

The Relationship between Multiple Sclerosis Prevalence and Density of Radon Gas in the Environment (Review)

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ABSTRACT

Introduction : Radon (Rn) is a chemically inert gas with no odor, color, and taste. It is created from the decay of uranium in the soil and can penetrate the building through the interiors. As a result, Rn can enter the human body with the release of alpha radiation along with airborne dust and cause chronic illnesses such as lung cancer and multiple sclerosis. The Multiple Sclerosis disease, as a complex multifactor disease, is the most common widespread neurotic disorder among the young people. The purpose of this study was to collect and review the past studies published in this field since 1996.

Materials and Methods: In this review, the related articles were searched and studied using key words such as "Radon, Action, Thoron, MS, MS Disseminated, and Sclerosis" using the PRISMA statement.

Results: After reviewing the studies, several effective factors in the prevalence of MS were identified. Some of these factors were a result of the exposure to high levels of radon gas. Penetrations from the building cracks of floor, soil bed, and dwelling materials as well as the water resources are among the most important sources of Rn.

Conclusion: According to the results, the amount of Rn and its daughters in the environment are recognized as the risk factors for the MS prevalence.

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Introduction

In addition to some positive aspects, the growth of human societies and human development in various fields also had some side effects, such as human diseases¹. Multiple Sclerosis (MS) is a complex multi-factor disease and the most

common neurotic disorder among the young adults². In this disease, the immune system attacks myelin (fat shells), protector of the cell of central nervous system, brain, and the spinal cord, and damages them. Consequently, the destruction of

myelin nervous cells leads to disorders in the transmission of nerve signals from the brain and the spinal cord to other parts of the body, which leads to the emergence of the special MS symptoms³. In fact, MS is recognized as a chronic disease of self-immunity and inflammation that is fully cost-effective. The treatment of MS includes disease symptom management. Moreover, MS is a highly debilitating chronic illness with social and economic consequences and is recognized as the second most common cause of young people's disability^{4,5}.

The most important symptoms of MS are having optical disorders, fingers and toes' fading, a momentum electric shock in the body, cold and warm sensation in some parts of the body, incoordination in body organs (especially feet in walking), impatience, too much sleep, body blemishes, laziness and numbness, early fatigue, general weakness of the body, muscle spasm, lack of coordination between words in the speech, headache, excessive urinary excretion, longer digestion, sensitive and early suffering, constipation, nightmare, and interest to eat the acidity foods with cold nature (such as dairy products, especially yogurt and ice cream). In the case of disease progress, MS leads to the lack of control in the urine discharge, hot/cold weather intolerance, decreased sexual desire, severe weakness in making intimate relationships with spouse, and experiencing premature ejaculation in men, depression and low self-esteem, isolation, and imbalance, as well as having muscle vibrations while moving and walking⁵.

The MS is more common among women than men and usually strikes at the age of 24 up to 40 years⁶. According to the International Federation of MS, the average outbreak of the disease was 30 in 100000 in 2008, which rose to 33 in 100000 in 2013. The highest prevalence rate was in the North America (140 in 100000) and Europe (108 in 100000); whereas, the lowest was in the south of African desert (1.2 in 1000000) and East Asia (2.2 in 100000). In Iran, the prevalence rate of MS is 15-30 in 1000000⁷. According to the WHO classification in the Atlas of MS in 2008, Iran belongs to the medium-range regions⁵. Based on a

study of the geographical distribution of MS, Iran is located in an area with a low MS prevalence rate⁸.

The conducted research is partly in agreement with the first category, but violates the second⁵. However, according to recent studies, it has become clear that Iran is now located in the area with medium to high prevalence⁹.

Although many studies have been conducted on MS, the cause of this disease is still unknown¹⁰. Yet, it is reported that a set of environmental causes, infections, genetic problems, immune system, viruses, toxins, and metabolic problems as well as materials such as nitric oxide are involved in its occurrence¹¹. Rn, as an external factor, was found to be effective on MS occurrence and aggravation. Radon is a gas that is chemically inert or ineffective and does not have any odor, color, and taste. It also decays naturally from ²³⁸U, ²³⁵U, and ²³²Th in many types of soil, rock, and water produced in the earth. The ²²²Rn is produced from the decay of ²³⁸U, as the most important source of internal radiation. Humans are generally exposed to it throughout their lives. Three radon isotopes (²¹⁹Rn, ²²⁰Rn, ²²²Rn) are in the form of gas and are released from the earth, stone, construction materials, and short-lived decay products gathered in closed spaces, especially in the building. ²¹⁹Rn and ²²⁰Rn are not as important as ²²²Rn due to their short lives. The most important sources of radon are soil, construction materials (e.g. rock, cement, etc.), water resources, and natural energy sources (such as gas, coal, etc.)¹².

Radon density in the buildings is also widely related to the geological structure, structure of the building, and the ventilation system. Therefore, radon density depends on many different factors. Although soil, rock, and foundation structure around the building is the most important source of radon, radon caused by building materials may increase its density in the indoor environment¹³. The half-life of ²²²Rn is 3.83 days that is enough to enter the indoor space of the building¹². Based on the WHO report, the effects of Rn on health are divided into two categories: the lung cancer and other diseases. Radon is known to be the second leading cause of lung cancer after cigarette

smoking. Radon also causes other diseases such as leukemia, liver cancer, cardiovascular disease, and MS^{14, 15}. Different studies are undertaken in this regard. As an example, MS has a significant positive correlation ($p < 0.01$) with Rn contents in indoor air. Based on these data, this hypothesis is proposed that the content of Rn in inhaled air is a risk factor in MS¹⁶. Nevertheless, to the best of our knowledge, no review study has been ever conducted in recent years aiming to do a synthesis review on the literature in this regard. Thus, this study aimed to conclude the findings by reviewing the recent studies published since 1996.

Materials and Methods

In this review, keywords were selected using mesh, thoron, radon, action, MS, disseminated

sclerosis, and multiple sclerosis. The search was conducted among the english sources and databases such as Science Direct, Google Scholar, Pub Med, Scopus, and ISI. The PRISMA statement was employed to select the articles (See Figure 1 for the flowchart).

As Figure1 represents, 249 articles were found from the general search results. Then, the duplicates and unrelated articles were removed, so that 235 articles remained as the final database of the study, including 6 ecological studies, 1 review, 3 pilot, 1 guidelines, and 3 case-control studies. All the articles were published from 1996 to 2019. The criteria for selecting articles included the type of study, subject relevance, and the articles availability.

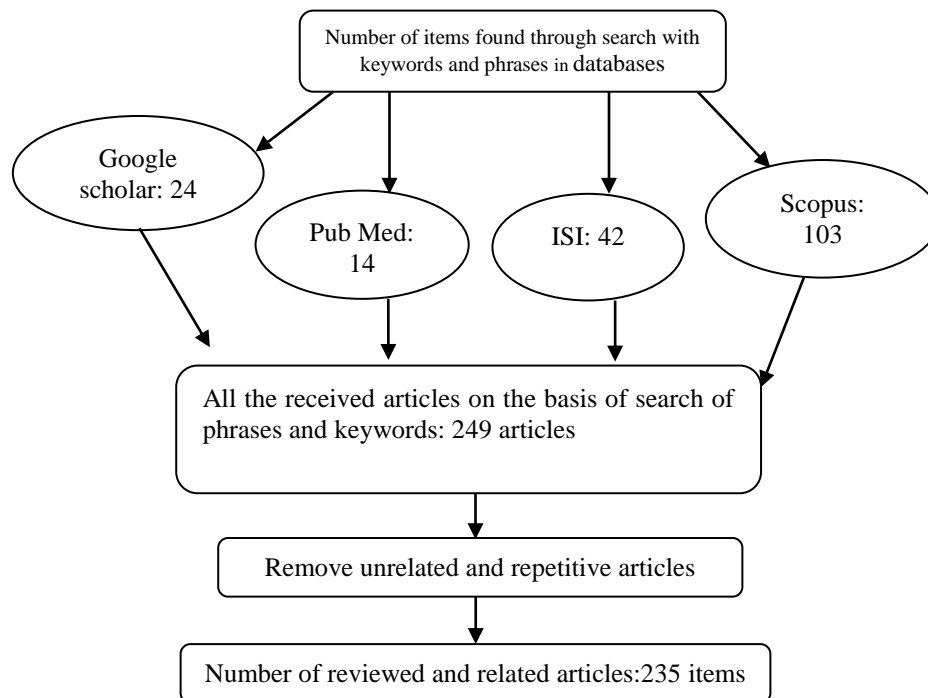


Figure 1: The process of selecting the relevant articles in this study

Results

Radon gas has not only positive functional effects, but also negative harmful effects¹⁷. In this review, the harmful effects of Rn on the development of the MS disease were addressed. Radon gas has an important role in the development of various diseases including lung

cancer, leukemia, skin cancer¹⁸, gastric cancer¹⁷, and MS¹⁴.

Numerous studies have been conducted on the relationship between Rn and MS in the countries with high risk of MS. These countries included the United States¹⁸⁻²⁰, England²¹, Ireland^{22, 23}, Norway²⁴, and Sweden²⁵. The relationship between the occurrence of MS and Rn has been

proven statistically and inferentially in the studied countries by measuring the density of Rn. In other words, if the area had a high Rn density, the rate of MS prevalence was also high. Neuberger et al. carried out a research in the city of Kansas, the United States. Their results showed that the adjusted odds-ratio for MS prevalence increased by 1.98 (95% CI = 0.98 to 3.98, $p = 0.06$) for each unit increase in the time-weighted average of the natural log of radon exposure. Although not statistically significant, a trend of increase was observed in the probability of MS prevalence with each unit increase in the time-weighted average of the natural log of radon exposure²⁶. Furthermore, the study carried out in Wales, England, by Groves et al. showed that although a trend of increasing MS incidence was identified with increased radon concentration, the correlation was not statistically significant²⁷.

Effective factors in increasing radon gas

Factors affecting the increasing indoor Rn include the type of building materials used in the building, cracks in the walls and the floor, type of the rock and soil, foundation of the building, and used water resources^{21, 28}. These factors are the main sources through which Rn enters into the building from the existing cracks and gaps on the floor of the building, so that Rn in the soil gradually accumulates under the building and its pressure rises. Because the air pressure inside the building is usually less than the air pressure in the soil, the Rn can enter the building through the wells, drains, and cracks on the building floors¹⁷. The amount of Rn in the closed environment is different in different days and seasons and depends on the seams and cracks of the floor, walls of the building, amount of ventilation, and air exchange in the building. Besides, concentration of Rn is usually more in the lower floors of the building and the underground level than in the top floors^{1, 17}.

Methods of measuring Rn concentration

Generally, in some ecological studies, the density of Rn has been measured by the radiation protection organization of the country. As a result, a certain amount is mentioned for each

house²¹⁻²³. In some studies, the nuclear track method²⁴, active Alpha track dosimeter²⁶, radon gas map²⁷, charcoal canisters¹⁸, whole body counter steel,²⁰ and responding to the questionnaire were conducted based on ionizing radiation²⁵.

The collected data on MS patients in the examined studies

Data on MS patients in Norway were collected based on the urban type, the mortality rate in 1951-1977, and cases of men/women disability in 1978²⁴. Data on MS patients in Ireland were collected by administering a questionnaire to 67 patients who referred to an MS center (33% of responses). The questionnaire included the heating type, building age, number of building floors, sewage drainage system, and used water source. There spondents responded to these questions in accordance with their childhood experience (before age 15)^{22, 23}.

The MS 20-65 year old patients in Sweden were selected from a large hospital in the southern and southeastern Sweden. In this case-control study, the control people were selected randomly from the Sweden Registry Office. The data were collected using questionnaires sent to individuals by email. The questionnaire covered these issues: type of occupation, specific exposures to certain agents or animas at work, treatment or examination by X ray, contact with animals, and prolonged use of medications²⁵.

In a pilot study in Kansas, the United States, the MS patients were selected from a clinic. The selected patients were treated for two years, their age was more than 68 years, and lived in the ame building since five years ago. The data were collected by a questionnaire²⁶. To collect the information about MS patients in Wales, the UK, clinical research database was employed. The study population consisted of all patients who lived in Wales, UK over the last five years¹⁹. Data over death rates from motor neuron disease (MND) in the countries of England and Wales in 1981-1989 were obtained from the office of population, censuses, and surveys (OPCS)²¹.

Effective factors in increasing the occurrence of MS

In the examined studies, the prevalence of MS increased in North America, which was attributed to the radiological sources emitted by a nuclear fall-out in Washington State. The original sources noted that the geographical distribution of MS incidence was affected by the potential influence of air-borne radioactive debris from atmospheric nuclear tests. Furthermore, presence of a major nuclear-material processing facility in that state was a more significant effective factor in this regard. The areas in these studies included East Washington, Northern Iowa, Norway, and the northern areas of the United States that showed the highest levels of Rn and MS¹⁹.

Another factor affecting the prevalence of MS is the exposure to high levels of Rn and some environmental factors during childhood, before age 15, especially for men^{22, 23, 29}. Furthermore, it was found that the prevalence rate of MS in arid regions was more than coastal areas¹⁹. Regarding latitude, in the Norwegian and English studies, northern regions located at higher latitudes had the highest prevalence rate of MS^{24, 29}. The other

environmental factors that cause MS include sunshine, carbon monoxide, ultraviolet radiation, temperature, latent virus, ionizing radiation, pets, and toxic chemicals¹⁹.

Given that the MS virus is mentioned as one of the causes for developing MS, the related hypothesis is that some types of viruses may remain latent in the body organs for a long time. These viruses can be re-activated due to a variety of factors, among which the most important one is exposure to high doses of ionizing radiation²⁴. The reason is that Rn is in the group of ionizing radiation derived from radon decay as well as alpha and beta particles. Release of these products have a risk of irradiation in causing MS^{15, 19, 24}. This gas has a particular dependence on fat, so it is stored in organs rich in fat-like neural systems and narrow bones. It also can cause breast cancer or tissue cancer²⁰, because the pod myelin sheaths (nerve fibers), made of fatty materials, are attacked in MS patients. Thus, it can be concluded that the pod myelin fat is solved by environmental radon^{18, 31}. The most convincing scientific studies on MS and ionizing radiation conducted in Norway showed that radon was an effective factor in MS²⁴.

Table 1: Characteristics of the included studies over the relationship MS prevalence with concentration of Rn in the environment

study	Year and country	Study Design	MS potions database	Number population study case of MS	Age (year)	Domestic radon concentration database	P value
Groves, 2016 ²¹	2005-2012 in England and Wales	Ecological	The Health Improvement Network (THIN) clinical research database	115 case	15-85	Radon gas map and utilized data at postcode sector level	0.096
Neuberger, 2011 ¹⁴	2000-2006 In Kansas, USA	A pilot case-control study	The University of Kansas Medical Center's Neurology Department clinic	97 MS patients and 51 non-MS controls	Mean age: 42.35	Long-term alpha track dosimeters for 5-6 months in the winter	0.06
Momcilovic, 2005 ²⁹	1988-2004 In Grand Forks, North Dakota	Ecological	Participating in community-based bioavailability studies over a period of 13 years	315 female and 179 male	-	Whole body counter data, steel room Bi ²¹⁴ background	< 0.05
Bolviken, 2003 ²⁴ 2001 ³¹	1987-1989 in 6 of Norway's 19 counties	Ecological	Based on municipal rates for the sum of deaths in the period from 1951 to 1977 and disability pension cases in 1978 for both sexes	195 case in rural and in urban areas	-	The nuclear track method for 6-month periods	< 0.01

study	Year and country	Study Design	MS potions database	Number population study case of MS	Age (year)	Domestic radon concentration database	P value
Carroll, 2005 ²³	1992 In Ireland	Pilot	Communications with General Practitioners, Neurologists, County Physicians, Hospital Coding Lists, Local MS Societies, Respite Care Facilities and Interferon Prescription Lists.	671 case	36.8	Radiological Protection Institute of Ireland(RPII) by sampling homes in 10-Km grid squares	No
Neilson, 1996 ²⁸	1981-1989 in England and Wales	Ecological	Data for deaths from motor neuron disease (MND)mortality were obtained from the Office of population censuses and Surveys(OPCS)	9220 Deaths	15 to 85 uper	The National Radiological Protection Board(NRPB) by sampling homes in 10-Km grid squares	< 0.05 < 0.01
Eidbo& Prater, 2004 ²⁰	1993 in 92 of Iowa's 99 counties	Ecological	National Multiple Sclerosis Society (NMSS) - Iowa Chapter	100000 population (cases/100k)	All ages	Environmental Protection Agency (Pekmezovic et al.)	No
Axelsson, 2001 ²⁵	1981-1985 in the two largest hospitals in south-central Sweden that two counties covered by these hospitals	Case-control	Cases of MS obtained in the two largest hospitals in south-central Sweden and controls were randomly drawn from this register of the population in these two counties from where the cases were obtained	From 83 cases (response rate 89%) and 467 controls (response rate 80%) in these two counties	20-65	9-page questionnaire x-ray examinations, radiological work, cosmic radiation, gamma radiation and treatment with ionizing radiation	No
Axelsson, 2001 ²⁵	1983-1988 in two counties in southeast Sweden	Case-control	Cases of MS obtained at the main hospitals in two counties in southeast Sweden and controls were randomly drawn from this register of the population in these two counties from where the cases were obtained	91 Responding cases (response rate 94%) and 348 population controls (response rate 87%)	20-65	9-page questionnaire X-ray examinations, radiological work, cosmic radiation, gamma radiation and treatment with ionizing radiation	No
Lykken, 2008 ¹⁷	In Grand Forks, North Dakota	Case-control	The Grand Forks MS Support Group, subjects with no apparent health problems were recruited locally	15 MS patients and 15 non-diseased controls	-	The ²²² Rn was measured with charcoal canisters	No
Gilmore, 2003 ²²	1971-1981 In Northwest Ireland	Pilot	Membership of the MS Society in Ireland	67 respondents, response rate 33%	Before the age of 15	Radiological Protection Institute of Ireland(RPII)	No

Discussion

Based on the findings, some of the reviewed studies over the relationship between Rn and MS were undertaken in countries where the prevalence of this disease was high. By measuring the concentration of Rn in these countries, a relationship was found between the incidence of MS and Rn. However, given that most of these studies were of ecological type, further precise case-control studies are required for finding the relationship of indoor Rn concentration and other environmental factors with development of MS.

The ecological studies seek to measure the density of in each building among the MS patients who referred to the treatment centers. The results of these studies indicated that increased density of Rn had a positive significant relationship with MS. In experimental studies, the density of Rn is measured by measuring devices. The data from MS patients were collected via questionnaires. The findings of these studies also revealed a relationship between the density of Rn and MS.

Gross et al. conducted a retrospective study on the incidence of MS and its association with Rn concentrations in the UK's Welsh area. In this study, 115 individuals were selected and the amount of Rn was calculated using a map of Rn concentration in the region, which was specified for each house. The results showed that although the prevalence of MS increased with increasing of the Rn concentration, the correlation was not significant²⁷.

Neoberger et al. examined a relationship between MS and concentration of indoor Rn in the city of Kansas, USA. In this research, 97 MS patients with less than five years of disease diagnosis and 51 healthy controls were employed. To measure the concentration of Rn in the air, active alpha dosimeters were used for a period of six months for people who had lived in the same houses for at least five years prior to the study. The results showed that the association of MS with Rn concentration was not statistically significant, but the increasing trend of the MS outbreak probability was found to increase with

each unit in the average remaining radon exposure time²⁶.

Bolviken et al. studied the association between the concentration of indoor Rn and airborne magnesium loss on MS patients in Norway. The researchers applied the alpha groove dosimeter in 7500 residential homes randomly selected in a continuous period of six months and found a significant positive correlation ($p < 0.01$) between MS and Rn concentration in the air²⁴.

Conclusion

As the finding revealed, Rn and its daughters, in respiratory air, are considered as serious risk factors of MS. Due to limited resources and data on MS patients, the relationship between Rn and MS cannot be definitely denied. Although the concentration of Rn was effective on MS, this finding needs further exploration.

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Conflict of interest

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References

1. Fahiminia M, Fouladi Fard R, Ardani R, et al. Indoor radon measurements in residential dwellings in Qom, Iran. *International Journal Radiation Research*. 2016;14(4):331-9.
2. Compston A, Coles A. Multiple sclerosis. *Lancet* (London, England). 2008;372(9648):1502-17.
3. Koriem KM. Multiple sclerosis: New insights and trends. *Asian Pac J Trop Biomed*. 2016;6(5): 429-40.
4. Ghanati EH, Daghighi A. Economic expenditures of multiple sclerosis medications and feasibility of

- providing health insurance policies for medications. *Journal of Health Administration*. 2011;14(45):37-54.
5. Nasri Nasrabadi M. Measurement of selenium level in blood of residents of Isfahan affected by multiple sclerosis. *Razi Journal of Medical Sciences*. 2015;22(137):75-83.
 6. Kroushavi M, Behrooz M, Rashidkhani B, et al. Association between index of nutritional quality and multiple sclerosis. *Journal of School of Public Health and Institute of Public Health Research*. 2015;12(3):53-67.
 7. Belbasis L, Bellou V, Evangelou E, et al. Environmental risk factors and multiple sclerosis: An umbrella review of systematic reviews and meta-analyses. *Lancet Neurol*. 2015;14(3):263-73.
 8. Mohebi N, Mamarabadi M, Moghaddasi M. Evaluation of the relation between *Helicobacter pylori* and Multiple sclerosis. *Razi Journal of Medical Science*. 2013;19(105):15-20.
 9. Sahraian MA, Khorramnia S, Ebrahim MM, et al. Multiple sclerosis in Iran: a demographic study of 8,000 patients and changes over time. *Eur Neurol*. 2010;64(6):331-6.
 10. Pekmezovic TD, Tepavcevic DBK, Mesaros ST, Et al. Food and dietary patterns and multiple sclerosis: a case-control study in Belgrade (Serbia). *Ital J Public Health*. 2012;6(1):320-7.
 11. Mahmoodi NE, Niaz Azari K. Evaluating mental (psychological) health in MS patients from Mazandran province in 1386. *Journal of Mazandaran University of Medical Sciences*. 2009;18(68):70-3.
 12. Abd-Elzaher M. Measurement of indoor radon concentration and assessment of doses in different districts of Alexandria city, Egypt. *Environ Geochem Health*. 2013;35(3):299-309.
 13. Cucos A, Cosma C, Dicu T, et al. Thorough investigations on indoor radon in Baita radon-prone area (Romania). *Sci Total Environ*. 2012;431:78-83.
 14. WHO. Guidelines for indoor air quality: selected pollutants. 2010:358-364.
 15. Bolviken B. Natural ionizing radiation and health. Trondheim, Norway. Det Norske Videnskaps-Akademi, 177 pp.
 16. Bolviken B, Celius EG, Nilsen R, et al. Radon: A possible risk factor in multiple sclerosis. *Neuroepidemiology*. 2003;22(1):87-94.
 17. Abbasnezhad A. Environmental impacts and implications of the Radon-222, and its urgency attention in Iran. *Iranian Journal of Science and Technology*. 2003;26:17-31.
 18. Lykken GI, Magness AT, Momcilovic B. Whole body Bi-214 and bedroom radon concentration in multiple sclerosis. *FASEB J*. 2008;22(1):708-9.
 19. Eidbo WB, Prater MP. Linkage-Multiple sclerosis and ionizing radiation. *Medical Veritas*. 2004;1:272-276.
 20. Momcilovic B, Lykken GI, editors. Men and Radon-A noble gas of many disguise Part I. Sixth Symposium of the Croatian Radiation Protection Association. 2005;235-247.
 21. Neilson S, Robinson I, Rose FC. Ecological correlates of motor neuron disease mortality: a hypothesis concerning an epidemiological association with radon gas and gamma exposure. *Journal of Neurology*. 1996;243(4):329-36.
 22. Gilmore M, Grennan E. A pilot study of the relationship between multiple sclerosis and the physical environment in northwest Ireland. *Environ Geochem Health*. 2003;25(1):157-63.
 23. Carroll D. An examination of the relationship between the prevalence of multiple sclerosis and the geological environment specifically exposure to indoor radon before the age of 15 years. MA, Institute of Technology, Sligo, 2005.
 24. Bolviken B, Celius E, Nilsen R, et al. Radon: A possible risk factor in multiple sclerosis. *Neuroepidemiology*. 2003;22(1):87-94.
 25. Axelson O, Landtblom AM, Flodin U. Multiple sclerosis and ionizing radiation. *Neuroepidemiology*. 2001;20(3):175-8.
 26. Neuberger JS, editor Residential radon exposure and multiple sclerosis: a pilot study. Proc 21st International Radon Symposium, American Association of Radon Scientists and Technologists, Orlando FL; 2011.
 27. Groves-Kirkby CJ, Denman AR, Campbell J, et al. 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.
28. Varhegyi A, Baranyi I, Gerzson I, et al. Application of underwater radon measurements in geology. *International Journal of Int J Rad Appl Instrum D.* 1988;15(1-4):609-12.
29. Groves-Kirkby C, Denman A, Woolridge A, et al. *Environmental Radon Gas and Degenerative Conditions An Overview.* European IRPA, Paris. 2006;370:1–12.