Spring 5-7-2024

The Link Between Radon Exposure and Neurodegenerative Disease Risk Factors

Serena Bruneaux
Eastern Kentucky University, serena_bruneaux@mymail.eku.edu

[HONORS THESIS]

Eastern Kentucky University

The Link Between Radon Exposure and Neurodegenerative Disease Risk Factors

Honors Thesis

Submitted

In Partial Fulfillment

Of The

Requirements of HON 420

Spring 2024

By

Serena Bruneaux

Mentor

Dr. Adam Lawson

Department of Psychology, Eastern Kentucky University

Eastern Kentucky University Honors Program

ABSTRACT

The Link Between Radon Exposure and Neurodegenerative Disease Risk Factors

Serena Bruneaux

Dr. Adam Lawson

Department of Psychology, Eastern Kentucky University

The current study investigated United States county-level ecological data concerning radon concentrations and disease mortality from two Centers for Disease Control (CDC) databases. The study aimed to determine if there is a relationship between indoor radon concentration and neurodegenerative disease mortality. Three neurodegenerative diseases were investigated, including Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. Additional analyses were conducted concerning nervous system diseases, cerebrovascular diseases, cancers, bronchus and lung cancer, and central nervous system cancer. Pearson bivariate correlations revealed that counties with higher radon concentrations also had significantly higher mortality rates for all three investigated neurodegenerative diseases. Furthermore, a multiple linear regression revealed that Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis were all significant predictors of radon concentration and accounted for 12.3% of radon concentration data. The current study also found that nervous system diseases, cerebrovascular diseases, and central nervous system cancer were all positively correlated with radon concentration. These results support the idea that radon exposure is related to mortality from neurodegenerative disease. They also provide support that radon exposure is related to

nervous system diseases, cerebrovascular diseases, and central nervous system cancer. Future studies are needed to determine if the relationships identified in this study are causal in nature.

Keywords and phrases: radon exposure, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis

Table of Contents

List of Tables

The Link Between Radon Exposure and Neurodegenerative Disease Risk Factors

Introduction

Radon (^{222}Rn) is a naturally occurring radioactive gas that is colorless, tasteless, and odorless. It is created from the breakdown of uranium and radium in soil and rock (Eidy et al., 2024; Langlois et al., 2015; Zeng et al., 2023). Radon naturally decays over time, resulting in the emission of alpha particles and radon decay products (Ruano-Ravina et al., 2017). Alpha particles are high-energy particles that can penetrate tissue and permanently damage DNA (Frumkin & Samet, 2001). Radon decay products include polonium (^{218}Po; ^{214}Po), lead (^{214}Pb), and other harmful elements that further the release of alpha particles (Porstendorfer, 2001). Radon and its products are the primary source of naturally occurring radiation in the United States (Papatheodorou et al., 2021) and across the globe (Palmer et al., 2022). While radon is present throughout the natural environment, humans have adapted to the normal background levels seen outdoors (Bølviken et al., 2003; Gómez-Anca & Barros-Dios, 2020). However, radon can accumulate to dangerous levels when trapped in homes (Reddy et al., 2022), schools (Gordon et al., 2018), child care centers (Poku & Hussani, 2021), and the workplace (Daniels & Schubauer-Berigan, 2017).

Radon Distribution

Across the globe, outdoor radon is typically between 0.14 pCi/L and 0.41 pCi/L (5 Bq/M^3 and 15 Bq/M^3) while indoor radon levels are between 0.27 pCi/L to 270.27 pCi/L (10 Bq/M^3 and 10,000 Bq/M^3) (World Health Organization, 2023). In the United States, the mean outdoor radon concentration is 0.4 pCi/L (14.8 Bq/M^3) while the mean indoor

level is 1.3 pCi/L (48.1 Bq/M^3) (Environmental Protection Agency [EPA], 2023). According to national standards set by the EPA (2023), levels between 2 pCi/L and 4 pCi/L (74 Bq/M^3 and 140 Bq/M^3) may pose a health risk, while levels above 4 pCi/L (140 Bq/M^3) are considered hazardous.

In the United States, it is estimated that 1 in every 15 homes have indoor radon concentrations exceeding 4 pCi/L (140 Bq/M^3) (Taylor et al., 2023). Radon concentration varies greatly between states, with some states having much higher rates of elevated residential radon. The states with the highest percentage of buildings above the EPA's limits are South Dakota (59.8%), North Dakota (58%), Iowa (57.9%), Nebraska (55.8%), and Ohio (48.8%) (American Lung Association, 2023). Table 1 lists the percentage of buildings above the EPA's limit of 4 pCi/L using data from the American Lung Association (2023).

Table 1

Rates of Elevated Radon by State According to the American Lung Association

Rank	State	Buildings Above Limit (%)
1	South Dakota	59.8%
2	North Dakota	58.0%
3	Iowa	57.9%
4	Nebraska	55.8%
5	Ohio	48.8%
6	Wisconsin	46.4%
7	Colorado	46.1%
8	Montana	45.6%
9	Wyoming	44.5%
10	Minnesota	41.7%
11	Utah	40.6%
12	Indiana	40.2%

13	Pennsylvania	39.1%
14	Kentucky	36.9%
15	Maine	36.5%
16	New Hampshire	35.3%
17	Kansas	34.5%
18	Illinois	33.5%
19	Idaho	33.3%
20	Missouri	31.0%
21	West Virginia	28.5%
22	Tennessee	26.8%
23	Connecticut	25.8%
24	Virginia	25.2%
25	New Mexico	24.8%
26	Michigan	22.8%
27	Massachusetts	21.8%
28	Vermont	21.7%
29	Georgia	21.5%
30	Rhode Island	21.4%
31	Maryland	20.8%
32	Arkansas	20.1%
33	Oregon	18.0%
34	Alaska	16.9%
35	Delaware	15.4%
36	Arizona	14.9%
37	New York	13.9%
38	Alabama	13.8%
39	North Carolina	13.5%
40	Nevada	12.8%
41	Florida	12.1%
42	Washington	10.5%
43	South Carolina	10.0%
44	New Jersey	9.8%
45	Oklahoma	9.5%
46	District of Columbia	8.7%
47	California	8.2%
48	Texas	7.7%
49	Mississippi	5.2%

50	Louisiana	3.1%
51	Hawaii	0.4%

*Data provided originates from the American Lung Association (2023)

These between-state variations demonstrate that radon levels can vary greatly over geographic areas. Radon levels vary not only between states, but also between counties, so the EPA (2016a) recommends that everyone test their home. Homeowners and renters can attain low-cost radon test kits from hardware stores or online to determine the radon level in their homes (EPA, 2016a). If elevated levels are found, then radon mitigation procedures can be done to decrease indoor radon concentration (EPA, 2016a).

Risk Factors for Elevated Radon

Most residential radon contamination comes directly from the subsurface, therefore the amount of uranium in the soil is an important determinant of indoor radon concentration (Bølviken et al., 2003). Homes built on uranium deposits are at increased risk for elevated radon (Sujo et al., 2004). Certain geographical areas (e.g. Appalachia, northwestern midwest) are more likely to have high uranium content in the soil due to their soil geology (Appleton, 2007). Additional environmental factors, such as bedrock permeability and soil moisture, impact how much radon can leave the subsurface and enter the air (Sujo et al., 2004).

Radon gas typically enters the home through cracks in the building's foundation (Zhang et al., 2022) and loose-fitting pipes and drains (Groves-Kirby et al., 2016). Since older homes are more likely to have cracked foundations, older homes typically have higher radon concentrations (Barros-Dios et al., 2007; Fathabadi et al., 2019; Symonds et al., 2019). Radon from the subsurface can also contaminate groundwater, which can enter

homes that use groundwater sources (Fathabadi et al., 2020). Once radon-contaminated groundwater enters the home, it can be directly ingested or dispersed into the air by off-gassing appliances, such as dishwashers and washing machines (Zhang et al., 2022).

Once inside the home, radon gas can become trapped due to poor ventilation (Symonds et al., 2019). This is why homes made of denser materials (e.g. concrete) commonly hold more radon than homes made of porous materials (e.g. wood) (Yazzie et al., 2020). Radon concentrations have been steadily increasing across the United States in recent years, possibly due to the implementation of modern energy-saving systems (Stanley et al., 2019). These systems aim to increase home insulation so that less heating and cooling is needed for the home to remain at the intended temperature (Symonds et al., 2019). One example of an energy-saving system is the use of double-paned rather than single-paned windows, a housing characteristic associated with higher radon concentrations (Symonds et al., 2019).

Health Effects of Radon

Radon primarily enters the body through inhalation of radon gas and ingestion of radon-contaminated water (Eidy et al., 2024; Langlois et al., 2015). Radon gas is heavier than air, so it accumulates mainly in basements and the lower floors of homes (Gómez-Anca & Barros-Dios, 2020). Individuals are more likely to inhale large amounts of radon if they live on lower floors, spend more time in closed rooms, and rarely open windows (Stanley et al., 2019; Sujo et al., 2004). Children are also particularly at risk for inhaling radon due to smaller lungs and faster breathing rates (Eidy et al., 2024). Individuals who drink groundwater are also at greater risk for radon exposure because they may ingest radon-contaminated water (Fathabadi et al., 2020). After an individual is exposed, radon

can enter the circulatory system where it is distributed throughout the body (Bräuner et al., 2013). This allows radon to produce both organ-specific and systematic health effects.

Radon's radioactive properties cause cellular injury and DNA damage, which greatly increase one's risk of developing cancer (Eidy et al., 2024; Stanley et al., 2019). Thus, radon is a well-established carcinogen and is the leading environmental cause of cancer mortality in North America (Field, 2011). Radon is best known for its role in increasing the prevalence of lung cancer, as it is considered the main cause of lung cancer in 3-15% of cases (Sethi et al., 2012). This makes radon the second-leading cause of lung cancer in the United States, second only to smoking (Sethi et al., 2012). Additionally, smokers who are exposed to elevated radon are more likely to develop lung cancer (Sujo et al., 2004). Radon has also been implicated in other cancers, such as leukemia (Tong et al., 2012) and stomach cancer (López-Abente et al., 2018). Due to radon's damaging effects on DNA, it can also lead to birth defects such as Down syndrome and skeletal defects of the spine (Langlois et al., 2016).

Radon can also have damaging effects on the brain and central nervous system. Radon enters the brain via systemic circulation through the blood-brain barrier (Bräuner et al., 2013; Lehrer et al., 2017) and more directly through neuronal pathways linked to the olfactory system (Zhang et al., 2022; Gómez-Anca & Barros-Dios, 2020). The olfactory pathway of radon exposure may be particularly harmful to the brain as it may result in local intense exposure to certain brain areas (Bräuner et al., 2013). Once in the brain, radon is naturally attracted to neurons and is absorbed by myelin sheaths (Gómez-Anca and Barros-Dios, 2020). Radon exposure is believed to cause brain cancer, as areas with higher radon have been linked to higher rates of brain cancer (Bräuner et al., 2013;

Ruano-Ravina et al.. 2017). Palmer et al. (2022) found that in areas with high radon, non-malignant brain tumor incidence was up to 26% higher. Recent studies have also implemented radon exposure as a possible risk factor in the development of neurodegenerative diseases (Gómez-Anca & Barros-Dios, 2020; Lehrer et al., 2017; Zhang et al., 2022; Yakhdani et al., 2019).

Alzheimer's Disease (AD) and Radon

The most common neurodegenerative disease in the United States is Alzheimer's disease (AD), which affects an estimated 6.9 million Americans (Alzheimer's Association, 2024). Approximately 10.9% of Americans aged 65 and older have AD, and this proportion is expected to increase over time (Alzheimer's Association, 2024). Alzheimer's disease is a progressive degeneration of brain cells and their connections, which causes a gradual loss of memory and other cognitive functions (Ahmed et al., 2018). While AD eventually affects the entire brain, damage to the hippocampus (important for forming new declarative memories) and prefrontal cortex (important for conscious planning and decision-making) are among the first and most pervasive areas of damage (Ahmed et al., 2018). Patients commonly present with neuropsychological deficits in memory, language, attention, visuospatial ability, and problem-solving (López & Dekosky, 2008). Alzheimer's disease is also associated with behavioral and psychological symptoms such as delusions, hallucinations, aggressive behavior, wandering, and depression (López & Dekosky, 2008).

The pathology of AD includes the buildup of several cerebrovascular formations, including beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) (Wilson & Marples, 2016). Aβ plaques and NFTs are clusters of abnormal proteins that result in the

death of nearby neurons (Wilson & Marples, 2016). In addition to these cerebrovascular formations, vascular risk factors such as hypertension (Lehrer et al., 2017; Walker et al., 2019), cerebrovascular disease (Li et al., 2011), and stroke (Kaffashian et al., 2013) are suspected to play a role in AD development.

This pathology provides a possible mechanism by which radon increases the risk of Alzheimer's disease. Zhang et al. (2022) propose that radon exposure may increase the risk of AD by inducing vascular dysfunction and cellular death. Indeed, radon exposure has been implicated in cerebrovascular disease (Lu et al., 2022; Rage et al., 2018), hypertensive disorders in pregnancy (Papatheodorou et al., 2021), and stroke in older adults (Kim et al., 2020). Since vascular risk factors play a role in AD development (Li et al., 2011), radon's influence on the vascular system may increase AD risk (Zhang et al., 2022). Radon decay also generates heavy metals which enhance Aβ plaque synthesis (Momčilović et al., 2006).

Furthermore, radon may directly increase the risk of AD through the killing of neurons (Zhang et al., 2022). Radon is neurotoxic, so radon deposits in the brain injure and even kill neurons (Gómez-Anca & Barros-Dios, 2020). Momčilović et al. (2006) conducted a case study on the natural distribution of radon decay products in a brain with AD. The authors discovered that the highest accumulation of radon decay products was found in the emotion-centered amygdala and the memory-focused hippocampus. Every year, radon was estimated to kill over 15% of cells in the amygdala and about 5% of cells in the hippocampus. Cell death in these areas may contribute to emotion-related and memory-related AD symptomology.

If radon exposure does increase the risk of Alzheimer's disease, then areas with higher radon should also have higher rates of AD. Only one study has examined this possibility. Lehrer et al. (2017) conducted an ecological study at the state level to determine if radon levels were associated with Alzheimer's disease mortality. A linear regression found a significant correlation between the average radon concentration and AD mortality rate. This relationship remained significant even when controlling for AD risk factors including age, diabetes, and hypertension. Therefore, radon appears to contribute to Alzheimer's disease mortality even when considering other relevant risk factors.

Parkinson's Disease (PD) and Radon

Another common neurodegenerative disease is Parkinson's disease (PD) which is estimated to affect over 930,000 Americans aged 45 years or older (Marras et al., 2018). Parkinson's disease is a motor functioning disorder resulting from nerve cell damage (Bartels & Leenders, 2009). Parkinson's disease presents with motor symptoms such as slower voluntary movements, muscular rigidity, resting tremors, gait disturbances, postural instability, speech problems, and difficulty swallowing (Sveinbjornsdottir, 2016). Parkinson's disease is also associated with non-motor symptoms including olfactory deficits, mood disturbances, sleep problems, memory complaints, excessive sweating, gastrointestinal symptoms, and visual hallucinations (Rey et al., 2018; Sveinbjornsdottir, 2016). The pathology of PD is seen in nerve cells, where abnormal clumps of proteins called Lewy bodies form (Braak, 2004). Lewy bodies can cause cells to cease functioning and eventually die (Braak, 2004).

Individuals who develop Parkinson's disease are believed to have a genetic predisposition that can become activated under certain environmental conditions (Pringsheim et al., 2014). Rey et al. (2018) explain that environmental contaminants likely enter the Parkinson's brain via the olfactory pathway. This is supported by the large number of Lewy bodies found in olfactory structures among individuals with PD (Rey et al., 2018). Furthermore, olfactory deficits develop four years before motor symptoms begin, making them one of the earliest signs of PD (Rey et al., 2018). Since radon is known to enter the brain through the olfactory pathway, radon may be an environmental risk factor for PD (Gómez-Anca & Barros-Dios, 2020).

There were no ecological studies found investigating residential radon concentrations and the development of Parkinson's disease, but Zeng et al. (2022) investigated occupational radon exposure and neurodegenerative disease risk among two groups of miners. The test group worked in underground uranium mines, while the reference group worked in underground non-uranium mines and surface mines. The test group was further sorted into subgroups of low exposure, medium exposure, and high exposure to radon. It was found that miners with medium exposure had more PD than the reference group. However, the highest exposure group did not have more PD than the reference group. Similarly, the lowest exposure group had more Alzheimer's disease than the reference group, but the medium and high exposure groups did not have more AD than the reference group. Zeng et al. (2022) use this contradiction to argue there is no dose-response relationship between occupational radon exposure and neurodegenerative disease. However, this study has a notable limitation because miners with higher exposure also worked longer in the mines (Zeng et al., 2022). Thus, miners with high

exposure were more likely to be affected by other mining hazards such as increased rates of head injury, diesel engine exhaust, and whole-body vibrations. Since these hazards are associated with negative health effects, including but not limited to neurological disease, these co-exposures may have obscured the effects of radon. Therefore, more studies need to be conducted on radon exposure and neurodegenerative disease risk.

Multiple Sclerosis (MS) and Radon

Another common neurodegenerative disease is Multiple Sclerosis (MS), which affects over 900,000 adults in the United States (Walton et al., 2020). Multiple Sclerosis is a progressive inflammatory disease related to sensory and motor impairment (Ghasemi et al., 2017). Multiple sclerosis typically affects younger adults, with disease onset at 20-40 years of age, and results in severe disability (Kister et al., 2013; Yakhdani et al., 2021). Common symptoms include walking difficulties, muscle spasms, tremors, loss of balance, somatosensory disturbances, vision problems, dizziness, vertigo, cognitive impairment, emotional difficulties, urinary system dysfunction, constipation, and sexual problems (Ghasemi et al., 2017). Multiple sclerosis pathology is characterized by central nervous system inflammation, neuron demyelination, and axon damage (Compston & Coles, 2008; Kutzelnigg & Lassmann, 2014). Damaged and demyelinated neurons can discharge spontaneously, resulting in motor twitches and sensory disturbances (Compston & Coles, 2008).

Similar to Parkinson's disease, Multiple Sclerosis is believed to occur due to a mix of genetic susceptibility and environmental exposure (Compston & Coles, 2008). When environmental factors impact someone with genetic susceptibility, an autoimmune attack may be triggered that begins MS pathology by damaging myelin and axons (Brück

& Stadelmann, 2005). Multiple Sclerosis has been linked to infection with Epstein-Barr virus (EBV), Vitamin D deficiency, and smoking (Ghasemi et al., 2017; Gómez-Anca & Barros-Dios, 2020). Several studies have also implicated radon as a possible environmental factor in MS pathogenesis (Bølviken et al., 2003; Fathabadi et al. 2020; Gómez-Anca & Barros-Dios, 2020; Yakhdani et al., 2021). Since radon is absorbed into myelin sheaths and releases radioactive particles, it can directly damage myelin (Gómez-Anca & Barros-Dios, 2020). Furthermore, radon exposure may re-activate latent viruses that cause Multiple Sclerosis (Bølviken et al., 2003; Yakhdani et al., 2019).

Fathabadi et al. (2020) found that individuals with anxiety and depression were more likely to develop MS, especially if they were exposed to radon gas. This presents the possibility that radon may induce MS via mental-health-related mechanisms. Since depression has also been implicated in both Alzheimer's disease and Parkinson's disease (Gustafsson et al., 2015), and chronic stress has been implicated in Alzheimer's disease (Wallensten et al., 2023), radon-induced mental health problems may be implicated in the development of these disorders as well.

Several studies have examined the possible relationship between radon exposure and the prevalence of Multiple Sclerosis. This includes three ecological studies that used estimated radon levels for a given area (Bølviken et al., 2003; Gilmore & Grennan, 2001; Groves-Kirby et al., 2016). Bølviken et al. (2003) conducted an ecological study at the municipality level and discovered that in most parts of southern Norway, areas with higher levels of radon also had a higher incidence of MS. Gilmore & Grennan (2001) conducted a small county-level analysis in northwest Ireland and found that counties with low radon levels also had lower estimated MS prevalence. Groves-Kirkby et al. (2016)

conducted a study by zip code in the United Kingdom and identified a trend of increasing MS incidence with increasing radon concentration, but insufficient data was available for statistical significance to be found. Overall, ecological studies support the theory that residential radon exposure is associated with Multiple Sclerosis rates.

Three studies directly measured radon concentration in the homes of participants with and without MS (Entezari et al., 2021; Fathabadi et al., 2020; Yakhdani et al., 2021). Yakhdani et al. (2021) tested homes with radon test kits and found that individuals with MS were more likely to have homes with radon concentrations above the World Health Organization's standards (91.8%) than individuals without MS (8.2%). Fathabadi et al. (2020) found that the mean total concentration of radon gas was higher in the homes of MS patients, but the difference was not statistically significant. This study may have not reached significance because of over-limiting exclusion criteria. More specifically, individuals were excluded from the study if they had other chronic illnesses or a family history of MS. Since radon exposure causes other chronic illnesses and is usually connected to several family members living in the same home or neighborhood, limiting these factors may have systematically excluded participants with radon-induced MS. Entezari et al. (2021) also conducted a case-control study. While they did not find a significant relationship between radon concentration and MS incidence, they did find that radon concentration above the EPA standard was 5.29% more prevalent in MS homes. The lack of significance may be caused by the way non-MS participants were selected. The authors chose to use neighbors of the MS patients as the control subjects, but since neighbors live in the same area and have similar homes, this could artificially limit group differences and lower statistical significance. This theory is supported by the study results

because the groups had very similar averages in total radon exposure. While these studies all trend in the right direction, only one of three reached statistical significance. Therefore, more studies are needed to determine if radon exposure increases the risk of developing MS.

Literature Summary

Overall, most studies support a relationship between residential radon exposure and neurodegenerative disease (Bølviken et al., 2003; Gilmore & Grennan, 2001; Gómez-Anca & Barros-Dios, 2020; Lehrer et al., 2017; Momčilović et al., 2006; Zhang et al., 2022). However, some studies did not reach statistical significance (Entezari et al., 2021; Fathabadi et al., 2020; Groves-Kirkby et al., 2016; Yakhdani et al., 2021). Additionally, several studies had serious limitations such as small sample size (Gilmore & Grennan, 2001; Momčilović et al., 2006; Groves-Kirkby et al., 2016) or weak participant selection criteria (Entezari et al., 2021; Fathabadi et al., 2020). Therefore, more research is needed to confirm the relationship between radon exposure and neurodegenerative disease.

The Current Study

The current study aimed to investigate whether radon exposure leads to the development of three neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. A county-level ecological study was conducted by combining two Centers for Disease Control (CDC) databases, one containing mean radon concentrations and the other containing disease mortality rates. In addition to mortality from these three neurodegenerative diseases, mortality rates from nervous system diseases, cerebrovascular diseases, cancer, bronchus and lung cancer, and central nervous

system cancer were examined. It was hypothesized that mean radon concentration would be positively associated with Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis.

Hypotheses

1. Radon concentration will be positively correlated with Alzheimer's disease mortality.
2. Radon concentration will be positively correlated with Parkinson's disease mortality.
3. Radon concentration will be positively correlated with Multiple Sclerosis mortality.

Method

Radon Concentration Measures

Radon exposure estimates were collected from the Centers for Disease Control (CDC) National Environmental Public Health Tracking Network database. Initial data was selected from the content area "Radon", the indicator "Radon Tests from Labs", and the measure "Mean Pre-mitigation Radon Level in Tested Buildings over a 10-year Period". National by county data from 2008-2017 was used. These years were selected because they were the most recent data available. With these parameters, data was not available for Kansas, New Jersey, Mississippi, and Hawaii. After excluding counties from these states and counties with less than 10 radon tests, data was missing for 1,028 counties (32.67% of total counties).

Different query parameters were also used to fill in missing data. Secondary data was selected from the indicator “Radon Tests from States” and the measure “Annual Mean Pre-Mitigation Radon Level in Tested Buildings”. The means from the years 2008-2017 were averaged into one mean radon concentration for each county over the 10 year period. Values and counties with less than 10 radon tests were excluded. Additionally, only counties that were not included in the “Radon Tests from Labs” dataset were included so that there was no duplication of counties. By including data from both primary and secondary datasets, with care to avoid duplication, it was possible to attain radon concentration means from 2,233/3,147 counties (70.97% of all counties). Notably, neither dataset included any counties from Mississippi, so all counties from that state were unavailable for analysis.

Mortality Measures

Mortality information was obtained from the CDC WONDER Underlying Cause of Death database. The query parameters included crude mortality rates for all counties across the United States between the years 2008-2017. The following International Classification of Diseases, Tenth Revision (ICD-10) codes and descriptors were pulled from the database: Diseases of the nervous system (G00-G98), Alzheimer’s disease (G30), Parkinson’s disease (G20), Multiple Sclerosis (G35), cerebrovascular diseases (I60-I69), mood disorders (F30-F39), viral infections of the central nervous system (A80-A89), malignant neoplasms (C00-C97), malignant neoplasms of bronchus and lung (C34), and malignant neoplasms of eye, brain, and other parts of central nervous system (C69-C72).

Due to confidentiality and reliability concerns, CDC WONDER does not provide mortality rates for counties with less than 10 individuals who died from the queried disorder and for counties whose death rate is based on less than 20 total deaths. Once these counties were removed, the data included 2,928 counties (93.04%) for diseases of the nervous system, 2,728 counties (86.89%) for Alzheimer's disease, 1,696 counties (53.89%) for Parkinson's disease, 444 counties (14.11%) for Multiple Sclerosis, 2,937 counties (93.33%) for cerebrovascular diseases, 49 counties (1.56%) for mood disorders, 47 counties (1.49%) for viral infections of the central nervous system, 3,110 counties (98.82%) for malignant neoplasms, 2,941 counties (93.45%) for malignant neoplasms of bronchus and lung, and 1,313 counties (41.72%) for malignant neoplasms of eye, brain, and other parts of the central nervous system.

Power Analyses

A-priori power analyses were conducted in G*Power 3.1.9.7 to determine the needed sample size (Faul et al., 2007; Faul et al., 2009). For a one-tailed bivariate correlation with a small effect size of 0.1 and a power of 0.8, the total sample size needed was 284. Since mood disorders and viral infections of the central nervous system had less than 284 counties, these disorders were excluded from the analysis. The remaining disorders included in the analysis were nervous system diseases, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, cerebrovascular diseases, cancer (i.e. malignant neoplasms), bronchus and lung cancer (i.e. malignant neoplasms of bronchus and lung), and central nervous system cancer (i.e. malignant neoplasms of eye, brain, and other parts of the central nervous system).

Data Analyses

Data analyses were conducted in Jamovi 2.3.28 (R Core Team, 2021; The Jamovi Project, 2022).

A Pearson correlation matrix was conducted with the variables radon concentration, nervous system diseases, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, cerebrovascular diseases, cancer, bronchus and lung cancer, and central nervous system cancer.

A multiple linear regression was conducted with the dependent variable radon concentration and covariates of Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis.

A second multiple linear regression was conducted with the dependent variable radon concentration and covariates of bronchus and lung cancer, and central nervous system cancer.

A third multiple linear regression was conducted with the dependent variable radon concentration and covariates of nervous system diseases and cancers.

Results

Table 2 shows the Pearson correlations between radon concentration, nervous system diseases, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, cerebrovascular diseases, cancer, bronchus and lung cancer, and CNS cancer. Radon concentration was positively correlated with nervous system diseases ($r = 0.145$, $p < .001$, $n = 2173$), Alzheimer's disease ($r = 0.147$, $p < .001$, $n = 2056$), Parkinson's disease ($r = 0.233$, $p < .001$, $n = 1459$), Multiple Sclerosis ($r = 0.317$, $p < .001$, $n = 439$), cerebrovascular diseases ($r = 0.117$, $p < .001$, $n = 2171$), cancer ($r = 0.084$, $p < .001$, $n =$

2227), and CNS cancer ($r = 0.176$, $p = .003$, $n = 280$). However, the relationship between radon concentration and bronchus and lung cancer was not significant ($r = 0.001$, $p = 0.957$, $n = 2170$).

Table 2

Correlation Matrix with All Variables

	Radon Concentration	Nervous System Diseases	Alzheimer's Disease	Parkinson's Disease	Multiple Sclerosis	Cerebrovascular Diseases	Cancer	Bronchus & Lung Cancer	CNS Cancer
Radon Concentration	—								
Nervous System Diseases	r (2173) = 0.145***	—							
Alzheimer's Disease	r (2056) = 0.147***	r (2728) = 0.965***	—						
Parkinson's Disease	r (1459) = 0.233***	r (1696) = 0.661***	r (1694) = 0.506***	—					
Multiple Sclerosis	r (439) = 0.317***	r (444) = 0.505***	r (444) = 0.415***	r (444) = 0.528***	—				
Cerebrovascular Diseases	r (2171) = 0.117***	r (2883) = 0.574***	r (2713) = 0.508***	r (1696) = 0.527***	r (444) = 0.447***	—			
Cancer	r (2227) = 0.084***	r (2928) = 0.526***	r (2728) = 0.449***	r (1696) = 0.550***	r (444) = 0.522***	r (2937) = 0.719***	—		
Bronchus & Lung Cancer	r (2170) = 0.001	r (2880) = 0.389***	r (2704) = 0.338***	r (1696) = 0.373***	r (444) = 0.466***	r (2892) = 0.583***	r (2941) = 0.885***	—	
CNS Cancer	r (280) = 0.176**	r (286) = 0.367***	r (286) = 0.312***	r (286) = 0.457***	r (286) = 0.521***	r (286) = 0.498***	r (286) = 0.578***	r (286) = 0.534***	—

*Green values are significant: * p < .05, ** p < .01, *** p < .001*

Tables 3a and 3b include results from a multiple linear regression with the dependent variable as radon concentration and the covariates as Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. The model was significant ($p < .001$) and accounted for 12.3% of data ($R^2 = 0.123$). Alzheimer's disease ($t = -2.84$, $p < .005$), Parkinson's disease ($t = 2.92$, $p = .004$), and Multiple Sclerosis ($t = 5.42$, $p < .001$) were all found to be significant predictors of radon concentration.

Table 3a

Radon and Neurodegenerative Diseases: Model Fit Measures

R	R^2	*F*	*df*	*p*
0.351	0.123	20.4	(3, 435)	< .001

Table 4b

Radon and Neurodegenerative Diseases: Model Coefficients

Predictor	Estimate	*SE*	*t*	*p*
Alzheimer's Disease	-0.0365	0.0129	-2.84	0.005
Parkinson's Disease	0.1769	0.0607	2.92	0.004
Multiple Sclerosis	1.4115	0.2606	5.42	< .001
Green rows are significant.				

Tables 4a and 4b show the results of a multiple linear regression completed with the dependent variable of radon concentration and covariates of bronchus and lung cancer, and CNS cancer. The model was significant ($p = 0.012$) and accounted for 3.12% of data ($R^2 = 0.0312$). CNS cancer was a significant predictor ($t = 2.566$, $p = 0.011$), but bronchus and lung cancer was not a significant predictor ($t = -0.129$, $p = 0.897$).

Table 4a

Radon and Cancer: Model Fit Measures

R	R^2	*F*	*df*	*p*
0.177	0.0312	4.46	(2, 277)	0.012

Table 4b

Radon and Cancer: Model Coefficients

Predictor	Estimate	*SE*	*t*	*p*
Bronchus & Lung Cancer	-0.00125	0.00968	-0.129	0.897
CNS Cancer	1.12666	0.43913	2.566	0.011

Green rows are significant.

Tables 5a and 5b show the results of a multiple linear regression completed with the dependent variable of radon concentration and covariates of nervous system diseases and cancers. The model was significant ($p < .001$) and accounted for 2.13% of data ($R^2 = 0.0213$). Nervous system diseases were a significant predictor ($t = 5.346$, $p < .001$) but cancers were not a significant predictor ($t = 0.688$, $p = 0.491$).

Table 5a

Radon, Nervous System Diseases, and Cancer: Model Fit Measures

R	R^2	*F*	*df*	*p*
0.146	0.0213	23.7	(2, 2170)	<.001

Table 5b

Radon, Nervous System Diseases, and Cancer: Model Coefficients

Predictor	Estimate	*SE*	*t*	*p*
Nervous System Diseases	0.01802	0.00337	5.346	<.001
Cancers	0.00101	0.00147	0.688	0.491

Green rows are significant.

Discussion

The current study investigated relationships between radon exposure and disease mortality. Three neurodegenerative diseases were investigated, including Alzheimer's disease (AD), Parkinson's disease (PD), and Multiple Sclerosis (MS). Other disease correlates included nervous system diseases, cerebrovascular diseases, cancers, bronchus and lung cancer, and central nervous system (CNS) cancer. A county-level ecological analysis for the United States was conducted using data from two separate CDC databases.

Alzheimer's Disease (AD)

In support of Hypothesis 1, a positive correlation was found between mean radon concentration and Alzheimer's disease (AD) mortality. In other words, counties with a higher average radon concentration had significantly more deaths from AD. Additionally, AD was a significant predictor of radon concentration. These results provide support for an association between radon exposure and AD.

Since correlational analyses were used, it could not be determined if radon exposure was directly causing Alzheimer's disease. It is also possible that both variables increased due to other ecological factors, such as socioeconomic status and healthcare availability. However, since this study supports a relationship between radon and AD, future research is needed to understand the impact of radon on AD. Future studies with more experimental control are needed to determine if the relationship between radon concentration and AD is causal.

Based on previous literature, it was expected that a correlation would be found between radon concentration and Alzheimer's disease. Studies indicate that radon may increase the incidence and severity of AD by inducing vascular risk factors (Li et al., 2011; Zhang et al., 2022) and directly killing neurons in the brain (Gómez-Anca & Barros-Dios, 2020; Momčilović et al., 2006). Furthermore, Lehrer et al. (2017) found that states with higher radon levels had significantly higher rates of AD mortality. However, radon concentration varies greatly not only between states but also between counties (Environmental Protection Agency, 2019). The current study aimed to see if the association between radon and AD could still be found at the county level. The current study confirms that this association exists at the county level, further supporting the idea that radon exposure and Alzheimer's disease are related.

Parkinson's disease (PD)

In line with Hypothesis 2, a positive correlation was found between radon concentration and Parkinson's disease (PD) mortality. Counties higher in radon were also higher in PD deaths. These results establish an association between radon exposure and PD, but the current study's design does not allow for causation to be determined. However, since an association was found, future research is needed to investigate if radon exposure causes increased PD mortality.

Previous literature explains that individuals who develop Parkinson's disease have a genetic predisposition that can be activated by environmental contaminants entering through the olfactory pathway (Pringsheim et al., 2014; Rey et al., 2018). Since radon is a neurotoxic contaminant that enters the brain through this pathway (Zhang et al., 2022), radon may be a risk factor for PD (Gómez-Anca & Barros-Dios, 2020). The current study

investigated this association and found that radon exposure may be a risk factor in Parkinson's disease mortality.

Multiple Sclerosis (MS)

In support of Hypothesis 3, radon concentration was positively correlated with Multiple Sclerosis (MS) mortality. Counties with higher average radon concentrations also had higher rates of MS mortality. This suggests that a significant relationship exists between radon and MS. However, as with other neurodegenerative diseases, future studies are needed to establish causation.

Several studies have investigated the relationship between radon concentration and Multiple Sclerosis. Radon exposure may induce MS by directly damaging myelin (Gómez-Anca & Barros-Dios, 2020) or re-activating latent viruses (Yakhdani et al., 2019). Ecological studies have been conducted examining mean radon levels and MS incidence. It has been found that municipalities in Norway (Bølviken et al., 2003) and counties in northwest Ireland (Gilmore & Grennan, 2001) with higher indoor radon concentrations also have higher MS prevalence. However, zip code regions in the United Kingdom with more radon did not significantly differ in MS incidence (Groves-Kirkby et al., 2016). Notably, the authors stated that their nonsignificant results came from insufficient data rather than a true effect. In line with the idea that radon influences MS, the current study found a significant correlation between radon concentration and MS mortality among counties in the United States.

Nervous System Diseases

The relationship between radon exposure and nervous system diseases was also examined. This measure included neurodegenerative diseases, inflammatory diseases, movement disorders, paralytic disorders, nerve disorders, epileptic disorders, systematic atrophies, and other nervous system diseases. It was found that radon concentration was positively correlated with nervous system diseases. Furthermore, nervous system diseases were a significant predictor of radon concentration.

These results support a relationship between radon concentration and nervous system diseases in general. Part of this effect is likely due to Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis, since mortality rates from these disorders are included in this overarching variable. However, it is also possible that other neurological diseases are being affected by radon. Gómez-Anca & Barros-Dios (2020) connect radon exposure to Amyotrophic Lateral Sclerosis (ALS). This is a neurodegenerative motor neuron disease that results in muscle atrophy and eventual death (Gómez-Anca & Barros-Dios, 2020). Radon exposure may be involved in ALS and other neurological diseases as well. Future studies may want to examine the relationship between radon and other specific nervous system disorders to see if radon correlates with these other disorders.

Cerebrovascular Diseases

The current study also investigated if radon exposure was related to cerebrovascular diseases. This variable included deaths from stroke, cerebral hemorrhage, cerebral infarction, cerebral aneurysm, cerebral atherosclerosis, hypertensive encephalopathy, and a variety of other cerebrovascular diseases. A positive correlation was found between radon concentration and cerebrovascular disease mortality. Counties with higher average radon concentrations also had a higher rate of deaths from

cerebrovascular diseases. While these results do not prove a causative relationship, they do suggest that a relationship exists between radon exposure and cerebrovascular diseases. These results are in line with previous research, which has linked radon exposure to cerebrovascular disease (Lu et al., 2022; Rage et al., 2018) and stroke (Kim et al., 2020).

Cancers

The current study also investigated the relationship between radon exposure and cancer mortality. Radon was positively correlated with overall cancer mortality and central nervous system (CNS) cancer mortality. However, no relationship was found between radon concentration and bronchus and lung cancer. Among these variables, only CNS cancer could significantly predict radon exposure.

Radon exposure can damage DNA and thus increase cancer risk (Eidy et al., 2024; Field 2011). Although radon is found throughout the body (Bräuner et al., 2013), it commonly accumulates in organs including the lungs and stomach (Kendall & Smith, 2002). Radon exposure has been linked to cancer in these organs (Sethi et al., 2012; López-Abente et al., 2018). Therefore, it was expected that a correlation would be found between radon concentration and overall cancer mortality. As anticipated, the two variables were correlated. However, cancer mortality was not a significant predictor of radon exposure. This could be because radon does not increase the risk of all cancers, but only specific cancers. Therefore, cancers not affected by radon could not predict radon concentrations. This could reduce the ability of overall cancer mortality to predict radon concentrations.

Radon concentrations were not correlated with bronchus and lung cancer, which was surprising since radon exposure is a well-established cause of lung cancer (Environmental Protection Agency, 2016a). One explanation for this result is that the effects of radon were obscured by the much greater effects of smoking. The amount of lung cancer cases attributed to radon exposure is minimal compared to smoking, with 78-92% of lung cancer cases attributed to smoking and only 3-15% of cases attributed to radon exposure (Sethi et al., 2012). Thus, radon concentration would likely have been much better predicted by smoking than radon, so areas with higher smoking rates were likely to have more lung cancer mortality regardless of their radon level. Future studies may want to account for this confound by gathering data on smoking rates and implementing this into their study designs.

Radon concentrations were accurately predicted by CNS cancer, but not by bronchus and lung cancer. This could be because of how radon deposits in the body. While proportionally more radon is found in the lungs than in the brain (Ruano-Ravina et al., 2017), radon deposits in some brain structures more than others (Momčilović et al., 2006). Certain brain structures have proportionately more radon than is found in the lungs (Momčilović et al., 2006), which may place these brain areas at a higher risk for cancer. This could explain why significance was found for CNS cancer even if it wasn't found for bronchus and lung cancer. This creates a good avenue for future research. It may be worthwhile to examine where cancer generally occurs in the brain to determine if it is linked to where higher deposits of radon are found.

CNS cancer mortality was positively correlated with radon concentration and was a significant predictor of radon. This suggests that there is an association between radon

exposure and CNS cancer mortality. This association was expected based on prior research on radon and CNS cancer. An ecological study (Ruano-Ravina et al., 2017) and a cohort study (Bräuner et al., 2013) both identified correlations between radon exposure and CNS cancer. However, Palmer et al. (2022) found that high radon areas were more likely to have non-malignant brain tumors but not malignant brain tumors. The current study only investigated mortality from malignant brain tumors, so the association between nonmalignant brain tumors could not be investigated. This is a good avenue for future research.

Disease Correlates

Correlations were also found between all diseases, including nervous system diseases, Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, cerebrovascular diseases, cancers, bronchus and lung cancer, and central nervous system cancer. This means that counties with higher mortality rates for one disorder also had higher mortality rates for the other disorders. Since correlations were found between all diseases, they likely arise from outside factors such as age distribution, healthcare availability, or socioeconomic status.

Limitations & Future Directions

The greatest limitation of this study is its ecological design, which makes the study vulnerable to ecological fallacy. Since geographic areas vary on many traits, not just the traits under observation, many confounding factors may influence the study results. Therefore, caution must be used when interpreting the study's findings. Another limitation is that the average radon concentration per county is used, but radon levels can

vary greatly between individual homes (Environmental Protection Agency, 2016a), so it would be flawed to assume that all houses in the area are near the average concentration. However, this study is more precise than a state-level study such as the one conducted by Lehrer et al. (2017). The current study also has a larger sample size than other county-level ecological studies such as those conducted by Bolviken et al. (2003) and Gilmore and Grennan (2001). Therefore, this study provides some strengths over previous research, but it still must be interpreted cautiously due to its ecological design.

Another limitation of this study is that mortality rates only included a single cause of death per individual. Individuals commonly die from a combination of different disorders (Frova et al., 2009), but these combinations were not available for analysis in the current study. For example, an individual may die from a combination of Alzheimer's disease and cerebrovascular disease, but only one of these disorders would be listed as the cause of death. This hinders the ability to investigate the complex relationships found between disorders. Most notably, it was difficult to determine any relationships between neurodegenerative risk factors and their respective neurodegenerative diseases. Future studies may want to use mortality rates that list multiple causes of death so that the relationships between disorders can be examined.

An additional study limitation is missing data from the original datasets. If the average radon concentration was based on less than ten radon tests, then the radon data for that county was not included. Similarly, if a county had less than twenty total deaths or less than ten individuals with the given disorder, mortality data for that county was not available. Since counties with smaller populations were less likely to reach these minimum standards, this may have led to the underrepresentation of rural or other small-

population counties. Furthermore, two variables (i.e. viral central nervous system infections and affective disorders) had to be excluded from the analysis because so few counties had data available. It is important to keep factors such as these in mind when conducting ecological studies based on publicly available databases.

Conclusions

In conclusion, the current study supports that higher radon concentrations are associated with higher mortality from neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis. Additionally, radon is correlated with higher mortality rates from nervous system cancer and cerebrovascular diseases. Since this county-level ecological analysis suggests that radon concentration is related to disease mortality, it may be worthwhile for future studies to determine if radon exposure is a direct cause of these diseases.

References

Ahmed, M. Q., Alenazi, F. S., Fazaludeen, M. F., Shahid, S. M., & Kausar, M. A. (2018). Pathology and Management of Alzheimer's disease: A review. *International Journal of Pharmaceutical Research & Allied Sciences, 7*(2), 30-42.

Alzheimer's Association. (2024). Alzheimer's disease facts and figures. *Alzheimer's Dementia, 20*(5), 1-145.

American Lung Association. (2023, October 25). *State of lung cancer*. American Lung Association. https://www.lung.org/research/state-of-lung-cancer/states

Appleton, J. D. (2007). Radon: Sources, health risks, and hazard mapping. *Ambio, 36*(1), 85-89.

Barros-Dios, J. M., Ruano-Ravina, A., Gastelu-Iturri, J., & Figueiras, A. (2007). Factors underlying residential radon concentration: Results from Galicia, Spain. *Environmental Research, 103*, 185-190. https://doi.org/10.1016/j.envres.2006.04.008

Bartels, A., & Leenders, K. L. (2008). Parkinson's disease: The syndrome, the pathogenesis and pathophysiology. *Cortex, 45*, 915-921. https://doi.org/10.1016/j.cortex.2008.11.010

Bølviken, B., Celiusb E.G., Nilsena, R., & Strand, T. (2003). Radon: A possible risk factor in multiple sclerosis. *Neuroepidemiology, 22*, 87-94. https://doi.org/10.1159/000067102

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H. & Tredici, K. D. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research, 318*, 121-134. https://10.1007/s00441-004-0956-9

Bräuner, E. V., Andersen Z. J., Andersen, C. E., Pedersen, C., Gravesen, P., Ulbak, K., Hertel, O., Steffen, L., & Raaschou-Nielson, O. (2013). Residential radon and brain tumour incidence in a Danish cohort. PLoS ONE, 8(9), 1-7. https://doi.org/10.1371/journal.pone.0074435

Bruck, W., & Stadelmann, C. (2005). The spectrum of Multiple Sclerosis: New lessons from pathology. *Current Opinion in Neurology, 18*(3), 221-224. https://doi.org/10.1097/01.wco.0000169736.60922.20

Centers for Disease Control and Prevention. *CDC WONDER* (Underlying Cause of Death). [Data set]. Centers for Disease Control and Prevention. https://wonder.cdc.gov/Deaths-by-Underlying-Cause.html

Centers for Disease Control and Prevention. *National Environmental Public Health Tracking Network*. (Radon). [Data set]. Centers for Disease Control and Prevention. https://ephtracking.cdc.gov/DataExplorer/

Compston, A., & Coles, A. (2008). Multiple Sclerosis. *Lancet, 372* (9648), 1502-1517. https://doi.org/10.1016/S0140-6736(08)61620-7

Daniels, R. D., & Schubauer-Berigan, M. K. (2017). Radon in US workplaces: A review. *Radiation Protection Dosimetry, 176*(3), 278-286. https://doi.org/10.1093/rpd/ncx007

Eidy, M., Regina, A. C., & Tishkowski (2024). *Radon Toxicity.* StatsPearls Publishing LLC.

Entezari, M., Ehrampoush, M. H., Rahimdel, A., Shahi, M. A., Keyghobady, N., Jalili, M., Fathabadi, Z. A., Fallah Yakhdani, M., & Ebrahimi, A. A. (2021). Is there a relationship between homes' radon gas of MS and non-MS individuals, and the patients' paraclinical magnetic resonance imaging and visually evoked potentials in Yazd-Iran? *Environmental Science and Pollution Research International, 28*(7), 8907–8914. https://doi.org/10.1007/s11356-020-10580-y

Environmental Protection Agency. (2016). *A citizen's guide to radon: The guide to protecting yourself and your family from radon.* United States Environmental Protection Agency.

Environmental Protection Agency (2016). *Radon zones map.* United States Environmental Protection Agency. https://www.epa.gov/radon/epa-map-radon-zones

Environmental Protection Agency (2023, July 6). What is EPA's action level for radon and what does it mean? https://www.epa.gov/radon/what-epas-action-level-radon-and-what-does-it-mean

Fathabadi, Z. A., Ehrampoush, M. H., Mirzaei, M., Mokhtari, M., Sakhvidi, M. N., Rahimdel, A., Tafti, A. D., Yakhdani, M. F., Atefi, A., Eslami, H., & Ebrahimi, A. A. (2020). The relationship of indoor radon gas concentration with multiple sclerosis: A case-control study. *Environmental Science and Pollution Research, 27*, 16350-16361. https://doi.org/10.1007/s11356-020-08147-y

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. https://doi.org/10.3758/BRM.41.4.1149

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175-191. https://doi.org/10.3758/bf03193146

Field, R. W. (2011). Radon: An overview of health effects. *Encyclopedia of Environmental Health,* 745-753. https://doi.org/10.1016/B978-0-444-52272-6.00095-7.

Frova, L., Salvatore, M. A., Pappagallo, M., & Egidi, V. (2009). The multiple cause of death approach to analyze mortality patterns. *Genus, 65*(1), 1-21.

Frumkin, H. & Samet, J. M. (2001). Radon. *CA A Cancer Journal for Clinicians, 51*(6), 337-344. https://doi.org/10.3322/canjclin.51.6.337

Ghasemi, N., Razavi, S., & Nikzad, E. (2017). Multiple Sclerosis: Pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell Journal, 19*(1), 1-10. https://doi.org/10.22074/cellj.2016.4867

Gilmore, M., & Grennan, E. (2003). A pilot study of the relationship between Multiple Sclerosis and the physical environment in northwest Ireland. *Environmental Geochemistry and Health, 25*(1), 157-163. https://doi.org/10.1023/a:1021229805676

Gómez-Anca, S., & Barros-Dios, J. M. (2020). Radon exposure and neurodegenerative disease. *International Journal of Environmental Research and Public Health, 17*(20), 1–16. https://doi.org/10.3390/ijerph17207439

Gordon, K., Terry, P. D., Liu, X., Harris, T., Vowell, D., Yard, B., & Chen, J. (2018). Radon in schools: A brief review of state laws and regulations in the United States. *International Journal of Environmental Research and Public Health, 15*(10), 2149. https://doi.org/10.3390/ijerph15102149

Groves-Kirkby, C. J., Denman, A. R., Campbell, J., Crockett, R. G., Phillips, P. S., & Rogers, S. (2016). 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. *Journal of Environmental Radioactivity, 154*, 1-14. https://doi.org/10.1016/j.jenvrad.2015.12.003

Gustafsson, H., Nordström, A., & Nordström, P. (2015). Depression and subsequent risk of Parkinson disease: A nationwide cohort study. *Neurology, 84*(24), 2422–2429. https://doi.org/10.1212/WNL.0000000000001684

Kaffashian, S., Dugravot, A., Elbaz, A., Shipley, M. J., Sabia, S., Kivimäki, M., & Singh-Manoux, A. (2013). Predicting cognitive decline: A dementia risk score vs the Framingham vascular risk scores. *Neurology, 80*(14), 1300-1306. https://doi.org/10.1212/WNL.0b013e31828ab370

Kendall, G. M., & Smith, T. J. (2002). Doses to organs and tissues from radon and its decay products. *Journal of Radiological Protection, 22*, 389-406. https://doi.org/10.1088/0952-4746/25/3/002

Kim, S. H., Park, J. M., & Hee, O. T. (2020). The prevalence of stroke according to indoor radon concentration in South Koreans. *Medicine, 99*(4), e18859. https://doi.org/10.1097/MD.0000000000018859

Kister, I., Chamot, E., Salter, A. R., Cutter, G. R., Bacon, T. E., & Herbert, J. (2013). Disability in Multiple Sclerosis: A reference for patients and clinicians. *Neurology, 80*(11), 1018-1024. https://doi.org/10.1212/WNL.0b013e3182872855

Kusumawardani, I. A., Indraswari, P. G., & Komalasari, N. L. (2023). Air pollution and lung cancer. *Journal of Respirology, 9*(2), 150-158. https://doi.org/10.20473/jr.v9-I.2.2023.150-158

Kutzelnigg, A., & Lassmann, H. (2014). Chapter 2 – Pathology of multiple sclerosis and related inflammatory demyelinating diseases. *Handbook of Clinical Neurology, 122*, 15-58. https://doi.org/10.1016/B978-0-444-52001-2.00002-9

Langlois, P. H., Lee, M., Lupo, P. J., Rahbar, M. H., & Cortez, R. K. (2015). Residential radon and birth defects: A population-based assessment. *Birth Defects Research Part A Clinical and Molecular Teratology, 106*(1), 5-15. https://doi.org/10.1002/bdra.23369

Lehrer, S., Rheinstein, P. H., & Rosenzweig, K. E. (2017). Association of radon background and total background ionizing radiation with Alzheimer's disease deaths in US states. *Journal of Alzheimer's Disease, 59*(2), 737–741. https://doi.org/10.3233/jad-170308

Li, J., Wang, Y. J., Zhang, M., Xu, Z. Q., Gao, C. Y., Fang, C. Q., Yan, J. C., Zhou, H. D., & Chongqing Ageing Study Group (2011). Vascular risk factors promote

conversion from mild cognitive impairment to Alzheimer disease. *Neurology*, *76*(17), 1485–1491. https://doi.org/10.1212/WNL.0b013e318217e7a4

López, O. L., & Dekosky, S. T. (2008). Clinical symptoms in Alzheimer's disease. *Handbook of Clinical Neurology, 89(3), 207-216.*

López-Abente, G., Núñez, O., Fernández-Navarro, P., Barros-Dios, J. M., Martín-Méndez, I., Bel-Lan, A., Locutura, J., Quindós, L., Sainz, C., & Ruano-Ravina, A. (2018). Residential radon and cancer mortality in Galicia, Spain. *Science of the Total Environment, 610*, 1125–1132. https://doi.org/10.1016/j.scitotenv.2017.08.144

Lu, L., Zhang, Y., Chen, C., Field, R. W., & Kahe, K. (2022). Radon exposure and risk of cerebrovascular disease: A systematic review and meta-analysis in occupational and general population studies. *Environmental Science and Pollution Research, 29*, 45031-45043. https://doi.org/10.1007/s11356-022-20241-x

Marras, C., Beck, J. C., Bower, J. H., Roberts, E., Ritz, B., Ross, G. W., Abbott, R. D., Savica, R., Van Den Eeden, S. K., Willis, A. W., Tanner, C. M., & Parkinson's Foundation P4 Group. (2018). Prevalence of Parkinson's disease across North America. *npj Parkinson's Disease, 10*(4), 21-27. https://doi.org/10.1038/s41531-018-0058-0

Momčilović, B., Lykken, G. I., & Cooley, M. (2006). Natural distribution of environmental radon daughters in the different brain areas of an Alzheimer

disease victim. *Molecular Neurodegeneration, 1*(11). https://doi.org/10.1186/1750-1326-1-11

Palmer, J. D., Prasad, R. N., Cioffi, G., Kruchtko, C., Zaorsky, N. G., Trifiletti, D. M., Gondi, V., Brown, P. D., Perlow, H. K., Mishra, M. V., Chakravarti, A., Barnholtz-Sloan, J. S., & Ostrom, Q. T. (2023). Exposure to radon and heavy particulate pollution and incidence of brain tumors. *Neuro-oncology, 25*(2), 407-417. https://doi.org/10.1093/neuonc/noac163

Papatheodorou, S., Yao, W., Vieira, C. L., Longxiang, L., Wylie, B. J., Schwartz, J., & Koutrakis, P. (2021). Residential radon exposure and hypertensive disorders of pregnancy in Massachusetts, USA: A cohort study. *Environment International, 146*. https://doi.org/10.1016/j.envint.2020.106285

Poku, B. & Hussaini, S. (2021). Radon in child care centers: An examination of state laws and regulations in the United States. *GSC Advanced Research and Reviews, 7*(3), 5-17. https://doi.org/10.30574/gscarr.2021.7.3.0101

Porstendörfer, J. (2001). Physical parameters and dose factors of the radon and thoron decay products. *Radiation Protection Dosimetry, 94*(4), 365-373. https://doi.org/10.1093/oxfordjournals.rpd.a006512

Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. (2014). The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583-1590. https://doi.org/10.1002/mds/25945

Qiang, Z., Yupeng, Y., Li, Z., Lin, D., Li, H., Kan, H., Zhuo, W., & Chen, B. (2023). Risk assessment of lung cancer caused by indoor radon exposure in China during 2006-

2016: A multicity, longitudinal analysis. *Indoor Air*, 1-11. https://doi.org/10.1155/2023/6943333

R Core Team. (2021). *R: A language and environment for statistical computing* (Version 4.1). https://cran.r-project.org

Rage, E., Caër-Lorho, S., & Laurier, D. (2017). Low radon exposure and mortality among Jouac uranium miners: an update of the French cohort (1946-2007). *Journal of Radiological Protection, 38*(1), 92-108. https://doi.org/10.1088/1361-6498/aa8d97

Reddy, A., Conde, C., Peterson, C., & Nugent, K. (2022). Residential radon exposure and cancer. *Oncology Reviews, 16*(1), 558-566. https://doi.org/10.4081/oncol.2022.558

Rey, N. L., Wesson, D. W., & Brundin, P. (2018). The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases. *Neurobiology of Disease, 109,* 226-248. http://dx.doi.org/10.1016/j.nbd.2016.12.013

Ruano-Ravina A., Aragonés N., Kelsey K. T., Pérez-Ríos, M., Piñeiro-Lamas, M., López-Abente, G., & Barros-Dios, J. M. (2017). Residential radon exposure and brain cancer: An ecological study in a radon prone area (Galicia, Spain). *Scientific reports, 7*(3595), 1-7. https://doi.org/10.1038/s41598-017-03938-9

Sethi, T. K., El-Ghamry, M. N., & Kloecker, G. H. (2012). Radon and lung cancer. *Clinical Advances in Hematology and Oncology, 10*(3), 157-164.

Stanley, F. K., Irvine, J. L., Jacques, W. R., Salgia, S. R., Innes, D. G., Winquist, B. D., Torr, D., Brenner, D. R., & Goodarzi, A. A. (2019). Radon exposure is rising steadily within the modern North American residential environment, and is increasingly uniform across seasons. *Scientific Reports, 9*(1). https://doi.org/10.1038/s41598-019-54891-8

Sujo, L. C., Montero Cabrera M. E., Villalba, L., Villalobos, M. R., Moye, E. T., León, M. G., García-Tenorio, R., García, F. M., Herrera Peraza, E. F., & Aroche, D. S. (2004). Uranium-238 and thorium-232 series concentrations in soil, radon-222 indoor and drinking water concentrations and dose assessment in the city of Aldama, Chihuahua, Mexico. *Journal of Environmental Radioactivity, 77*(2), 205-219. https://doi.org/10.1016/j.jenvrad.2004.03.008

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry, 139*(1), 318-324. https://doi.org/10.1111/jnc.13691

Symonds, P., Rees, D., Daraktchieva, Z., McColl, N., Bradley, J., Hamilton, I., & Davies, M. (2019). Home energy efficiency and radon: An observational study. *Indoor Air, 29*(5), 854-864. https://doi.org/10.1111/ina.12575

Taylor, B. K., Smith, O. V., & Miller, G. E. (2023). Chronic home radon exposure is associated with higher inflammatory biomarker concentrations in children and adolescents. *International Journal of Environmental Research and Public Health, 20(1)*, 246-261. https://doi.org/10.3390/ijerph20010246

The Jamovi Project. (2022). *jamovi* (Version 2.3). https://www.jamovi.org

Tong, J., Qin, L., Cao, Y., Li, J., Zhang, J., Nie, J., & An, Y. (2012). Environmental radon exposure and childhood leukemia. *Journal of Toxicology and Environmental Health, 15*(5), 332-347. https://doi.org/10.1080/10937404.2012.689555

Walker, K. A., Sharrett, R., Wu, A., Schneider, A. L., Albert, M., Lutsey, P. L., Bandeen-Roche, K., Coresh, J., Gross, A. L., Windham, G., Knopman, D. S., Power, M. C., Rawlings, A. M., Mosley, T. H., Gottesman, R. F. (2019). Association of midlife to late-life blood pressure patterns with incident dementia. *JAMA, 322*(6), 535-545. https://doi.org/10.1001/jama.2019.10575

Wallensten, J., Ljunggren, G., Nager, A. Wachtler, C., Bogdanovic, N., Petrovic, P., & Carlsson, A. C. (2023). Stress, depression, and risk of dementia – A cohort study in the total population between 18 and 65 years old in Region Stockholm. *Alzheimer's Research and Therapy 15*(161). https://doi.org/10.1186/s13195-023-01308-4

Walton, C., King, R., Rechtman, L., Kaye, W., Leray, E., Marrie, R. A., Robertson, N., Rocca, N. L., Uitdehaag, B., Mei, I., Wallin, M., Helme, A., Napier, C. A., Rijke, N., & Baneke, P. (2020). Rising prevalence of Multiple Sclerosis worldwide: Insights from the Atlas of MS, third edition. *Multiple Sclerosis Journal, 26*(14), 1816-1821. https://doi.org/10.1177/1352458520970841

Wilson, G. D., & Marples, B. (2016). A new use for an old treatment: Radiation therapy and Alzheimer's disease. *Radiation Research, 185*(5), 443-448. https://doi.org/10.1667/RR143671.1

World Health Organization. (2023, January 25). *Radon.* World Health Organization. https://www.who.int/news-room/fact-sheets/detail/radon-and-health

Yakhdani, M., Fathabadi, Z., Fard, R., Salehi-Abargouei, A., & Ebrahimi, A. (2019). The relationship between multiple sclerosis prevalence and density of radon gas in the environment (review). *Journal of Environmental Health and Sustainable Development, 4*(3), 913-921. https://doi.org/10.18502/jehsd.v4i4.2024

Yakhdani, M. F., Jalili, M., Salehi-Abargouei, A., Mirzael, M., Rahimdel, A., & Ebrahimi, A. A. (2021). Interaction of MS prevalence, radon gas concentration, and patient nutrition: A case-control study. *Scientific Reports, 11*, 17906. https://doi.org/10.1038/s41598-021-96816-4

Yazzie, S. A., Davis, S., Seixas, N., & Yost, M. G. (2020). Assessing the impact of housing features and environmental factors on home indoor radon concentration levels on the Navajo nation. *International Journal of Environmental Research and Public Health, 17*(8), 2813. https://doi.org/10.3390/ijerph17082813

Zeng, X., Berriault, C., Arrandale, V. H., DeBono, N. L., Harris, M. A., & Demers, P. A. (2023). Radon exposure and risk of neurodegenerative diseases among male miners in Ontario, Canada: A cohort study. *American Journal of Industrial Medicine, 66*(2), 132–141. https://doi.org/10.1002/ajim.23449

Zhang, Y., Lü, L., Chen, C., Field, R. W., D'Alton, M., & Kahe, K. (2022). Does protracted radon exposure play a role in the development of dementia? *Environmental Research, 210*, 1–6. https://doi.org/10.1016/j.envres.2022.112980