis	Mg	Administrative division	Methodological	Confounding	Correlation	None
[115]	England (2016)	Multiple sclerosis	Rn	Residence	Ecological	Sampling, Statistics, Unassessed patients	Correlation, Chi-squared, Linear regression	Correlation, Coefficients
[116]	USA (2017)	Paediatric Multiple sclerosis	Index	GIS, Residence	Case-control	Exposure assessment, Statistics, Time related, Unassessed patients	Logistic regression	Odds ratio, Coefficients

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

9 of 25

Table 3. *Cont.*

Ref	Country (year)	Neurodege-Generative Disease	Environmental Factor	Geographic Factor	Study Design	Study Limitations	Statistical Methods	Outcome
[117]	USA (2018)	Paediatric Multiple sclerosis	PM_{10}, $PM_{2.5}$, NO_X, SO_2, CO, O_3, Pb	Administrative division, GIS, Residence	Case-control	Exposure assessment, Referral bias, Time related	T-test, Logistic regression	Odds ratio
[118]	USA (2010)	Parkinson's disease	Cu, Pb, Mg	Administrative division	Ecological	Confounding, Exposure assessment, Statistics	Logistic regression, Sensitivity analysis	Relative risk, Odds ratio
[119]	Spain (2016)	Parkinson's disease	Pb	Administrative division, GIS	Ecological	Exposure assessment, Sampling, Unassessed patients	Correlation, T-test	Correlation, Coefficients
[120]	Canada (2007)	Parkinson's disease	NO_X, Mn	Residence, Remote Sensing, Spatial interpolation	Case-control	Confounding, Exposure assessment, Interpolation, Study design, Time related	Correlation, Linear regression, Logistic regression, Cox regression, Sensitivity analysis	Prevalence, Correlation, Odds ratio
[121]	USA (2016)	Parkinson's disease	PM_{10}, $PM_{2.5}$, NO_X	GIS, Residence	Case-control	Exposure assessment, Recall bias, Statistics, Time related	Correlation, Logistic regression, Sensitivity analysis	Correlation, Odds ratio
[122]	Australia (2020)	Parkinson's disease	$PM_{2.5}$, NO_X	Residence, Remote Sensing	Cross-sectional	Recall bias, Referral bias, Sampling	Logistic regression, Sensitivity analysis	Odds ratio
[123]	Taiwan (2016)	Parkinson's disease	NO_X, CO	GIS, Residence	Case-control	Confounding, Sampling, Statistics	Correlation, Chi-squared, Logistic regression, Sensitivity analysis	Correlation, Odds ratio

Int. J. Environ. Res. Public Health **2020**, 17, 8414

10 of 25

Table 3. *Cont.*

Ref	Country (year)	Neurodege-Generative Disease	Environmental Factor	Geographic Factor	Study Design	Study Limitations	Statistical Methods	Outcome
[124]	France (2017)	Parkinson's disease	Sun exposure, $PM_{2.5}$	Administrative division, Remote Sensing	Ecological	Ecological bias, Exposure assessment, Migration	Correlation, Poisson regression, Sensitivity analysis	Correlation, Relative risk
[125]	USA (2019)	Dementia	Temperature	Administrative division, Residence, Remote Sensing	Cohort	Confounding, Exposure assessment, Statistics	Correlation, Cox regression, Sensitivity analysis	Correlation, Hazard ratio
[126]	Taiwan (2019)	Dementia	PM_{10}, NO_X, SO_2, CO, O_3	Clustering	Case-control	Confounding, Exposure assessment, Statistics, Unassessed patients	Correlation, Logistic regression, Sensitivity analysis	Odds ratio
[127]	Canada (2017)	Dementia	$PM_{2.5}$, NO_X, O_3	GIS, Residence, Remote Sensing	Cohort	Confounding, Exposure assessment, Time related, Unassessed patients	Cox regression, Sensitivity analysis	Hazard ratio
[128]	Spain (2018)	Amyotrophic lateral sclerosis	PM_{10}, PM_{25}, NO_X, SO_2, CO, O_3, Cu, Pb, As, Ni, Cd, C_6H_6, H_2S, C_6OH_{12}	GIS	Case-control	Ecological bias, Exposure assessment, Sampling, Statistics	T-test, Chi-squared, Linear regression, Sensitivity analysis	Prevalence, Odds ratio
[129]	Taiwan (2013)	Amyotrophic lateral sclerosis	Sun exposure, Temperature, Precipitation, Humidity, Pressure	Administrative division	Case-control	Exposure assessment, Migration, Sampling, Time related	Correlation, Spatial autoregressive model, Clustering	Correlation, Coefficients
[130]	Spain (2016)	Motor neuron disease	Pb	Administrative division, GIS	Ecological	None given by the authors	Correlation, T-test, ANOVA	Correlation, Coefficients

The country with the highest number of published papers under the criteria of this systematic review was the United States of America (USA), with nine included papers. It was followed by Canada with five papers. However, Europe, with the aggregation of articles from Bulgaria, England, France, Italy, Norway, and Spain totals twelve included papers. The Middle East and Asia had three papers, and Australia had two papers. Table 4 contains the papers studied by each geographical region, grouped by neurodegenerative disease.

Table 4. Studies published by each geographic region, grouped by neurodegenerative disease.

	Amyotrophic Lateral Sclerosis	Dementia	Motor Neuron Disease	Multiple Sclerosis	Paediatric Multiple Sclerosis	Parkinson
Asia	[129]	[126]				[123]
Australia				[100]		[122]
Europe	[128]		[130]	[99,102,106,108,109,111,114,115]		[119,124]
Middle East				[98,112,113]		
North America		[125,127]		[97,101,103–105,107,110]	[116,117]	[118,120,121]

Of the 34 included papers, 19 were published in the last 5 years. Until 2000, only four studies were found corresponding to the criteria of this systematic review, all of which focused on multiple sclerosis. Until 2007, except for a paper focusing on Parkinson's disease, no other neurodegenerative disease had been considered.

3.2. Qualitative Synthesis

Among the 19 papers focused on MS, with sun exposure being the most studied environmental factor (n = 13), one was methodological and did not measure any outcome related to MS [97]. An inverse association between MS and sun exposure was reported in seven studies [98–104]. In contrast, in the other three studies, no significant association was found [105–107], one of which attributed the results to the adjusting for latitude [105].

As for temperature, five studies found it to be negatively related to MS [98–100,103,108] and one found this association to be due to its high correlation with latitude [105]. Precipitation was found to be uncorrelated [98,100,105] or only weakly positively correlated [99,108] to MS. Humidity was focused only on two studies, both of which found no correlation to MS [98,105].

Concerning the environmental pollutants, $PM_{2.5}$ was found to be positively correlated with MS in one study [109] and not significantly correlated with another [110]. SO_2 had no correlation [110,111] except in one study [112]. PM_{10} and NO_X (nitrogen oxides) were studied only twice and studies disagree in the reported correlation [110,112]. Additionally, a study found a positive association between an air quality index (AQI) and MS [113], and magnesium (Mg) was found to be negatively correlated [114], while radon was not found to be associated with MS [115]. In the domain of paediatric MS, PM_{10} was found to be related to it [116,117], as well as $PM_{2.5}$, Pb (lead), SO_2, and CO [117].

Of the seven studies concerning Parkinson's Disease (PD), Pb was found to be positively spatially related [118,119], as well as Cu (copper), Mg [118], and Mn (manganese) [120]. PM_{10} and $PM_{2.5}$ were not correlated [121], even though one study found a positive non-significant relation [122]. NO_2 is the most controversial environmental factor studied in the context of PD, with one study finding positive associations [122,123] and another not finding any association [121]. Another study found an association only when adjusting for smoking [122] and one study found it to be both associated and not associated when comparing different cities [120]. Only one study explored sun exposure and found it to be associated when adjusting for age, positively in older subjects, and inversely in subjects below 70 years [124].

Three studies were included in the context of dementia, which comprehended Alzheimer's, one of which found a positive relation to temperature [125]. The other two studies agreed that NO_2 and PM_{10}

were positively correlated with dementia [126,127]. Furthermore, a study found CO to be inversely correlated with dementia and SO_2 and O_3 not to be correlated [126].

Concerning amyotrophic lateral sclerosis (ALS), two studies were found but with no overlapping environmental factors. A study found NO (nitrogen oxide), NO_2, and Cd (cadmium) to be positively correlated with ALS and O_3 to be inversely correlated, while benzopyrene was not found to be correlated [128]. The other study found positive correlations between ALS and both precipitation and sun exposure [129].

As for motor neuron disease, in the only study included, it was found to be correlated with Pb [130].

Most studies simply used administrative divisions as geographic analysis to assess exposure to atmospheric factors, but GIS and remote sensing were also broadly used to spatially compute and model those factors. Specifically, studies that used remote sensing focused on NASA's (National Aeronautics and Space Administration) satellite TOMS (Total Ozone Mapping Spectrometer) to compute the amount of sun exposure [97,101,104,107].

4. Discussion

Multiple sclerosis is known to be tied to latitude, thus raising the suggestion that sun exposure, as well as temperature and humidity, are probably the environmental factors behind that relationship [105]. Sun exposure is one of the strongest correlates to latitude [59] and its relation to MS may be explained by biological mechanisms that suggest that ultraviolet radiation may be immunosuppressive [131]. However, these mechanisms seem to be most relevant in early life [60]. The studies retrieved in this systematic review mostly corroborated this hypothesis [98–104], although three studies did not [105–107], with one even attributing the relationship between sun exposure and MS to the high correlation between sun exposure and latitude [105]. Amyotrophic lateral sclerosis also has an environment hypothesis linked to the genetics of the disease and its prevalence. However, studies found in this systematic review focused mostly on water and soil exposures, and are thus outside the scope of this systematic review [61,79]. Another study identified a substantial gap in studies addressing environmental risk factors that may cause ALS [64]. The low incidence rate may be related to the low number of studies concerning the disease [64].

There is evidence that PD is mediated by environmental risk factors such as manganese or lead with the need to better model the exposure geographically model was noted [62]. This corroborates the findings of this systematic review. Dementia risk has been related to occupational exposure to air pollutants such as PM, CO_2, CO, and SO_2 [90], corroborating the findings in this systematic review. However, as dementia encloses Alzheimer's disease, but is not limited to it, no studies were found that approached AD individually, and thus the results might have been slightly different if only AD were studied. The geographic distribution of the included studies shows a lack of studies in South America and Africa, creating the opportunity for research in the field of environmental epidemiology of neurodegenerative diseases in these regions. Analysing the source of data from each study closer, the constatation of the lack of studies from these regions remains. Although Africa has the lowest rates of neurodegenerative diseases in the world, the same cannot be said about South America, so this is a good region to develop further research.

The increasing number of papers published over the years reflects not only the general increase in scientific publications but also the availability of the technology to proceed with the geographic analysis of environmental factors. The rising interest and research investment in this thematic are also reflected in the increased number of studies over the last few years. In particular, papers referring to the new COVID-19 pandemic effects on neurodegenerative diseases have raised awareness of the synergy between this virus and the environment, which increases the risk of developing these diseases. Knowing the risk the atmospheric pollution already represents upon the central nervous system, and by adding the risk of COVID-19, which may penetrate the brain through similar pathways to those of air pollution, there is a higher potential for neuroinflammation and neurodegeneration [39].

Interesting positive relations between NO_2 levels and COVID-19 fatality rates have been retrieved from a spatial analysis study [132], indicating that this pollutant may weaken the immunity of the lungs, thus allowing the virus to access the bloodstream and eventually reach the brain [133]. Vitamin D has been described as having antiviral properties, and thus the lack of sun exposure may be problematic in people already with neurological conditions, such as MS and PD [134].

One possible limitation of our study might be not having found studies concerning other neurodegenerative diseases, such as Creutzfeldt-Jakob and Huntington's, therefore not covering the whole domain of neurodegenerative diseases defined at the start of this review. The lack of studies regarding other neurodegenerative diseases is due to the low number of studies using geospatial analysis when considering these diseases. Notwithstanding, most of the included studies focused on MS since it is mostly related to sun exposure—often derived from remote sensing—thus making it the disease most geographically studied. Grey literature was not screened, thus non-indexed papers may have escaped our research. Including this literature could have mitigated the lack of studies focussing on the remaining neurodegenerative diseases that were not found under the scope of this review. As such, further inclusion of this literature could pose an interesting opportunity for future research.

5. Conclusions

The most studied neurodegenerative disease in the context of this systematic review was MS, having over half the studies covering it. It is mostly unanimous that sun exposure is a preventive factor in the development of MS. The relationship to air pollutants remains unknown, and further investigation is needed to understand if such a relationship exists. As for the other diseases, air pollutants have become more broadly studied. Metals such as Pb and Mn were found to be related with Parkinson's disease and ALS, respectively. NO_X is the most common pollutant to be studied, but also the most ambiguous, being found to be both related and unrelated with Parkinson's disease, and positively correlated with dementia and ALS. The geospatial analysis was mostly used to estimate exposure assessment, either by attributing a value to each administrative division and matching it to the residence of the patient or care unit location or by using remote sensing and GIS to compute the atmospheric factor's concentration or value geographically. The present systematic review provides a basis of the available evidence regarding the influence of environmental factors on neurodegenerative diseases using geospatial analysis. The ever-increasing amount of data and technological possibilities to advance on this analysis supports the development of further research on this topic. It is important to identify mitigation measures to reduce exposure to air pollution. Regulation on the levels of air pollution and accurate monitoring of these same levels could help ensure that the population isn't over-exposed to harmful components of the atmosphere.

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

14 of 25

Appendix A

Table A1. List of the 56 excluded papers.

Ref	Country (Year)	Title	Authors	Exclusion Reasons
[43]	Poland (1969)	Epidemiological study of multiple sclerosis in western Poland	W. Cendrowski, M. Wender, W. Dominik, Z. Flejsierowicz, M. Owsianowski, M. Popiel	No ENV
[44]	Germany (1969)	Multiple sclerosis in Europe	R. C. Behrend	No ENV
[45]	Republic of South Africa (1975)	Comparative epidemiological studies of multiple sclerosis in South Africa and Japan	A. V. Bird, E. Satoyoshi	No ENV
[46]	Germany (1984)	Epidemiological investigations into multiple sclerosis in Southern Hesse	Klaus Lauer, Wolfgang Firnhaber, Robert Reining, Brigitte Leuchtweis	No ENV
[47]	Italy (1993)	Multiple sclerosis: does epidemiology contribute to providing etiological clues	Enrico Granieri, Ilaria Casetta, Maria R. Tola, Vittorio Govoni, Ezio Paolino, Susanna Malagù, Vincenza C. Monetti, Mirko Carreras	No ENV
[48]	Czech Republic (1994)	Geographic aspects in the epidemiology of multiple sclerosis	P. Lenský	No full paper
[49]	France (1995)	Epidemiology of Creutzfeldt-Jakob disease	N. Delasnerie-Laupretre, A. Alperovitch	No full paper
[50]	Hungria (1997)	Monthly distribution of multiple sclerosis patients' births	Padmanabhan Bharanidharan	No GEO
[51]	USA (1997)	The Epidemiology of Multiple Sclerosis	W. E. Hogancamp, M. Rodriguez, B. G. Weinshenker	No ENV
[52]	Canada (1999)	Parkinson's disease, multiple sclerosis and amyotrophic lateral sclerosis: The iodine-dopachrome-glutamate hypothesis	Harold D. Foster	No ENV
[53]	United Kingdom (2000)	Amyotrophic lateral sclerosis: toxins and environment	J. D. Mitchell	No ENV, No GEO
[54]	Spain (2002)	Epidemiologia genetica de la esclerosis multiple	D.F. Uría	No ENV
[55]	USA (2004)	Environmental risk factors in multiple sclerosis aetiology	Ruth Ann Marrie	No GEO
[56]	Italy (2004)	Genes environment and susceptibility to multiple sclerosis	Stefano Sotgiu, Maura Pugliatti, Maria Laura Fois, Giannina Arru, Alessandra Sanna, Maria Alessandra Sotgiu, Giulio Rosati	No ENV
[57]	USA (2005)	Autoimmunity: Multiple Sclerosis	Beau M. Ances, Nancy J. Newman, Laura J. Balcer	No ENV, No GEO

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

15 of 25

Table A1. *Cont.*

Ref	Country (Year)	Title	Authors	Exclusion Reasons
[58]	USA (2006)	Studies of Multiple Sclerosis in Communities Concerned about Environmental Exposures	Dhelia M. Williamson	No ENV
[59]	USA (2007)	Environmental risk factors for multiple sclerosis Part II Noninfectious factors	Alberto Ascherio, Kassandra L. Munger	No ENV, No GEO
[60]	United Kingdom (2008)	Environmental factors and multiple sclerosis	George C. Ebers	No ENV
[61]	France (2011)	Contribution of geolocalisation to neuroepidemiological studies incidence of ALS and environmental factors in Limousin France	F. Boumediène, M. Druet-Cabanac, B. Marin, Pierre-Marie Preux, P. Couratier	No ENV
[62]	USA (2012)	Environmental risk factors	Gill Nelson, Brad A. Racette	No GEO
[63]	USA (2012)	Predictors of Survival in Patients with Parkinson Disease	Allison W. Willis, Mario Schootman, Nathan Kung, Bradley A. Evanoff, Joel S. Perlmutter, Brad A. Racette	No ENV
[64]	USA (2012)	Spatial clustering of amyotrophic lateral sclerosis and the potential role of BMAA	Tracie A. Caller, Nicholas C. Field, Jonathan W. Chipman, Xun Shi, Brent T. Harris, Elijah W. Stommel	No ENV
[65]	United Kingdom (2013)	Epidemiology of neurologically disabling disorders	Alan Tennant	No ENV, No GEO
[66]	Kuwait (2013)	Risk factors for multiple sclerosis in Kuwait a population-based case control study	Hanan H. Al-Afasy, Mohammed A. Al-Obaidan, Yousef A. Al-Ansari, Sarah A. Al-Yatama, Mohammed S. Al-Rukaibi, Nourah I. Makki, Anita Suresh, Saeed Akhtar	No ENV, No GEO
[67]	Spain (2014)	Geographical analysis of the sporadic Creutzfeldt Jakob disease distribution in the autonomous community of the Basque Country for the period 1995 2008	Saioa Chamosa, Ibon Tamayo, José M. Arteagoitia-Axpe, Ramón A. Juste, Ana Belém Rodríguez-Martínez, Juan J. Zarranz-Imirizaldu	No ENV
[68]	USA (2015)	Association Between Alzheimer Dementia Mortality Rate and Altitude in California Counties	Stephen Thielke, Christopher G. Slatore, William A. Banks	No ENV
[69]	United Kingdom (2015)	Geographical variation in dementia~: examining the role of environmental factors in Sweden and Scotland	Tom C. Russ, Margaret Gatz, Nancy L. Pedersen, Jean Hannah, Grant Wyper, G. David Batty, Ian J. Deary, John M. Starr	No ENV
[70]	Norway (2015)	Socio economic factors and immigrant population studies of multiple sclerosis	P. Berg-Hansen, E. G. Celius	No ENV

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

16 of 25

Table A1. *Cont.*

Ref	Country (Year)	Title	Authors	Exclusion Reasons
[71]	Canada (2015)	The EnvIMS Study Design and Methodology of an International Case Control Study of Environmental Risk Factors in Multiple Sclerosis	Sandra Magalhaes, Maura Pugliatti, Ilaria Casetta, Jelena Drulovic, Enrico Granieri, Trygve Holmøy, Margitta T. Kampman, Anne-Marie Landtblom, Klaus Lauer, Kjell-Morten Myhr, Maria Parpinel, Tatjana Pekmezovic, Trond Riise, David Wolfson, Bin Zhu, Christina Wolfson	No ENV, No GEO
[72]	Sweden (2015)	Vitamin D and multiple sclerosis from epidemiology to prevention	P. Sundström, J. Salzer	No ENV
[73]	USA (2016)	Environmental control of autoimmune inflammation in the central nervous system	Veit Rothhammer, Francisco J. Quintana	No NEURO
[74]	USA (2016)	Epidemiology of Multiple Sclerosis From Risk Factors to Prevention An Update	Alberto Ascherio, Kassandra L. Munger	No ENV
[75]	USA (2016)	Fine Particulate Matter Residential Proximity to Major Roads and Markers of Small Vessel Disease in a Memory Study Population	Elissa H. Wilker, Sergi Martinez-Ramirez, Itai Kloog, Joel Schwartz, Elizabeth Mostofsky, Petros Koutrakis, Murray A. Mittleman, Anand Viswanathan	No NEURO
[76]	United Kingdom (2016)	Geographical Variation in Dementia Mortality in Italy New Zealand and Chile The Impact of Latitude Vitamin D and Air Pollution	Tom C. Russ, Laura Murianni, Gloria Icaza, Andrea Slachevsky, John M. Starr	No ENV
[77]	Ecuador (2016)	Prevalence of multiple sclerosis in Latin America and its relationship with European migration	Edgar Correa, Víctor Paredes, Braulio Martínez	No ENV
[1]	USA (2016)	Seeking environmental causes of neurodegenerative disease and envisioning primary prevention	Peter S. Spencer, Valerie S. Palmer, Glen E. Kisby	No ENV
[78]	USA (2017)	Associations of Spatial Disparities of Alzheimer's Disease Mortality Rates and Soil Selenium Sulfur Concentrations and Risk Factors in the United States	Hongbing Sun	No ENV
[79]	Italy (2017)	Incidence of amyotrophic lateral sclerosis in the province of Novara Italy and possible role of environmental pollution	Marina Tesauro, Michela Consonni, Tommaso Filippini, Letizia Mazzini, Fabrizio Pisano, Adriano Chiò, Aniello Esposito, Marco Vinceti	No ENV

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

17 of 25

Table A1. *Cont.*

Ref	Country (Year)	Title	Authors	Exclusion Reasons
[80]	France (2017)	Small area distribution of multiple sclerosis incidence in western France in search of environmental triggers	Karima Hammas, Jacqueline Yaouanq, Morgane Lannes, Gilles Edan, Jean-François Viel	No ENV
[81]	Spain (2017)	The Geography of the Alzheimer's Disease Mortality in Spain Should We Focus on Industrial Pollutants Prevention	Èrica Martínez-Solanas, Montse Vergara-Duarte, Miquel Ortega Cerdà, Juan Carlos Martín-Sánchez, Maria Buxó, Eduard Rodríguez-Farré, Joan Benach, Glòria Pérez	No ENV
[82]	Iran (2017)	The relationship between the amount of radiation, relative humidity, and temperature with the risk of multiple sclerosis in Isfahan province, Iran, during the years 2001–2014	A. Karimi, A. Delpisheh, F. Ashtari, K. Sayehmiri, R. Meamar	No full paper
[83]	Netherlands (2018)	Assessment of residential environmental exposure to pesticides from agricultural fields in the Netherlands	Maartje Brouwer, Hans Kromhout, Roel Vermeulen, Jan Duyzer, Henk Kramer, Gerard Hazeu, Geert de Snoo, Anke Huss	No ENV
[84]	France (2018)	Environmental factors in the development of multiple sclerosis	L. Michel	No ENV, No GEO
[85]	Iran (2018)	Estimated incidence rate of multiple sclerosis and its relationship with geographical factors in Isfahan province between the years 2001 and 2014	Fereshteh Ashtari, Arezoo Karimi, Ali Delpisheh, Rokhsareh Meamar, Kourosh Sayehmiri, Salman Daliri	No ENV
[86]	Australia (2018)	Health outcomes and lifestyle in a sample of people with multiple sclerosis HOLISM Longitudinal and validation cohorts	Tracey J. Weiland, Alysha M. De Livera, Chelsea R. Brown, George A. Jelinek, Zoe Aitken, Steve L. Simpson Jr., Sandra L. Neate, Keryn L. Taylor, Emily O'Kearney, William Bevens, Claudia H. Marck	No ENV
[87]	USA (2019)	ALS and environment Clues from spatial clustering	P. S. Spencer, E. Lagrange, W. Camu	No ENV
[88]	Italy (2019)	Amyotrophic Lateral Sclerosis Descriptive Epidemiology: The Origin of Geographic Difference	Giancarlo Logroscino, Marco Piccininni	No ENV
[89]	Iran (2019)	Can environmental factors increase the risk of multiple sclerosis A narrative review	Hoda Naghshineh, Seyed Mohammad Masood Hojjati, Ali Alizadeh Khatir, Payam Saadat, Alijan Ahmadi Ahangar	No ENV

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

18 of 25

Table A1. *Cont.*

Ref	Country (Year)	Title	Authors	Exclusion Reasons
[90]	USA (2019)	Increased Dementia Mortality in West Virginia Counties with Mountaintop Removal Mining	A. K. Salm, Michael J. Benson	No ENV
[7]	China (2019)	The interplay of aging genetics and environmental factors in the pathogenesis of Parkinson's disease	Shirley Yin-Yu Pang, Philip Wing-Lok Ho, Hui-Fang Liu, Chi-Ting Leung, Lingfei Li, Eunice Eun Seo Chang, David Boyer Ramsden, Shu-Leong Ho	No ENV
[91]	Turkey (2002)	The etiology and the epidemiology of multiple sclerosis	Meral Mirza	No GEO
[92]	Russia (2009)	Risk factors of multiple sclerosis development in the population of the Rostov region	Z.A. Goncharova, V.A. Baliazin	No full paper
[93]	China (2011)	Reference value of left atrial diameter of presenile women and geographical factors based on principal component analysis	J. Jing, M. Ge, A.Z. Zhao, G.Z. Liu, S.T. Xiang, X. Wang, Y.P. Zhang	No full paper
[94]	Russia (2014)	Multiple sclerosis in the Bashkortostan Republic and the Rostov region: A comparative epidemiologic study	K. Z. Bakhtiyarova, Z. A. Goncharova	No full paper
[95]	China (2015)	Clinical features of amyotrophic lateral sclerosis in south–west China	Qianqian Wei, Xueping Chen, Zhenzhen Zheng, Rui Huang, Xiaoyan Guo, Bei Cao, Bi Zhao, Huifang Shang	No ENV
[96]	USA (2016)	Multiple Sclerosis Epidemiology	M.T.Wallin, J.F.Kurtzke	No ENV

References

1.　Spencer, P.S.; Palmer, V.S.; Kisby, G.E. Seeking environmental causes of neurodegenerative disease and envisioning primary prevention. *NeuroToxicology* **2016**, *56*, 269–283. [CrossRef] [PubMed]

2.　World Health Organisation (WHO). Ageing and Health. Available online: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (accessed on 4 September 2020).

3.　Garre-Olmo, J. Epidemiology of Alzheimer's Disease and Other Dementias. *Rev. Neurol.* **2018**, *66*, 377–386. [CrossRef] [PubMed]

4.　Liu, Z.; Zhou, T.; Ziegler, A.C.; Dimitrion, P.; Zuo, L. Oxidative Stress in Neurodegenerative Diseases: From Molecular Mechanisms to Clinical Applications. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 2525967. [CrossRef]

5.　World Health Organisation (WHO). *Neurological Disorders: Public Health Challenges*; WHO: Geneva, Switzerland, 2006; ISBN 9789241563369.

6.　Campanozzi, M.D.; Casali, E.; Neviani, F.; Martini, E.; Neri, M. Evaluation of the Slopes of Cognitive Impairment and Disability in Alzheimer's Disease (Ad) Patients Treated with Acetylcholinesterase Inhibitors (Achel). *Arch. Gerontol. Geriatr.* **2007**, *44* (Suppl. 1), 91–96. [CrossRef]

7.　Pang, S.Y.-Y.; Ho, P.W.-L.; Liu, H.-F.; Leung, C.-T.; Li, L.; Chang, E.E.S.; Ramsden, D.B.; Ho, S.-L. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. *Transl. Neurodegener.* **2019**, *8*, 23. [CrossRef]

8.　Brown, R.C.; Lockwood, A.H.; Sonawane, B.R. Neurodegenerative Diseases: An Overview of Environmental Risk Factors. *Environ. Health Perspect.* **2005**, *113*, 1250–1256. [CrossRef]

9.　World Health Organization. Air Pollution. Available online: https://www.who.int/health-topics/air-pollution#tab=tab_2 (accessed on 4 September 2020).

10.　Almetwally, A.A.; Bin-Jumah, M.; Allam, A.A. Ambient air pollution and its influence on human health and welfare: An overview. *Environ. Sci. Pollut. Res.* **2020**, *27*, 24815–24830. [CrossRef]

11.　Putta, S.N. Atmospheric-Pollution, Its History, Origins and Prevention. *J. Am. Chem. Soc.* **1984**, *106*, 3066.

12.　Calderón-Garcidueñas, L.; Calderón-Garcidueñas, A.; Torres-Jardón, R.; Avila-Ramírez, J.; Kulesza, R.J.; Angiulli, A.D. Air Pollution and Your Brain: What Do You Need to Know Right Now. *Prim. Health Care Res. Dev.* **2015**, *16*, 329–345. [CrossRef]

13.　Block, M.L.; Calderón-Garcidueñas, L. Air Pollution: Mechanisms of Neuroinflammation and Cns Disease. *Trends Neurosci.* **2009**, *32*, 506–516. [CrossRef]

14.　Calderón-Garcidueñas, L.; Mora-Tiscareño, A.; Ontiveros, E.; Gómez-Garza, G.; Barragán-Mejía, G.; Broadway, J.; Chapman, S.; Valencia-Salazar, G.; Jewells, V.; Maronpot, R.R.; et al. Air pollution, cognitive deficits and brain abnormalities: A pilot study with children and dogs. *Brain Cogn.* **2008**, *68*, 117–127. [CrossRef] [PubMed]

15.　Tamagawa, E.; Van Eeden, S.F. Impaired Lung Function and Risk for Stroke: Role of the Systemic Inflammation Response? *Chest* **2006**, *130*, 1631–1633. [CrossRef]

16.　Rückerl, R.; Greven, S.; Ljungman, P.; Aalto, P.; Antoniades, C.; Bellander, T.; Berglind, N.; Chrysohoou, C.; Forastiere, F.; Jacquemin, B.; et al. Air Pollution and Inflammation (Interleukin-6, C-Reactive Protein, Fibrinogen) in Myocardial Infarction Survivors. *Environ. Health Perspect.* **2007**, *115*, 1072–1080. [CrossRef]

17.　Calderón-Garcidueñas, L.; Villarreal-Calderon, R.; Valencia-Salazar, G.; Henríquez-Roldán, C.; Gutiérrez-Castrellón, P.; Torres-Jardón, R.; Osnaya-Brizuela, N.; Romero, L.; Solt, A.; Reed, W. Systemic Inflammation, Endothelial Dysfunction, and Activation in Clinically Healthy Children Exposed to Air Pollutants. *Inhal. Toxicol.* **2008**, *20*, 499–506. [CrossRef]

18.　Valavanidis, A.; Fiotakis, K.; Vlachogianni, T. Airborne Particulate Matter and Human Health: Toxicological Assessment and Importance of Size and Composition of Particles for Oxidative Damage and Carcinogenic Mechanisms. *J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev.* **2008**, *26*, 339–362. [CrossRef]

19.　Nemmar, A.; Inuwa, I.M. Diesel exhaust particles in blood trigger systemic and pulmonary morphological alterations. *Toxicol. Lett.* **2008**, *176*, 20–30. [CrossRef]

20.　Oberdörster, G.; Sharp, Z.; Atudorei, V.; Elder, A.; Gelein, R.; Kreyling, W.; Cox, C. Translocation of Inhaled Ultrafine Particles to the Brain. *Inhal. Toxicol.* **2004**, *16*, 437–445. [CrossRef]

21.　Wang, B.; Feng, W.; Wang, M.; Shi, J.W.; Zhang, F.; Ouyang, H.; Zhao, Y.L.; Chai, Z.F.; Huang, Y.Y.; Xie, Y.N.; et al. Transport of Intranasally Instilled Fine Fe_2O_3 Particles into the Brain: Micro-distribution, Chemical States, and Histopathological Observation. *Biol. Trace Element Res.* **2007**, *118*, 233–243. [CrossRef]

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

20 of 25

22. Wang, J.; Liu, Y.; Jiao, F.; Lao, F.; Li, W.; Gu, Y.; Li, Y.; Ge, C.; Zhou, G.; Li, B.; et al. Time-dependent translocation and potential impairment on central nervous system by intranasally instilled TiO(2) nanoparticles. *Toxicology* **2008**, *254*, 82–90. [CrossRef]

23. Calderón-Garcidueñas, L.; Solt, A.C.; Henríquez-Roldán, C.; Torres-Jardón, R.; Nuse, B.; Herritt, L.; Villarreal-Calderón, R.; Osnaya, N.; Stone, I.; García, R.; et al. Long-Term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid Beta-42 and Alpha-Synuclein in Children and Young Adults. *Toxicol. Pathol.* **2008**, *36*, 289–310. [CrossRef]

24. Mühlfeld, C.; Rothen-Rutishauser, B.; Blank, F.; Vanhecke, D.; Ochs, M.; Gehr, P. Interactions of nanoparticles with pulmonary structures and cellular responses. *Am. J. Physiol. Cell. Mol. Physiol.* **2008**, *294*, L817–L829. [CrossRef]

25. Simkhovich, B.Z.; Kleinman, M.T.; Kloner, R.A. Air Pollution and Cardiovascular Injury Epidemiology, Toxicology, and Mechanisms. *J. Am. Coll. Cardiol.* **2008**, *52*, 719–726. [CrossRef] [PubMed]

26. Peters, A.; Veronesi, B.; Calderón-Garcidueñas, L.; Gehr, P.; Chen, L.-C.; Geiser, M.; Reed, W.; Rothen-Rutishauser, B.; Schürch, S.; Schulz, H. Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Part. Fibre Toxicol.* **2006**, *3*, 13. [CrossRef]

27. Pryor, W.A.; Squadrito, G.L.; Friedman, M. A new mechanism for the toxicity of ozone. *Toxicol. Lett.* **1995**, *82*, 287–293. [CrossRef]

28. Hollingsworth, J.W.; Kleeberger, S.R.; Foster, W.M. Ozone and Pulmonary Innate Immunity. *Proc. Am. Thorac. Soc.* **2007**, *4*, 240–246. [CrossRef]

29. Guevara-Guzman, R.; Arriaga, V.; Kendrick, K.M.; Bernal, C.; Vega, X.; Mercado-Gómez, O.; Rivas-Arancibia, S. Estradiol prevents ozone-induced increases in brain lipid peroxidation and impaired social recognition memory in female rats. *Neuroscience* **2009**, *159*, 940–950. [CrossRef]

30. Pereyra-Muñoz, N.; Rugerio-Vargas, C.; Angoa-Pérez, M.; Borgonio-Pérez, G.; Rivas-Arancibia, S. Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone. *J. Chem. Neuroanat.* **2006**, *31*, 114–123. [CrossRef]

31. Angoa-Pérez, M.; Jiang, H.; Rodríguez, A.I.; Lemini, C.; Levine, R.A.; Rivas-Arancibia, S. Estrogen counteracts ozone-induced oxidative stress and nigral neuronal death. *NeuroReport* **2006**, *17*, 629–633. [CrossRef]

32. Fu, P.; Guo, X.; Cheung, F.M.H.; Yung, K. The association between PM2.5 exposure and neurological disorders: A systematic review and meta-analysis. *Sci. Total Environ.* **2019**, *655*, 1240–1248. [CrossRef]

33. Shah, A.S.V.; Lee, K.K.; McAllister, D.A.; Hunter, A.; Nair, H.; Whiteley, W.; Langrish, J.P.; Newby, D.E.; Mills, N.L. Short term exposure to air pollution and stroke: Systematic review and meta-analysis. *BMJ* **2015**, *350*, h1295. [CrossRef]

34. Willis, A.W.; Evanoff, B.A.; Lian, M.; Criswell, S.R.; Racette, B.A. Geographic and Ethnic Variation in Parkinson Disease: A Population-Based Study of US Medicare Beneficiaries. *Neuroepidemiology* **2010**, *34*, 143–151. [CrossRef] [PubMed]

35. Scott, K.M.; Abhinav, K.; Stanton, B.R.; Johnston, C.; Turner, M.R.; Ampong, M.-A.; Sakel, M.; Orrell, R.W.; Shaw, C.E.; Leigh, P.N.; et al. Geographical Clustering of Amyotrophic Lateral Sclerosis in South-East England: A Population Study. *Neuroepidemiology* **2008**, *32*, 81–88. [CrossRef] [PubMed]

36. Noonan, C.W.; White, M.C.; Thurman, D.J.; Wong, L.-Y. Temporal and geographic variation in United States motor neuron disease mortality, 1969–1998. *Neurology* **2005**, *64*, 1215–1221. [CrossRef] [PubMed]

37. Viana, J.; Santos, J.V.; Neiva, R.; Souza, J.; Duarte, L.; Teodoro, A.; Freitas, A. Remote Sensing in Human Health: A 10-Year Bibliometric Analysis. *Remote. Sens.* **2017**, *9*, 1225. [CrossRef]

38. Achar, A.; Ghosh, C.; Favreau, D.J.; Desforges, M.; St-Jean, J.R.; Talbot, P.J. Covid-19-Associated Neurological Disorders: The Potential Route of Cns Invasion and Blood-Brain Relevance. *Cells* **2020**, *9*, 2360. [CrossRef]

39. Calderón-Garcidueñas, L.; Torres-Jardón, R.; Franco-Lira, M.; Kulesza, R.; González-Maciel, A.; Reynoso-Robles, R.; Brito-Aguilar, R.; García-Arreola, B.; Revueltas-Ficachi, P.; Barrera-Velázquez, J.A.; et al. Environmental Nanoparticles, SARS-CoV-2 Brain Involvement, and Potential Acceleration of Alzheimer's and Parkinson's Diseases in Young Urbanites Exposed to Air Pollution. *J. Alzheimer's Dis.* **2020**, 1–25. [CrossRef]

40. Bougakov, D.; Podell, K.; Goldberg, E. Multiple Neuroinvasive Pathways in COVID-19. *Mol. Neurobiol.* **2020**, 1–12. [CrossRef]

41. Rossby, C.G. Über die Vertikalverteilung von Windgeschwindigkeit und Schwerestabilität in Freistrahlbewegungen der oberen Troposphäre. *Archiv Meteorologie Geophysik Bioklimatologie Serie A* **1951**, *4*, 3–23. [CrossRef]

42. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The Prisma Statement. *PLoS Med.* **2009**, *339*, b2535.

43. Cendrowski, W.; Wender, M.; Dominik, W.; Flejsierowicz, Z.; Owsianowski, M.; Popiel, M. Epidemiological Study of Multiple Sclerosis in Western Poland. *Eur. Neurol.* **1969**, *2*, 90–108. [CrossRef]

44. Behrend, R. Multiple Sclerosis in Europe. *Eur. Neurol.* **1969**, *2*, 129–145. [CrossRef] [PubMed]

45. Bird, A.V.; Satoyoshi, E. Comparative epidemiological studies of multiple sclerosis in South Africa and Japan. *J. Neurol. Neurosurg. Psychiatry* **1975**, *38*, 911–918. [CrossRef] [PubMed]

46. Lauer, K.; Firnhaber, W. Epidemiological Investigations into Multiple Sclerosis in Southern Hesse. Ii. The Distribution of Cases in Relation to Exogenous Features. *Acta Neurol. Scand.* **1984**, *70*, 266–273. [CrossRef] [PubMed]

47. Granieri, E.; Casetta, I.; Tola, M.R.; Govoni, V.; Paolino, E.; Malagù, S.; Monetti, V.C.; Carreras, M. Multiple sclerosis: Does epidemiology contribute to providing etiological clues? *J. Neurol. Sci.* **1993**, *115*, S16–S23. [CrossRef]

48. Lensky, P. Geographic Aspects in the Epidemiology of Multiple Sclerosis. *Epidemiol. Mikrobiol. Imunol.* **1994**, *43*, 174–176.

49. Delasnerie-Laupretre, N.; Alperovitch, A. Epidemiology of Creutzfeldt-Jakob Disease. *Pathol. Biol.* **1995**, *43*, 22–24.

50. Bharanidharan, P. Monthly Distribution of Multiple Sclerosis Patients' Births. *Int. J. Biometeorol.* **1997**, *40*, 117–118. [CrossRef]

51. Hogancamp, W.E.; Rodriguez, M.; Weinshenker, B.G. The Epidemiology of Multiple Sclerosis. *Mayo Clin. Proc.* **1997**, *72*, 871–878. [CrossRef]

52. Foster, H.D. Parkinson's Disease, Multiple Sclerosis and Amyotrophic Lateral Sclerosis: The Iodine-Dopachrome-Glutamate Hypothesis. *J. Orthomol. Med.* **1999**, *14*, 128–136.

53. Mitchell, J.D. Amyotrophic lateral sclerosis: Toxins and environment. *Amyotroph. Lateral. Scler. Other Motor Neuron Disord.* **2019**, *1*, 235–250. [CrossRef]

54. Uria, D.F. Genetic Epidemiology of Multiple Sclerosis. *Rev. Neurol.* **2002**, *35*, 979–984. [PubMed]

55. Marrie, R.-A. Environmental risk factors in multiple sclerosis aetiology. *Lancet Neurol.* **2004**, *3*, 709–718. [CrossRef]

56. Sotgiu, S.; Pugliatti, M.; Fois, M.L.; Arru, G.; Sanna, A.; Sotgiu, M.A.; Rosati, G. Genes, environment, and susceptibility to multiple sclerosis. *Neurobiol. Dis.* **2004**, *17*, 131–143. [CrossRef] [PubMed]

57. Ances, B.M.; Newman, N.J.; Balcer, L.J. Autoimmunity—Multiple Sclerosis. In *Measuring Immunity*; Elsevier Ltd.: Amsterdam, The Netherlands, 2005; Chapter 45; pp. 515–524. [CrossRef]

58. Williamson, D.M. Studies of Multiple Sclerosis in Communities Concerned about Environmental Exposures. *J. Women's Health* **2006**, *15*, 810–814. [CrossRef]

59. Ascherio, A.; Munger, K.L. Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Ann. Neurol.* **2007**, *61*, 504–513. [CrossRef]

60. Ebers, G.C. Environmental factors and multiple sclerosis. *Lancet Neurol.* **2008**, *7*, 268–277. [CrossRef]

61. Boumédiène, F.; Druet-Cabanac, M.; Marin, B.; Preux, P.M.; Allée, P.; Couratier, P. Contribution of geolocalisation to neuroepidemiological studies: Incidence of ALS and environmental factors in Limousin, France. *J. Neurol. Sci.* **2011**, *309*, 115–122. [CrossRef]

62. Nelson, G.; Racette, B.A. Environmental Risk Factors. In *Handbook of Parkinson's Disease*; CRC Press: Boca Raton, FL, USA, 2013; pp. 341–357.

63. Willis, A.W.; Schootman, M.; Kung, N.; Evanoff, B.A.; Perlmutter, J.S.; Racette, B.A. Predictors of Survival in Patients with Parkinson Disease. *Arch. Neurol.* **2012**, *69*, 601–607. [CrossRef]

64. Caller, T.A.; Field, N.C.; Chipman, J.W.; Shi, X.; Harris, B.T.; Stommel, E. Spatial clustering of amyotrophic lateral sclerosis and the potential role of BMAA. *Amyotroph. Lateral Scler.* **2012**, *13*, 25–32. [CrossRef]

65. Tennant, A. Epidemiology of Neurologically Disabling Disorders. *Handb. Clin. Neurol.* **2013**, *110*, 77–92. [CrossRef]

66. Al-Afasy, H.H.; Al-Obaidan, M.A.; Al-Ansari, Y.A.; Al-Yatama, S.A.; Al-Rukaibi, M.S.; Makki, N.I.; Suresh, A.; Akhtar, S. Risk Factors for Multiple Sclerosis in Kuwait: A Population-Based Case-Control Study. *Neuroepidemiology* **2013**, *40*, 30–35. [CrossRef] [PubMed]

67. Chamosa, S.; Tamayo, I.; Arteagoitia-Axpe, J.M.; Juste, R.; Rodríguez-Martínez, A.B.; Zarranz-Imirizaldu, J.J.; Arriola, L. Geographical Analysis of the Sporadic Creutzfeldt-Jakob Disease Distribution in the Autonomous Community of the Basque Country for the Period 1995–2008. *Eur. Neurol.* **2014**, *72*, 20–25. [CrossRef] [PubMed]

68. Thielke, S.; Slatore, C.G.; Banks, W.A. Association Between Alzheimer Dementia Mortality Rate and Altitude in California Counties. *JAMA Psychiatry* **2015**, *72*, 1253–1254. [CrossRef] [PubMed]

69. Russ, T.C.; Gatz, M.; Pedersen, N.L.; Hannah, J.; Wyper, G.; Batty, G.D.; Deary, I.J.; Starr, J.M. Geographical Variation in Dementia: Examining the Role of Environmental Factors in Sweden and Scotland. *Epidemiology* **2015**, *26*, 263–270. [CrossRef]

70. Berg-Hansen, P.; Celius, E.G. Socio-economic factors and immigrant population studies of multiple sclerosis. *Acta Neurol. Scand.* **2015**, *132*, 37–41. [CrossRef]

71. Magalhaes, S.; Pugliatti, M.; Casetta, I.; Drulovic, J.; Granieri, E.; Kampman, M.T.; Landtblom, A.-M.; Lauer, K.; Myhr, K.-M.; Parpinel, M.; et al. The EnvIMS Study: Design and Methodology of an International Case-Control Study of Environmental Risk Factors in Multiple Sclerosis. *Neuroepidemiology* **2015**, *44*, 173–181. [CrossRef]

72. Sundström, P.; Salzer, J. Vitamin D and multiple sclerosis-from epidemiology to prevention. *Acta Neurol. Scand.* **2015**, *132*, 56–61. [CrossRef]

73. Rothhammer, V.; Quintana, F.J. Environmental control of autoimmune inflammation in the central nervous system. *Curr. Opin. Immunol.* **2016**, *43*, 46–53. [CrossRef]

74. Ascherio, A.; Munger, K. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention—An Update. *Semin. Neurol.* **2016**, *36*, 103–114. [CrossRef]

75. Wilker, E.H.; Martinez-Ramirez, S.; Kloog, I.; Schwartz, J.; Mostofsky, E.; Koutrakis, P.; Mittleman, M.A.; Viswanathan, A. Fine Particulate Matter, Residential Proximity to Major Roads, and Markers of Small Vessel Disease in a Memory Study Population. *J. Alzheimer's Dis.* **2016**, *53*, 1315–1323. [CrossRef]

76. Russ, T.C.; Murianni, L.; Icaza, G.; Slachevsky, A.; Starr, J.M. Geographical Variation in Dementia Mortality in Italy, New Zealand, and Chile: The Impact of Latitude, Vitamin D, and Air Pollution. *Dement. Geriatr. Cogn. Disord.* **2016**, *42*, 31–41. [CrossRef] [PubMed]

77. Correa, E.; Paredes, V.; Martinez, B. Prevalence of Multiple Sclerosis in Latin America and Its Relationship with European Migration. *Mult. Scler. J. Exp. Transl. Clin.* **2016**, *2*. [CrossRef] [PubMed]

78. Sun, H. Associations of Spatial Disparities of Alzheimer's Disease Mortality Rates with Soil Selenium and Sulfur Concentrations and Four Common Risk Factors in the United States. *J. Alzheimer's Dis.* **2017**, *58*, 897–907. [CrossRef] [PubMed]

79. Tesauro, M.; Consonni, M.; Filippini, T.; Mazzini, L.; Pisano, F.; Chiò, A.; Esposito, A.; Vinceti, M. Incidence of amyotrophic lateral sclerosis in the province of Novara, Italy, and possible role of environmental pollution. *Amyotroph. Lateral Scler. Front. Degener.* **2017**, *18*, 284–290. [CrossRef]

80. Hammas, K.; Yaouanq, J.; Lannes, M.; Edan, G.; Viel, J.-F. Small-area distribution of multiple sclerosis incidence in western France: In search of environmental triggers. *Int. J. Health Geogr.* **2017**, *16*, 35. [CrossRef]

81. Martínez-Solanas, È.; Vergara-Duarte, M.; Ortega Cerdà, M.; Martín-Sánchez, J.; Buxó, M.; Rodríguez-Farré, E.; Benach, J.; Pérez, G. The Geography of the Alzheimer's Disease Mortality in Spain: Should We Focus on Industrial Pollutants Prevention? *Healthcare* **2017**, *5*, 89. [CrossRef]

82. Karimi, A.; Delpisheh, A.; Ashtari, F.; Sayehmiri, K.; Meamar, R. The Relationship between the Amount of Radiation, Relative Humidity, and Temperature with the Risk of Multiple Sclerosis in Isfahan Province, Iran, During the Years 2001–2014. *J. Isfahan Med. Sch.* **2017**, *35*, 434–439.

83. Brouwer, M.; Kromhout, H.; Vermeulen, R.; Duyzer, J.; Kramer, H.; Hazeu, G.; De Snoo, G.; Huss, A. Assessment of residential environmental exposure to pesticides from agricultural fields in the Netherlands. *J. Expo. Sci. Environ. Epidemiol.* **2017**, *28*, 173–181. [CrossRef]

84. Michel, L. Environmental Factors in the Development of Multiple Sclerosis. *Rev. Neurol.* **2018**, *174*, 372–377. [CrossRef]

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

23 of 25

85. Karimi, A.; Ashtari, F.; Delpisheh, A.; Meamar, R.; Sayehmiri, K.; Daliri, S. Estimated incidence rate of multiple sclerosis and its relationship with geographical factors in Isfahan province between the years 2001 and 2014. *Int. J. Prev. Med.* **2018**, *9*, 103. [CrossRef]

86. Weiland, T.J.; De Livera, A.M.; Brown, C.R.; Jelinek, G.A.; Aitken, Z.; Simpson, S.L.J.; Neate, S.L.; Taylor, K.L.; O'Kearney, E.; Bevens, W.; et al. Health Outcomes and Lifestyle in a Sample of People With Multiple Sclerosis (HOLISM): Longitudinal and Validation Cohorts. *Front. Neurol.* **2018**, *9*, 1074. [CrossRef] [PubMed]

87. Spencer, P.S.; Lagrange, E.; Camu, W. ALS and environment: Clues from spatial clustering? *Rev. Neurol.* **2019**, *175*, 652–663. [CrossRef] [PubMed]

88. Logroscino, G.; Piccininni, M. Amyotrophic Lateral Sclerosis Descriptive Epidemiology: The Origin of Geographic Difference. *Neuroepidemiology* **2019**, *52*, 93–103. [CrossRef] [PubMed]

89. Naghshineh, H.; Hojjati, S.M.M.; Khatir, A.A.; Saadat, P.; Ahangar, A.A. Can environmental factors increase the risk of multiple sclerosis? A narrative review. *Biomed. Res. Ther.* **2019**, *6*, 3513–3517. [CrossRef]

90. Salm, A.K.; Benson, M.J. Increased Dementia Mortality in West Virginia Counties with Mountaintop Removal Mining? *Int. J. Environ. Res. Public Health* **2019**, *16*, 4278. [CrossRef]

91. Mirza, M. The Etiology and the Epidemiology of Multiple Sclerosis. *Erciyes Med. J.* **2002**, *24*, 40–47.

92. Goncharova, Z.A.; Balyazin, V.A. Risk Factors of Multiple Sclerosis Development in the Population of the Rostov Region. *Zhurnal Nevrologii Psikhiatrii Imeni SS Korsakova* **2009**, *109*, 10–15.

93. Jing, J.; Ge, M.; Zhao, A.Z.; Liu, G.Z.; Xiang, S.T.; Wang, X.; Zhang, Y.P. Reference Value of Left Atrial Diameter of Presenile Women and Geographical Factors Based on Principal Component Analysis. *J. Jilin Univ. Med. Ed.* **2011**, *37*, 1144–1148.

94. Bakhtiiarova, K.Z.; Goncharova, Z.A. Multiple Sclerosis in the Bashkortostan Republic and the Rostov Region: A Comparative Epidemiologic Study. *Zhurnal Nevrologii Psikhiatrii Imeni SS Korsakova* **2014**, *114*, 5–9.

95. Wei, Q.; Chen, X.; Zheng, Z.; Huang, R.; Guo, X.; Cao, B.; Zhao, B.; Shang, H. Clinical features of amyotrophic lateral sclerosis in south-west China. *Amyotroph. Lateral Scler. Front. Degener.* **2015**, *16*, 512–519. [CrossRef]

96. Wallin, M.T.; Kurtzke, J.F. Multiple Sclerosis; Epidemiology. In *Encyclopedia of the Neurological Sciences*; Elsevier Ltd.: Amsterdam, The Netherlands, 2014; pp. 153–160. [CrossRef]

97. Schuurman, N.; Amram, O.; Saeedi, J.; Rieckmann, P.; Yee, I.; Tremlett, H. A proposed methodology to estimate the cumulative life-time UVB exposure using geographic information systems: An application to multiple sclerosis. *Mult. Scler. Relat. Disord.* **2013**, *2*, 29–35. [CrossRef] [PubMed]

98. Leibowitz, U. Multiple Sclerosis: Progress in Epidemiologic and Experimental Research. A Review. *J. Neurol. Sci.* **1971**, *12*, 307–318. [CrossRef]

99. Kalafatova, O. Geographic and Climatic Factors and Multiple Sclerosis in Some Districts of Bulgaria. *Neuroepidemiology* **1987**, *6*, 116–119. [CrossRef] [PubMed]

100. Van Der Mei, I.A.F.; Ponsonby, A.-L.; Blizzard, L.; Dwyer, T. Regional variation in multiple sclerosis prevalence in Australia and its association with ambient ultraviolet radiation. *Neuroepidemiology* **2001**, *20*, 168–174. [CrossRef]

101. Sloka, S.; Silva, C.; Pryse-Phillips, W.; Patten, S.B.; Metz, L.; Yong, V.W. A quantitative analysis of suspected environmental causes of MS. *Can. J. Neurol. Sci.* **2011**, *38*, 98–105. [CrossRef]

102. Ramagopalan, S.V.; Handel, A.E.; Giovannoni, G.; Siegel, S.R.; Ebers, G.C.; Chaplin, G. Relationship of UV exposure to prevalence of multiple sclerosis in England. *Neurology* **2011**, *76*, 1410–1414. [CrossRef]

103. Sun, H. Temperature Dependence of Multiple Sclerosis Mortality Rates in the United States. *Mult. Scler.* **2017**, *23*, 1839–1846. [CrossRef]

104. Gallagher, L.G.; Ilango, S.; Wundes, A.; Stobbe, G.A.; Turk, K.W.; Franklin, G.M.; Linet, M.S.; Freedman, D.M.; Alexander, B.H.; Checkoway, H. Lifetime exposure to ultraviolet radiation and the risk of multiple sclerosis in the US radiologic technologists cohort study. *Mult. Scler.* **2018**, *25*, 1162–1169. [CrossRef]

105. Norman, J.E., Jr.; Kurtzke, J.F.; Beebe, G.W. Epidemiology of multiple sclerosis in U.S. veterans: 2. Latitude, climate and the risk of multiple sclerosis. *J. Chronic Dis.* **1983**, *36*, 551–559. [CrossRef]

106. Monti, M.C.; Guido, D.; Montomoli, C.; Sardu, C.; Sanna, A.; Pretti, S.; Lorefice, L.; Marrosu, M.G.; Valera, P.; Cocco, E. Is Geo-Environmental Exposure a Risk Factor for Multiple Sclerosis? A Population-Based Cross-Sectional Study in South-Western Sardinia. *PLoS ONE* **2016**, *11*, e0163313. [CrossRef]

107. Amram, O.; Schuurman, N.; Randall, E.; Zhu, F.; Saeedi, J.; Rieckmann, P.; Yee, I.; Tremlett, H. The use of satellite data to measure ultraviolet-B penetrance and its potential association with age of multiple sclerosis onset. *Mult. Scler. Relat. Disord.* **2018**, *21*, 30–34. [CrossRef] [PubMed]

108. Risberg, G.; Aarseth, J.H.; Nyland, H.; Lauer, K.; Myhr, K.-M.; Midgard, R. Prevalence and incidence of multiple sclerosis in Oppland County—A cross-sectional population-based study in a landlocked county of Eastern Norway. *Acta Neurol. Scand.* **2010**, *124*, 250–257. [CrossRef] [PubMed]

109. Tateo, F.; Grassivaro, F.; Ermani, M.; Puthenparampil, M.; Gallo, P. PM2.5 levels strongly associate with multiple sclerosis prevalence in the Province of Padua, Veneto Region, North-East Italy. *Mult. Scler.* **2018**, *25*, 1719–1727. [CrossRef] [PubMed]

110. Gregory, A.C., 2nd; Shendell, D.G.; Okosun, I.S.; Gieseker, K.E. Multiple Sclerosis disease distribution and potential impact of environmental air pollutants in Georgia. *Sci. Total. Environ.* **2008**, *396*, 42–51. [CrossRef]

111. Iuliano, G. Geography Based Hypotheses About Multiple Sclerosis. *Riv. Ital. Neurobiol.* **2005**, *2*, 213–220.

112. Heydarpour, P.; Amini, H.; Khoshkish, S.; Seidkhani, H.; Sahraian, M.A.; Yunesian, M. Potential Impact of Air Pollution on Multiple Sclerosis in Tehran, Iran. *Neuroepidemiology* **2014**, *43*, 233–238. [CrossRef]

113. Ashtari, F.; Esmaeil, N.; Mansourian, M.; Poursafa, P.; Mirmosayyeb, O.; Barzegar, M.; Pourgheisari, H. An 8-year study of people with multiple sclerosis in Isfahan, Iran: Association between environmental air pollutants and severity of disease. *J. Neuroimmunol.* **2018**, *319*, 106–111. [CrossRef]

114. Bølviken, B.; Nilsén, R.; Ukkelberg, A. A new method for spatially moving correlation analysis in geomedicine. *Environ. Geochem. Health* **1997**, *19*, 143–154. [CrossRef]

115. Groves-Kirkby, C.J.; Denman, A.R.; Campbell, J.; Crockett, R.G.; Phillips, P.S.; Rogers, S. Is environmental radon gas associated with the incidence of neurodegenerative conditions? A retrospective study of multiple sclerosis in radon affected areas in England and Wales. *J. Environ. Radioact.* **2016**, *154*, 1–14. [CrossRef] [PubMed]

116. Lavery, A.M.; Waldman, A.T.; Casper, T.C.; Roalstad, S.; Candee, M.; Rose, J.; Belman, A.; Weinstock-Guttman, B.; Aaen, G.; Tillema, J.-M.; et al. Examining the contributions of environmental quality to pediatric multiple sclerosis. *Mult. Scler. Relat. Disord.* **2017**, *18*, 164–169. [CrossRef] [PubMed]

117. Lavery, A.M.; Waubant, E.; Casper, T.C.; Roalstad, S.; Rose, A.; Belman, J.; Weinstock-Guttman, B.; Aaen, G.; Tillema, J.M.; Rodriguez, M.; et al. Urban Air Quality and Associations with Pediatric Multiple Sclerosis. *Ann. Clin. Transl. Neurol.* **2018**, *5*, 1146–1153. [CrossRef] [PubMed]

118. Willis, A.W.; Evanoff, B.; Lian, M.; Galarza, A.; Wegrzyn, A.; Schootman, M.; Racette, B. Metal Emissions and Urban Incident Parkinson Disease: A Community Health Study of Medicare Beneficiaries by Using Geographic Information Systems. *Am. J. Epidemiol.* **2010**, *172*, 1357–1363. [CrossRef] [PubMed]

119. Santurtun, A.; Delgado-Alvarado, M.; Villar, A.; Riancho, J. Geographical Distribution of Mortality by Parkinson's Disease and Its Association with Air Lead Levels in Spain. *Med. Clin. (Barc.)* **2016**, *147*, 481–487. [CrossRef] [PubMed]

120. Finkelstein, M.M.; Jerrett, M. A Study of the Relationships between Parkinson's Disease and Markers of Traffic-Derived and Environmental Manganese Air Pollution in Two Canadian Cities. *Environ. Res.* **2007**, *104*, 420–432. [CrossRef] [PubMed]

121. Liu, R.; Young, M.T.; Chen, J.-C.; Kaufman, J.D.; Chen, H. Ambient Air Pollution Exposures and Risk of Parkinson Disease. *Environ. Health Perspect.* **2016**, *124*, 1759–1765. [CrossRef]

122. Salimi, F.; Hanigan, I.; Jalaludin, B.; Guo, Y.; Rolfe, M.; Heyworth, J.S.; Cowie, C.T.; Knibbs, L.D.; Cope, M.; Marks, G.B.; et al. Associations between long-term exposure to ambient air pollution and Parkinson's disease prevalence: A cross-sectional study. *Neurochem. Int.* **2020**, *133*, 104615. [CrossRef]

123. Lee, P.-C.; Raaschou-Nielsen, O.; Lill, C.M.; Bertram, L.; Sinsheimer, J.S.; Hansen, J.; Ritz, B. Gene-environment interactions linking air pollution and inflammation in Parkinson's disease. *Environ. Res.* **2016**, *151*, 713–720. [CrossRef]

124. Kravietz, A.; Kab, S.; Wald, L.; Dugravot, A.; Singh-Manoux, A.; Moisan, F.; Elbaz, A. Association of UV radiation with Parkinson disease incidence: A nationwide French ecologic study. *Environ. Res.* **2017**, *154*, 50–56. [CrossRef]

125. Wei, Y.; Wang, Y.; Lin, C.-K.; Yin, K.; Yang, J.; Shi, L.; Li, L.; Zanobetti, A.; Schwartz, J.D. Associations between seasonal temperature and dementia-associated hospitalizations in New England. *Environ. Int.* **2019**, *126*, 228–233. [CrossRef]

126. Li, C.-Y.; Li, C.-H.; Martini, S.; Hou, W.-H. Association between air pollution and risk of vascular dementia: A multipollutant analysis in Taiwan. *Environ. Int.* **2019**, *133*, 105233. [CrossRef]

Int. J. Environ. Res. Public Health **2020**, *17*, 8414

25 of 25

127. Chen, H.; Kwong, J.C.; Copes, R.; Hystad, P.; Van Donkelaar, A.; Tu, K.; Brook, J.R.; Goldberg, M.S.; Martin, R.V.; Murray, B.J.; et al. Exposure to ambient air pollution and the incidence of dementia: A population-based cohort study. *Environ. Int.* **2017**, *108*, 271–277. [CrossRef] [PubMed]

128. Povedano, M.; Saez, M.; Martínez-Matos, J.-A.; Barceló, M.A. Spatial Assessment of the Association between Long-Term Exposure to Environmental Factors and the Occurrence of Amyotrophic Lateral Sclerosis in Catalonia, Spain: A Population-Based Nested Case-Control Study. *Neuroepidemiology* **2018**, *51*, 33–49. [CrossRef] [PubMed]

129. Tsai, C.-P.; Lee, C.T.-C. Climatic factors associated with amyotrophic lateral sclerosis: A spatial analysis from Taiwan. *Geospat. Health* **2013**, *8*, 45–52. [CrossRef]

130. Santurtún, A.; Villar, A.; Delgado-Alvarado, M.; Riancho, J. Trends in motor neuron disease: Association with latitude and air lead levels in Spain. *Neurol. Sci.* **2016**, *37*, 1271–1275. [CrossRef]

131. DeLuca, H.F.; Cantorna, M.T. Vitamin D: Its role and uses in immunology 1. *FASEB J.* **2001**, *15*, 2579–2585. [CrossRef]

132. Ogen, Y. Assessing nitrogen dioxide (NO2) levels as a contributing factor to coronavirus (COVID-19) fatality. *Sci. Total. Environ.* **2020**, *726*, 138605. [CrossRef]

133. Bornstein, S.R.; Voit-Bak, K.; Schmidt, D.; Morawietz, H.; Bornstein, A.B.; Balanzew, W.; Julius, U.; Rodionov, R.N.; Biener, A.M.; Wang, J.; et al. Is There a Role for Environmental and Metabolic Factors Predisposing to Severe COVID-19? *Horm. Metab. Res.* **2020**, *52*, 540–546. [CrossRef]

134. Hribar, C.A.; Cobbold, P.H.; Church, F.C. Potential Role of Vitamin D in the Elderly to Resist COVID-19 and to Slow Progression of Parkinson's Disease. *Brain Sci.* **2020**, *10*, 284. [CrossRef]

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.