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

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Abstract

To test whether an association exists between radon gas concentration in the home and increased multiple sclerosis (MS) incidence, a retrospective study was undertaken of MS incidence in known areas of raised domestic radon concentration in England and Wales, using The Health Improvement Network (THIN) clinical research database.

The study population comprised 20,140,498 person-years of clinical monitoring (males: 10,056,628: 49.93%; females: 10,083,870: 50.07%), representing a mean annual population of 2.5 million individuals. To allow for the possible latency of MS initiation following exposure, data extraction was limited to patients with at least five years registration history with the same GP practice before first diagnosis. Patient records were allocated to one of nine radon concentration bands depending on the average radon level in their postcode sector.

MS incidence was analysed by searching for patients with first MS diagnosis over the eight calendar years 2005 to 2012 inclusive. 1,512 new MS cases were diagnosed, 1,070 females, 442 males, equivalent to raw incidence rates of 7.51, 10.61 and 4.40 per 10^5 person-years respectively, comparable to previously reported results. Of these new cases, 115 could be allocated to one of the radon bands representing high radon areas.

Standardising to the UK 2010 population, excess relative risk (ERR) figures for MS were calculated for each radon band. Linear regression of ERR against mean band radon concentration shows a positive gradient of 0.22 per 100 $Bq.m^{-3}$ ($R^2 = 0.25$, $p = 0.0961$) when forced through the origin to represent a linear-no-threshold response. The null hypothesis falls inside the 95% confidence interval for the linear fit and therefore this fit is not statistically significant. We conclude that, despite THIN sampling around 5% of the population, insufficient data was available to confirm or refute the hypothesised association between MS incidence and radon concentration.

Keywords

Radon

Multiple Sclerosis

Retrospective population-based study

Clinical extraction database

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1 Introduction

1.1 Environmental Radon Gas

1.1.1 Origins

Radon, a naturally occurring radioactive gaseous decay product of uranium, is widely distributed in the environment in rocks and soils, with varying geographical concentration, and in building materials incorporating or manufactured from these. On generation, radon migrates to the atmosphere by diffusion and convection, giving a mean outdoor air concentration in the British Isles in the range 4 – 6 $Bq \cdot m^{-3}$ (Wrixon *et al.*, 1998; Gunning *et al.*, 2014). Although radon dissipates rapidly in outdoor air, it concentrates in the built environment, typical ingress routes being cracks in walls and floors, and drains and loose-fitting pipes, the mean UK domestic radon concentration being around 20 $Bq \cdot m^{-3}$ (Wrixon *et al.*, 1998).

1.1.2 Physiology and Health

The most significant radon isotope, ^{222}Rn, decays by α-emission (half-life 3.8 days) via ^{218}Po and ^{214}Bi (both also α-emitters) to ^{210}Po, the final decay product being the stable lead isotope ^{206}Pb. These heavy-metal daughters, all highly toxic and readily adsorbed onto atmospheric particles and lung tissue, pose a significant health hazard, inhalation of ^{222}Rn and its progeny providing the majority of the radiation dose received by the respiratory system (Darby *et al.*, 2001). A direct consequence of the trapping of radon decay products in the lung has been the association between enhanced levels of environmental radon and increased risk of lung-cancer, leading to recognition of radon as a significant factor in the incidence of lung-cancer among smokers (BEIR, 1999).

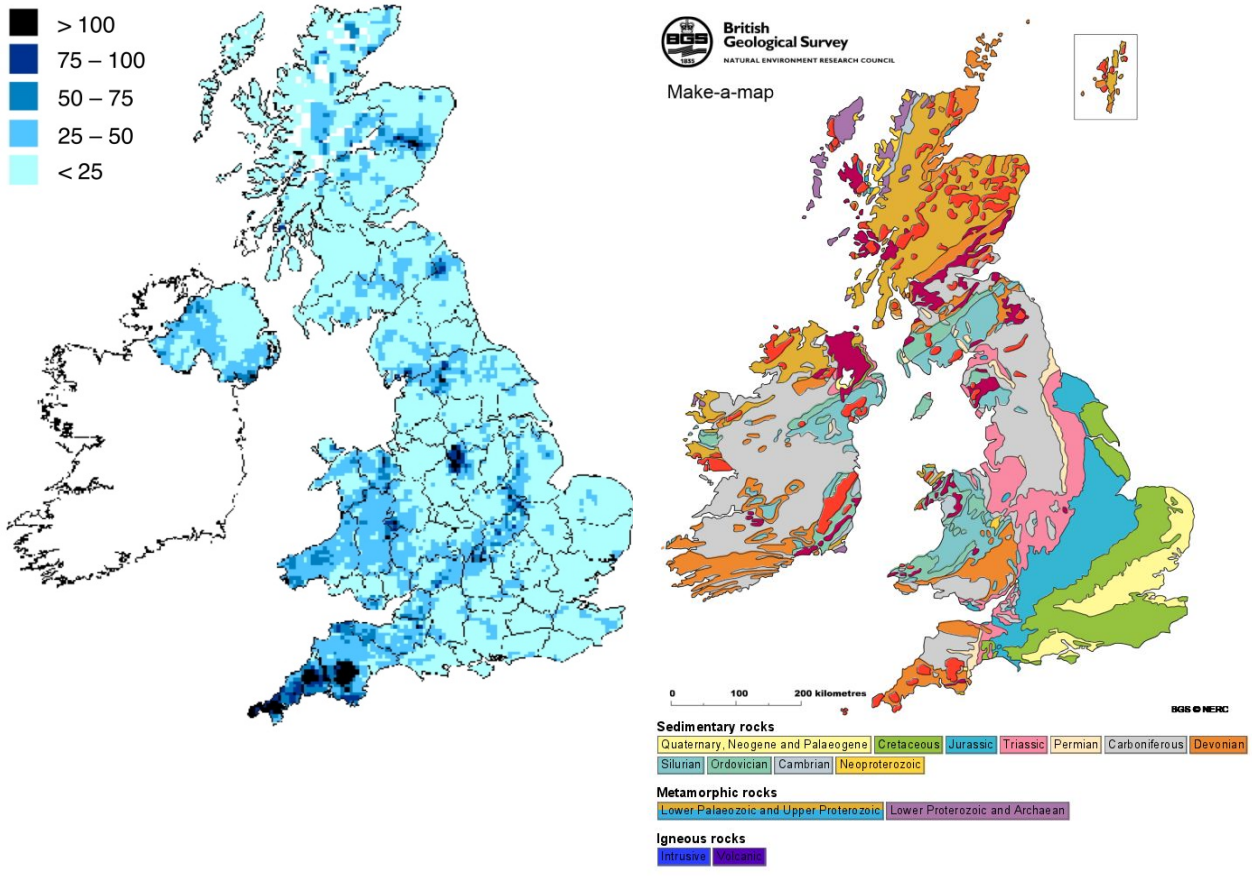
Radon, nearly two orders of magnitude more soluble in polar hydrocarbons than in water, is lipid-soluble, its solubility depending on the number of carbon atoms per lipid molecule and peaking in the region of heptanoic acid at a level 7.4 times that in ambient air (Lykken and Momčilović, 2003, 2006). Radon forms clathrates with water and alcohols, both abundant in animal tissue. Although most inhaled radon is immediately exhaled, some becomes trapped in the lungs and migrates to the blood-stream, where it is soluble at a level of 42% of its solubility in water at 310 K (Knaffl-Lenz, 1912; IUPAC, 1979), moving freely around the body, including into and out of the brain despite the blood-brain barrier. In contrast, radon's lipid-insoluble neurotrophic and neurotoxic heavy-metal decay products remain trapped at the locations where they are generated, acting as localised sources of radioactivity and heavy-metal toxicity, causing radiation damage and chemical injury to body cells.

1.1.3 Geographical Occurrence

Environmental radon concentration levels are geographically variable in response to local geological conditions, and may fluctuate significantly across relatively small distances. This is particularly true in the British Isles, which possess a complex geology extending continuously from the Pre-Cambrian to the Holocene. In mainland Britain, the highest domestic radon concentration levels are associated with the granite of the south-west peninsula (Devon and Cornwall). Elevated radon levels also occur along the Jurassic escarpment crossing the Midlands from Somerset to Lincolnshire, in the Derbyshire Peak District, and in well-defined localities in the Welsh borders and in Aberdeenshire in Scotland. In Ireland, high radon areas are distributed principally along the South-East and North-West coastal areas, with outliers in Co. Kerry in the Republic of Ireland (RoI) and in Co. Armagh in Northern Ireland. Figure 1 compares (a) the geographical distribution of radon across the UK (NRPB, 2000) and (b) an indication of the complex bedrock geology

underlying the observed radon variability generated using *Make-a-Map* (BGS, 2015), an interactive online geological map of the British Isles provided by the British Geological Survey [1].

Radiation protection in England and the Devolved Administrations (Scotland, Wales and Northern Ireland) within the United Kingdom (UK), formerly administered by the National Radiological Protection Board (NRPB), is currently the responsibility of the Centre for Radiation, Chemical and Environmental Hazards[2] (CRCE), lately part of the UK Health Protection Agency (HPA) and now a division of Public Health England. The Radiological Protection Institute of Ireland (RPII) fulfils the same function in the RoI. Responding to the health threat posed by domestic radon in the UK, the NRPB initially established a residential Action Level of 200 $Bq \cdot m^{-3}$ (NRPB, 1990), declaring as Radon Affected Areas (RAAs) those geographical entities where over 1% of domestic measurements showed radon concentrations above the Action Level. Initially comprising Devon, Cornwall, parts of Somerset, Northamptonshire and Derbyshire, subsequent study by NRPB and its successors has identified further RAAs in England and Wales, with increasingly enhanced geographical resolution (Miles *et al.*, 1996). Numerical and cartographical data on RAAs are published in the Radon Atlas for England and Wales (Green *et al.*, 2002; Miles *et al.*, 2007, Rees *et al.,* 2010), reporting radon levels at scales ranging from county to postcode sector. Corresponding atlases are published by CRCE for Scotland (Miles *et al.*, 2011) and Northern Ireland (Daraktchieva *et al.*, 2015), and by RPII for the RoI (Fennell *et al.*, 2002; Hodgson *et al.*, 2014).



(a) (b)

Figure 1: (a) Distribution of domestic radon across the United Kingdom (NRPB, 2000). Units $Bq \cdot m^{-3}$.

[1] British Geological Survey, Keyworth, Nottingham, NG12 5GG, UK.
[2] CRCE, Chilton, Didcot, Oxfordshire, OX11 0BR, UK

(b) Simplified bedrock geology of the British Isles. Source: BGS Make-a-Map. Online at: http://www.bgs.ac.uk/discoveringgeology/geologyofbritain/makeamap/home.html *Reproduced with the permission of the British Geological Survey ©NERC. All Rights Reserved.*

Research has identified substantial geographical variability in domestic radon concentrations, demonstrating spatial correlation between mean annual radon concentration and the underlying geology, and studies of the influence of radon on the incidence of radon-induced conditions, principally cancers and cancer-related diseases, have been reported. Metadata analysis of thirteen European case-control studies (Darby *et al.*, 2005) demonstrated the excess relative risk (ERR) of residential radon-induced lung-cancer to be 0.16 per 100 $Bq \cdot m^{-3}$ (95% C.I. 0.05 – 0.31). A contemporaneous North American study (Krewski *et al.*, 2005) reported ERR of 0.18 per 100 $Bq \cdot m^{-3}$ (95% C.I. 0.02 – 0.43), compatible with the previous ERR estimate from the same team of 0.12 (Lubin *et al.*, 1997), predicted by extrapolation from the earlier Colorado Miners studies (Lubin *et al.*, 1995). Independent meta-analysis of seventeen studies worldwide (Pavia *et al.*, 2003), some of which formed the basis of the later, more focussed, studies, reported ERR at 150 $Bq \cdot m^{-3}$ of 0.24 (95% C.I. 0.11 – 0.38), equivalent to 0.16 per 100 $Bq \cdot m^{-3}$. More recently, a Canadian population-based case-control study (Hystad *et al.*, 2014) found positive association between lung-cancer incidence and domestic radon exposures derived from maps, with ERR of 0.13 per 100 $Bq \cdot m^{-3}$ (95% C.I. -0.12 – 0.46).

Although epidemiological studies have confirmed a link between domestic radon exposure and increased lung-cancer risk, with further studies suggesting that other cancers, especially leukaemia, kidney cancer, and malignant melanoma, are related to indoor radon, direct radon causality of other cancers has not been convincingly demonstrated. The current view is that if radon and its decay products do have carcinogenic effects on organs other than the lung, then the effect is so weak as to be generally undetectable in the published epidemiological studies (AGIR, 2009).

1.2 Multiple Sclerosis and Radon

In addition to lung-cancer and related conditions, environmental radon exposure has been postulated to be responsible for the triggering, often late in life, of certain neurodegenerative conditions, including Alzheimer's and Parkinson's diseases (Momčilović *et al.*, 2001), motor neurone disease (Nielson *et al.*, 1996), and multiple sclerosis (MS) (Bølviken *et al.*, 2003; Eidbo and Prater, 2004; Gilmore and Grennan, 2003; Neuberger *et al.*, 2011). Pilot studies of the influence of geographic variability, and hence, indirectly, of the influence of local radon concentration, on the incidence of non-cancer conditions, particularly MS, have been reported, and are discussed in more detail subsequently.

1.2.1 Aetiology and Prevalence

Multiple sclerosis, a disorder of the central nervous system, manifests as acute focal inflammatory demyelination and axonal loss with limited re-myelination, culminating in the chronic multifocal sclerotic plaques from which the disease gets its name (Compston and Coles, 2003). On a global scale, prevalence increases with latitude in both hemispheres (Kurtzke, 2000; Simpson *et al.*, 2011), with broad areas of Africa and Asia relatively unaffected. MS is the most common cause of serious neural disability in young adults in the UK, with exposure to some environmental agent before the age of 15 years being postulated as a factor in its later development in genetically susceptible individuals (Compston *et al.*, 1998). Belbasis *et al*. (2015), in a recent umbrella review of systematic reviews and meta-analyses of environmental risk factors, noted that the causes of MS are still largely unknown. Early studies of MS in the UK were supportive of an increasing latitudinal gradient between the south of England and the north of Scotland (Swingler and Compston, 1986). Re-analysis of earlier results suggests that evidence for a latitudinal gradient within England is less

convincing (Robertson and Compston, 1995), although increased prevalence remains in Scotland compared with England and Wales (Forbes and Swingler, 1999).

1.2.2 Possible Mechanism for Radon

The oligodendrocyte, a principal target of immune attack in MS, synthesises and maintains the myelin sheath of up to 40 neighbouring nerve axons in the central nervous system. Compact myelin consists of a condensed membrane, spiralled around axons to form the insulating segmented sheath needed for saltatory axonal conduction. In MS, the lipoproteins of the myelin sheaths around the axon of the nerve cell are lost in a degenerative process of demyelination, severely affecting saltatory conduction. Lykken and Momčilović (2003a, 2003b) proposed that myelin sheath lipids take up inhaled lipid-soluble environmental radon; in this delicate and sensitive environment, subsequent α- and β-particle bombardment irreversibly damages myelin cell nuclei, puncturing the myelin sheaths beyond the point of repair and causing permanent nerve impulse propagation failure. An additional outcome of this irradiation is free-radical generation, leading to potential peroxidative damage to the myelin lipid portion (Cooper, 1997). Together with other studies (Hursh *et al.*, 1965; Nussbaum and Hursh, 1965), this potentially provides a mechanism for delivering a significant radiation dose to the cells involved in MS.

1.2.3 Ecological Studies

A number of northern-hemisphere ecological studies suggest a possible correlation between domestic radon levels and MS, with higher incidence identified in regions with higher mean domestic radon concentrations.

In Ireland, MS prevalence in the mountainous north-west, an area with extensive high-uranium granite bedrock geology and high radon-emission, is among the highest in the island. Good county-by-county correlation was observed between mean radon level and the membership level of MS-Ireland, with lowest prevalence across the Midlands (Gilmore and Grennan, 2003). A questionnaire survey showed that MS sufferers in the north-west were more likely to be living in their childhood home or its locality, and more likely to live in homes with private (well) water supplies, both factors implying potential higher lifetime radon exposure. Extending this study, Carroll (2005) observed MS clustering in high-radon areas, with sparser distribution in low-radon areas, concluding that the potential for MS development is greater with higher childhood radon exposure, especially among males, and that the observed increased incidence since the 1970s coincides with greater exposure to indoor radon, due to improvements in the housing stock.

Using spatially-moving bivariate correlation, Bølviken *et al.* (2003) studied MS mortality in 73 rural municipality aggregates in Norway, demonstrating positive correlation (p <0.01) between MS and indoor air radon content, and negative correlation (p <0.01) with precipitation and magnesium fallout. Under their hypothesis, air-borne radon levels are influenced by atmospheric fall-out of magnesium and other marine-origin elements through their ion-exchange with the radon precursor, radium, and by annual precipitation through its effect on soil moisture and outwash of radium and related constituents in the soil. Some of the epidemiological characteristics of MS were shown to be not incompatible with observed environmental conditions, with plausible explanations of the role of environmental radon being offered.

A latitudinal MS prevalence gradient exists in the USA, ranging from 57 per 10^5 in the south to 150 per 10^5 in the north (NMSS, 1994). Following identification of elevated radon concentrations in 92 of the 99 counties in Iowa, Eidbo and Prater (1994) confirmed correspondingly high MS prevalence, using National Multiple Sclerosis Society (NMSS) membership data. Similar correlations, also using NMSS data, were subsequently identified in Idaho, Minnesota and Washington (Eidbo and Prater, 2004). In Washington state, the highest prevalence (255 per 10^5)

was found in Spokane county, which had the highest radon exposure in the state; King county, with the lowest MS prevalence (121 per 10^5), is the lowest radon exposure region.

In North Dakota, Lykken *et al.* (2008) analysed ambient air radon and whole body retention of a radon daughter (^{214}Bi) from the bedrooms of fifteen MS subjects and fifteen controls with no apparent health problems. Preliminary data indicated that bedroom ^{222}Rn exposure and ^{214}Bi retention were higher in the MS subjects than in the controls.

Neuberger *et al.* (2011), also noting the latitudinal MS-prevalence and residential radon gradients in the USA, reported a pilot case-control study involving 97 MS patients diagnosed for less than 5 years, and 51 non-MS controls. Although they identified a trend in the radon measurements in the homes of a sub-group resident in one home for at least five years prior to diagnosis, suggesting an increased probability of radon exposure, it did not reach statistical significance (Odds Ratio = 1.98; 95% CI = 0.98 - 3.98, p =0.06), the small sample size being deemed a limiting factor.

In a study to assess whether other ionising radiation sources are associated with MS, Axelson *et al.* (2001) demonstrated correlation between MS and both occupational (Odds Ratio = 4.4, 95% CI 1.6 - 11.6) and diagnostic (Odds Ratio = 1.8, 95% CI 1.2 - 2.6) X-ray exposure from two areas of southern Sweden. Cases were noted where X-ray examination of MS patients accelerated demyelination, suggesting firstly, that ionising radiation bombardment triggers demyelination in susceptible individuals (Peterson *et al.*, 1993) and, secondly, that radiation-induced free-radical generation and oxidative damage are of importance in MS pathogenesis (Cooper, 1997).

2 Method

2.1 Hypothesis

This study tested the hypothesis that association exists between local domestic radon concentration and MS incidence, by comparing MS diagnosis data, obtained anonymously from patient records held by General Practitioners (GPs) in England and Wales, to the known geographical variation of radon, tabulated by postcode sector in the Radon Atlas of England and Wales (Green *et al.*, 2002). A preliminary estimate of the expected patient numbers and the statistical power of the proposed analysis, made prior to commencing the study, indicated that, for the eight years of incidence data, sufficient statistical power was potentially available to justify the exercise.

2.2 Study Design

This was a retrospective population-based study using the clinical database maintained by The Health Improvement Network (THIN)[3], a computerised longitudinal GP database with demographic scope similar to that of the overall UK population (Bourke *et al.*, 2004). The THIN data recording scheme, initially developed from the General Practice Research Database (GPRD) (Walley and Mantagini, 1997) under a non-exclusive license, collects anonymised clinical data from collaborating practices that use the *Vision 360* practice management software[4], following agreed protocols to preserve anonymity, and collates and organises this information for research purposes. *Vision* is currently used by approximately 20% of GPs in England, 30% in Scotland and Northern Ireland and just over 50% in Wales.

THIN contains the medical records of 12.4 million patients, 3.6 million of whom are currently registered with a practice and who can be followed prospectively; retrospective data are available for the remaining patients who have either died or transferred from THIN practices. This is equivalent to 85.8 million patient-years of data from 587 general practices in the UK, covering

[3] IMS Health, 8-14 St. Pancras Way, London NW1 0QG, UK
[4] Vision: In Practice Systems Ltd, 1a Broughton Street, Battersea, London SW8 3QJ, UK

5.67% of the UK population (2013 figures, national breakdown unavailable) (IMS Health, 2015). Patient data in THIN, including clinical notes, referrals, downloaded test results, prescriptions and demographics, are catalogued using Read Codes (Bentley *et al.*, 1996), complemented by Multilex[5] codes identifying prescribed medications. All patient data extracted from practice database systems are fully anonymised and validated and are representative of the entire UK population and each National Health Service (NHS) region (Blak *et al.*, 2011).

2.2.1 Domestic Radon Concentration Database

Radon concentration data for England and Wales are publicly available in the Radon Atlas for England and Wales (Green *et al.*, 2002; Miles *et al*., 2007; Rees *et al.,* 2010), which reports radon concentration levels in administrative and geographical units at granularities ranging from postcode sector to county.

This study utilised data at postcode sector level, the finest granularity available. UK postcodes follow a hierarchical system (Area, District, Sector, Unit), comprising two alpha-numeric text components separated by a space, a typical example for Northamptonshire being NN1 2AB. The code component before the space, the Outward code, directs mail from the originating sorting office to the destination sorting office, while the component after the space, the Inward code, sorts mail into individual delivery rounds. In the Northamptonshire example, the initial pair of letters of the outward code (NN) represents the Northampton Area, while the following digit or digits represent the District (1, corresponding to the central area of Northampton town) within that area. The first component of the inward code (2 in this example, representing part of the central business area) defines the Postcode Sector, which usually contains several thousand individual addresses depending on the locality, with an average area across the UK of 22 km^2. The final component, AB in this example, may represent between ten and twenty residential addresses or a single business address.

In addition to arithmetic and geometric mean radon levels, the Atlas tabulates total numbers of homes in each geographical unit with the corresponding number of homes tested for radon, and projects the percentage of homes anticipated to show mean annual radon concentration levels exceeding the UK Action Level of 200 $Bq \cdot m^{-3}$. For confidentiality, the Atlas does not publish data for areas where few (<10) measurements have been made. To further improve the estimates of average radon concentration, only postcode sectors where at least 50 houses had been tested were considered here, reducing the potentially usable dataset to around 50% of the total housing tested for radon in England and Wales.

Using the published data, each postcode sector reporting results from 50 or more radon measurements was assigned to one of nine radon bands, defined by the percentage of homes in that sector with radon levels above the 200 $Bq \cdot m^{-3}$ Action Level. Band 1 contained postcode sectors with between 0 and 1% of measured homes with radon concentrations above the Action Level. Bands 2 to 9 correspond to the RAAs (NRPB, 1990). Table 1 summarises the radon band allocations, together with the corresponding numbers of houses tested and the annual mean radon concentration for each band, weighted to compensate for the numbers of homes in each postcode sector. Geographically, the radon bands represent groups of spatially-distributed, potentially discontinuous areas, chosen to ensure approximately equal sample size in each of the nine groups. All postcode sectors represented in the THIN database but not appearing in the Radon Atlas, along with all sectors appearing in the Radon Atlas but with less than 50 radon measurements, were allocated to Band 0; incomplete data records were allocated to a further Band 10, the contents of which (68,066 records comprising 2.82% of the total 20,137,547 person-years encompassed by the

[5] FDB, Swallowtail Road, Exeter, Devon EX1 3LH, UK

study) were discarded in subsequent analysis. Figure 2, generated using the open-source mapping software QGIS (2015), indicates the geographical spread of the radon bands on a map of British postcode sectors.

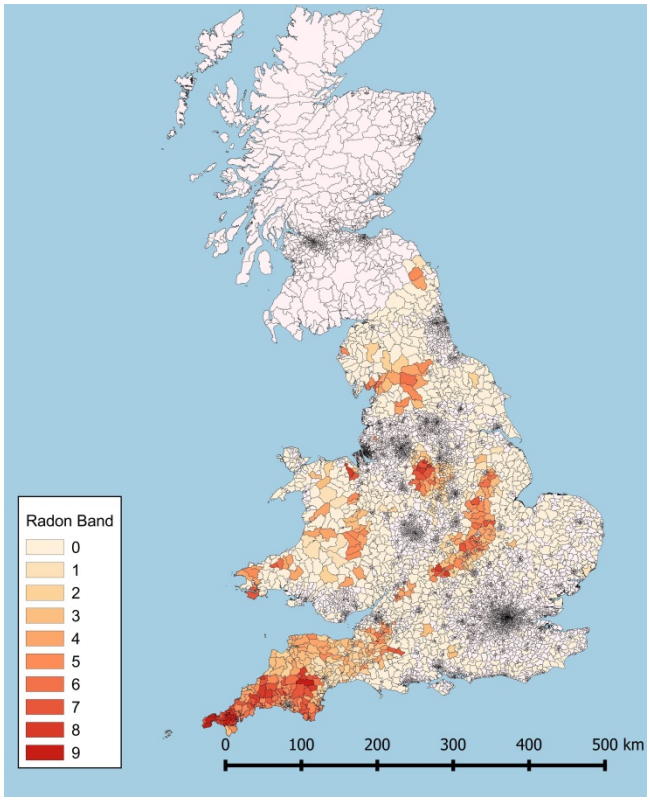


Figure 2: Geographical distribution of postcode sectors comprising Radon Bands 0 – 9. *Contains Ordnance Survey data © Crown copyright and database right 2012. Contains Royal Mail data © Royal Mail copyright and database right 2012. Contains National Statistics data © Crown copyright and database right 2012.*

2.2.2 Case Identification

The resultant dataset was interrogated to extract the numbers of patients diagnosed with MS (numerator population) and total patient numbers (denominator population). The principal clinical search criteria, listed in Table 2, were Read Code F20, its subsidiaries and a further set of related codes. To ensure that any relevant radon exposure was received in the patient's current home, and assuming that radon-induced MS initiation might replicate radon-induced lung-cancer, characterised by a linear-no-threshold process (BEIR, 1999; Darby *et al.*, 2005) with latency period of the order of five years (Field *et al.*, 2000), interrogation was limited to those patients with at least five years of registration history with the same general practice before first diagnosis.

Data interrogation was carried out for England and Wales separately for each year of the period 2005 to 2012 individually, with output presented as annual country-specific tables of incidence for males and females, classified by radon band and age. To generate a sufficiently large population for reliable subsequent statistical analysis, the results from these eight years and from the two geographic entities were combined. Modelling based on the known geographic incidence of environmental radon gas, the variation of lung-cancer incidence with radon, and the relative overall incidence figures for lung-cancer and MS, suggested that the study might identify 156 new MS diagnoses in RAAs during the eight-year period.

3 Results

3.1 Study Population

The study population was defined as those individuals identified from their residential address as living in a postcode sector situated in one of the radon bands defined in Table 1, and whose medical records were held in one of the GP databases participating in THIN. Overall, this represented 20,140,498 person years of clinical monitoring, distributed approximately equally between males (10,056,628: 49.93%) and females (10,083,870: 50.07%).

Although the Radon Atlas reports the number of homes within each geographical measurement unit, no data are available in this source regarding populations in each area. Assuming average household size of 2.47 across England and Wales (ONS, 2011), Figure 3 compares on a band-by-band basis the normalised population derived from the Radon Atlas and the correspondingly normalised THIN base population. Chi-squared testing confirmed ($\chi^2 > 0.99$) these distributions to be essentially identical.

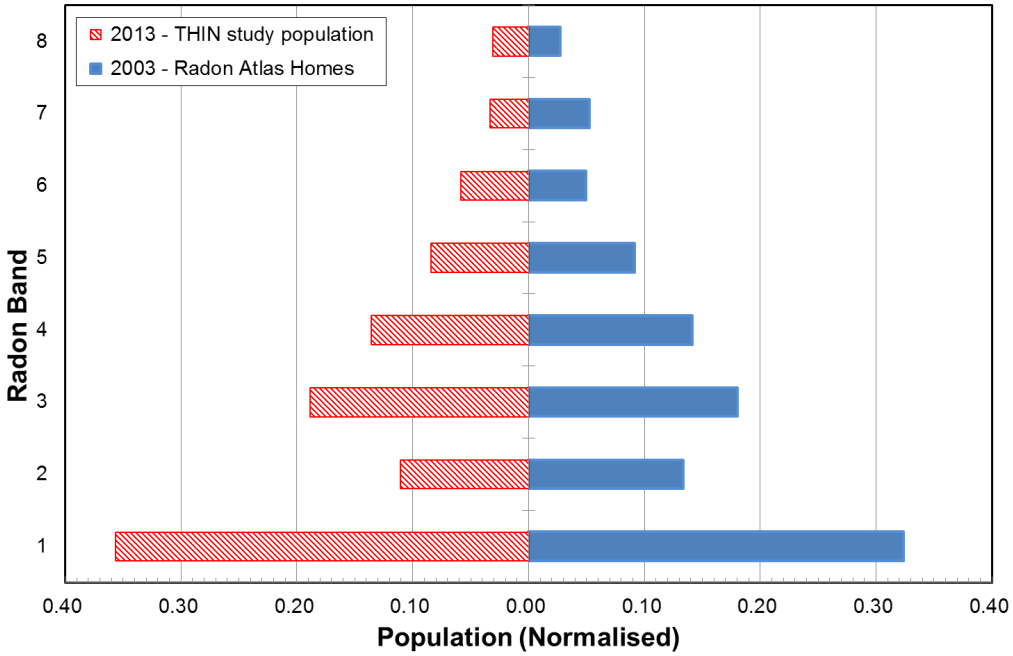


Figure 3: Population profiles of radon bands
Hatched bars – THIN base population
Solid bars – homes tabulated in Radon Atlas

Using standard age-bands, Figure 4 compares the normalised age profile within the base population with the corresponding age profile of the population of England and Wales (E&W) in the year 2010 (ONS, 2011). While the five-year registration condition inevitably makes direct comparison difficult, the reduced presence of individuals aged 20 - 30 years in the extracted data, possibly due to the additional mobility of this age group, which encompasses students and young adults taking up their first employment, deserves notice and highlights the need for care in comparisons.

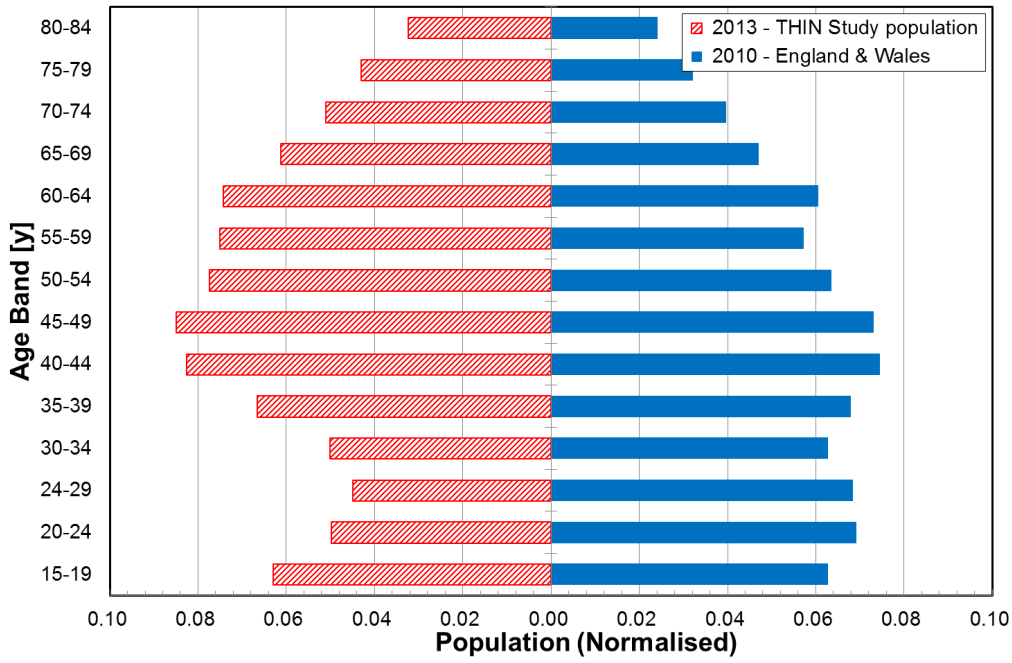


Figure 4: Age profiles of populations
Hatched bars – THIN base population
Solid bars - England and Wales (mid-2010) (ONS, 2011)

3.2 Raw MS Incidence

A total of 1,512 new MS cases were diagnosed, from a mean annual population of around 2.5 million people. Females (1,070 cases) outnumbered males (442 cases) by a factor of 2.42, comparable with the factor of 2.38 found by Mackenzie *et al*. (2014) in their recent review of MS incidence in the UK. Of the 1,512 new cases, just 115 could be allocated to one of the radon bands representing RAAs, compared with the 156 expected from the modelling referred to above.

Using corresponding data for MS diagnoses (numerators) and source population (denominators), raw incidence rates (population fraction diagnosed with MS per 10^5 person-years) were derived for each year/patient-age/radon-band locus. Table 3 summarises the raw output data aggregated over the study period for England and Wales combined, presenting MS incidence and underlying population for males, females and the total population. Results for the full population, Table 3(a), and for the subset of validated residents of the radon bands, Table 3(b), are shown separately.

Raw incidence rates among the overall population were 10.61 and 4.40 per 10^5 person-years for females and males respectively, with an overall population incidence of 7.51 per 10^5 person-years. Among the validated residents of radon band areas, the corresponding figures were 11.30 and 4.67 per 10^5 person-years for females and males respectively, with an overall population incidence of 7.89 per 10^5 person-years. These are, respectively, 6.60%, 4.54% and 5.05% greater than the figures from the base population. Raw incidence data from the base population (Table 3(a)) are shown graphically in Figure 5. The distribution of incidence across the age-bands and between the genders is comparable in form with that found nationally in previous studies (Bray, 2002; Mackenzie *et al.*, 2014).

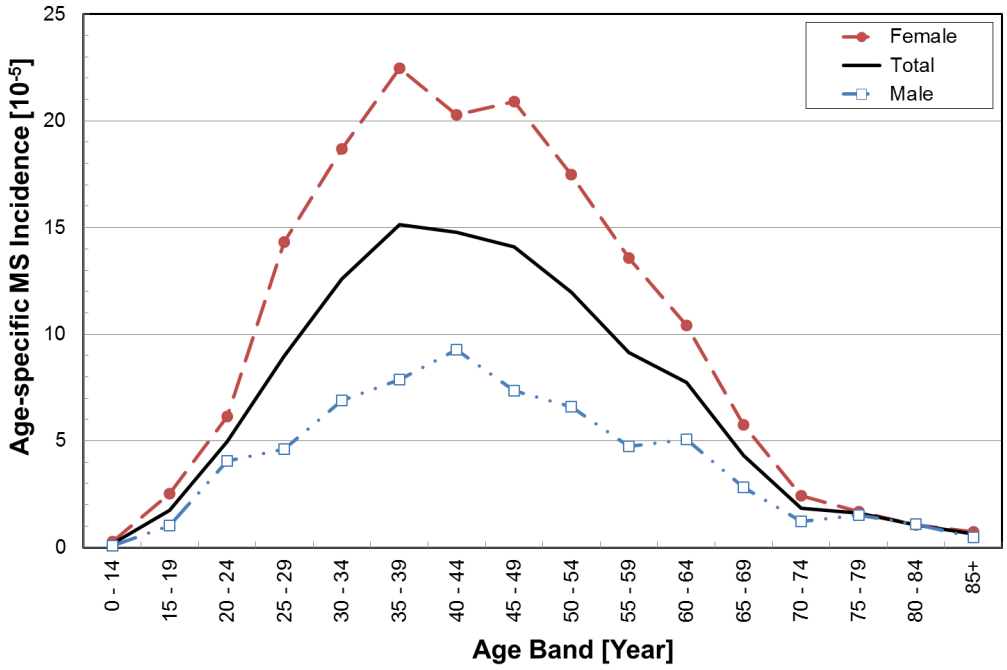


Figure 5: Age distribution of MS incidence among the full study population (Bands 0 – 9)
Dashed line/solid circles (red): Female
Chain line/open squares (blue): Male
Continuous line (black) Full population

Raw MS incidence was standardised to both the 2010 England and Wales Population (Bray, 2002) allowing comparison with previous MS incidence studies in these countries, and to the Standard World Population (Segi, 1960), facilitating comparison with international studies. Standardising to the 2010 England and Wales population gives incidence of 11.43 per 10^5 person-years for females, 4.88 per 10^5 person-years for males and 8.12 per 10^5 person-years overall. As Table 4 shows, these results show good agreement with those of a recent evaluation of MS incidence in the UK over the period 1990 to 2010 (Mackenzie at al., 2014); this utilised the GPRD (Walley and Mantagini, 1997), an alternative extraction of GP records, with coverage comparable to that of THIN. Both studies show higher incidence than those obtained by Alonso *et al.* (2007) in their UK investigation covering the period 1993 to 2010, again using the GPRD.

3.3 MS Incidence and Radon Concentration Level

Table 3 summarises the identified cases and corresponding base populations, by individual radon band, along with overall population estimates derived from the Radon Atlas and assuming a mean household occupancy of 2.47. With the exception of Band 9, which encompassed just 14 person-years and returned no new MS diagnoses during the study period, the proportion of the Radon Atlas population sampled by THIN was moderately consistent, ranging from 2.35% to 4.31%.

Using both raw and population-corrected data, MS incidence rates were determined for each radon band. Results are summarised in Table 6 for males and females separately and together, by radon band over the eligible population, and totalled for England and Wales. In addition to the raw data, incidence standardised to the ONS 2010 and World Standard populations is also tabulated.

4 Analysis of Results

As discussed above, meta-analysis of an expanding portfolio of epidemiological studies indicates that the ERR of radon-induced lung-cancer exhibits linear-no-threshold dependence on mean radon

exposure of the exposed population. If radon has a triggering role in the development of MS, then correlation might reasonably be assumed to exist between the incidence of the condition and the radon concentration level experienced by the exposed population, similar to that observed to exist between radon and lung-cancer.

Using incidence data standardised to the ONS 2010 population (Table 6), ERR for MS due to radon exposure was calculated for each radon band, taking mean incidence for the full THIN population as normalising parameter. Results are plotted in Figure 6 (solid line). As the figure shows, no simple monotonic relationship exists between ERR and radon concentration; indeed Band 1, which has the lowest average radon level, exhibits relatively high MS incidence and ERR. The observed scatter is attributed to the small sample size.

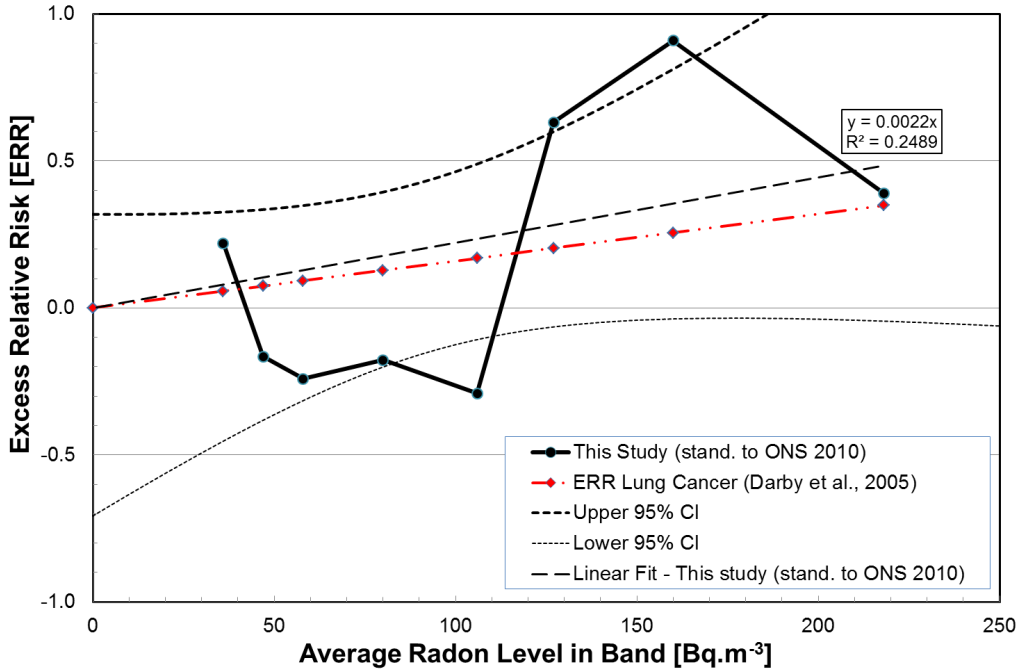


Figure 6: Excess relative risk for MS (standardised to England and Wales 2010 population) by radon band

Heavy continuous line/circles (black):	Experimental results from this study
Light continuous line (black):	Linear fit from this study
Light dashed lines (black):	95% CI limits
Heavy chain-dashed line/diamonds (red):	ERR vs radon for lung-cancer (Darby et al., 2005)

Linear regression of ERR against mean radon, plotted as the dashed black line in the figure, shows a positive gradient of 0.22 per 100 Bq·m^{-3} when forced to pass through the origin (representing a linear-no-threshold response), and 0.44 per 100 Bq·m^{-3} when unconstrained. The experimental data exhibit wide scatter ($R^2 = 0.25$, $p = 0.0961$) and the fit is not statistically significant at 95% Confidence Interval. Statistical significance was not achieved by relaxing the criterion to 90%. Note that the line of best fit, the null hypothesis represented by the x-axis (y = 0) and the linear increase expected for radon-induced lung-cancer from the European case-studies (Darby *et al.*, 2005) (chain-dashed red line, 0.16 per 100 Bq·m^{-3}) all lie inside the 95% Confidence Interval of the linear regression (Liengme, 2015) (light dotted hyperbolae).

Pearson's Chi-squared test was used to compare MS cases in the minimal radon band (Band 1: 44 cases in 505,566 patient-years) with those for RAAs (Bands 2 to 9: 71 cases in 911,199 patient-

years), yielding χ^2 for the null hypothesis of 0.632 with continuity correction, 0.564 without continuity correction, and the difference in incidence between Band 1 and Bands 2 to 9 is therefore not statistically significant. Similar results were obtained when comparing males and females separately.

The methodology employed here provides estimates of overall MS incidence similar to those provided by previous studies (Alonso *et al.*, 2007; Mackenzie *et al.*, 2014), as shown in Table 4. However, although the geographical spread of postcode sectors within each radon band contributes to ensuring that local non-uniformities of coverage are averaged on a band-by-band basis, the relatively low and non-uniform patient coverage by THIN in England and Wales (Table 5) ensures that insufficient data are currently available to confirm or refute the hypothesised correlation between MS incidence and radon concentration statistical significance.

5 Discussion

5.1 Study Design

Domestic radon concentrations can exhibit extreme variability over relatively short geographical ranges, and these variations tend to be smoothed out as the size of the sampled locale increases. In the UK, domestic radon concentration levels are now known with high geographical resolution, the Radon Atlas for England and Wales providing data at the level of postcode sector, the average area of which is 22 km^2. While this development, together with the advent of large computerised anonymised databases has facilitated the present investigation of the association between radon and MS incidence, the definitive demonstration of such an association would comprise a longitudinal case-control study, measuring radon in the homes of individual MS patients and controls and modelling their exposure, especially if they had previously moved house. This could be a complex, lengthy and expensive process, which might need to be international in scope and collaboration to recruit sufficient participants.

A prime aim of the present study was to improve on the sensitivity of previous studies by directly accessing patient records in order to establish diagnoses, central to this objective being (a) the precision of diagnosis and recording into clinical notes by GPs and specialists and (b) the representative nature of the database derived from these notes and other data. Mackenzie *et al.* (2014) addressed the second of these issues, noting that a major strength of using an extraction database such as THIN is that it covers a representative sample of GPs, spread geographically, with a patient population broadly representative of that of the country as a whole. The present study population, 2.5 million patients tracked across a time-span of 8 years, provides greater statistical precision than that achievable through a regional survey, such as that recently reported by Neuberger *et al.* (2011).

In addition to THIN, two further data extraction systems are in use in the UK. GPRD (now subsumed into Clinical Practice Datalink (CPRD) with an expanded source base) also interrogates *Vision 360* systems, some practices contributing to both THIN and CPRD. QResearch (Hippisley-Cox *et al.*, 2004), formed as a partnership between EMIS and Nottingham University, accesses EMIS-based practices, around 50% of the UK total. Neither of these approaches full coverage of the clinical population, with both appearing to access comparable patient numbers to THIN.

The representative nature of THIN data has been evaluated independently by comparing observed demographics, chronic condition prevalence, deprivation and deaths with UK national estimates (Blak *et al.*, 2011), confirming that THIN can be generalised to the UK in terms of demographics and crude prevalence of major conditions, and that data collected outside GPRD appear as valid as the data collected within it (Herrett *et al.*, 2010; Lewis *et al.*, 2007). The principal weakness in the present methodology is the low penetration of data extraction from UK GP records, since the study

population results from the intersection of the two sparsely-populated geographical distributions, the RAAs and the extracted practices. Modelling of the penetration prior to commencement of the study failed to project the lack of patients in Band 9 (Cornwall), despite the relatively uniform distribution across the remainder of England and Wales. Although more radon results would improve the RAA mapping, the most important factor currently restricting the power of this analysis is the modest percentage of the population accessed by THIN.

The *Health and Social Care Act 2012* requires GP practices to provide information to the Health and Social Care Information Centre in specified circumstances, and authorises NHS England, the body responsible for managing public health services in England, to extract this data, along with data collected by the Hospital Episodes Statistics service, to provide an integrated data service, known as *Care.Data*. This builds on existing data services, linking GP and hospital records for the first time, eventually expanding to cover all care settings, both in and outside of hospital, and will extract data from all GP databases, not just from those choosing to opt in to an existing proprietary scheme. Although currently in its pilot phase, eventual full nationwide roll-out is anticipated to provide a future opportunity to repeat this study with a database potentially 20 times larger than that explored here, with correspondingly enhanced statistical confidence.

5.2 Confounding Factors

In interpreting the study results, a number of potential confounding factors require consideration.

5.2.1 Vitamin D and Exposure to Sunlight

There is clear evidence that reduced exposure to sunlight, and the consequent lack of vitamin D, increases MS risk. Meta-analysis of 321 studies (Simpson *et al.*, 2011) found significant positive association (change in prevalence per degree-latitude) between age-standardised prevalence (1.04, $p<0.001$) and latitude, diminishing at high latitudes; adjustment for prevalence year strengthened the association with latitude (2.60, $p<0.001$). The persistence of a positive gradient in Europe after adjustment for HLA-DRB1 allele frequencies strongly supports a role for latitude-dependent environmental factors, the most prominent candidates being ultraviolet-B (UV-B) radiation and Vitamin D. Mackenzie *et al.* (2014) note (a) that significant ($p<0.001$) variations in incidence and prevalence exist between different regions of the UK and (b) that, despite the difference in MS incidence between Scotland and the England, no statistically significant trend with latitude exists within the twelve English regions.

Using a publicly-accessible tabulation of postcode coordinates[6], the geographical centroids of the sets of postcode sectors comprising the individual radon bands were determined, a further publicly-accessible data tool[7] being used to model the mean annual UV-B irradiation at each band centroid. Bands 1 to 7 have relatively wide spatial distribution, standard deviations for latitude and longitude of their sets of postcode sector centroids being around 1.2 and 1.4 degrees (132 km and 94 km at latitude 52 degrees) respectively. Band 8 is largely (18 of 27 sectors) located in south-west England, with the remainder located in Oxfordshire (two sectors) and the Peak District (seven sectors), and Band 9 (contributing no MS cases to the study) is entirely so, with significantly smaller centroid standard deviations. Geographical centroids of the bands migrate in a consistent south-westerly direction from Gloucester (Band 1) to Lynmouth, Devon (Band 8) and to Redruth, Cornwall (Band 9) a distance of approximately 300 km. Along this track, annual UV-B irradiation increases linearly ($R^2 = 0.81$) from 27.7 $kJ \cdot m^{-2}$ in Band 1 to 31.0 $kJ \cdot m^{-2}$ in Band 9. Bands 1 to 7 show reduced

[6] *PostcodePal – Database Generator*: Vulcan Logix UK Ltd, 145-157 St. John Street, London EC1V 4PW, UK. Online at http://www.postcodepal.com/?page=database-generator

[7] *SoDa - Integration and exploitation of networked solar radiation databases for environment monitoring.* European Commission, Contract IST-1999-12245 (2000 – 2003). Calculation tool online at http://www.soda-is.com.

UV-B irradiation range of 27.7 – 28.4 $kJ \cdot m^{-2}$; for the present study, therefore, UV-B irradiation can be regarded as geographically invariant except over the limited area encompassed by Bands 8 and 9, and can be discounted as a first order confounding factor.

In addition to the general latitudinal UV exposure gradient, variation in time spent indoors, sun-bathing, use of tanning studios and vitamin pill consumption will affect individual vitamin D levels. Increased time indoors will also increase overall radon dose, and it has been postulated that, if a link to radon exposure exists, this might explain increased MS incidence in women (Eidbo and Prater, 2004). At the level of the present study, however, these effects could not be quantified and a countrywide uniformity was therefore assumed.

5.2.2 Tobacco Smoking

Recent reviews confirm association between cigarette smoking and MS onset, with ERR of 0.4 - 0.8 among smokers (Hedstromm *et al.*, 2013; Jafari and Hintzen, 2011; Wingerchuk, 2012). In England, smoking prevalence is highest in the major conurbations (London, Manchester, Liverpool and Leeds-Bradford), all predominantly low-radon areas in Bands 0 and 1. Denman *et al.* (2014) analysed smoking prevalence and the percentage of houses above the radon action level in English local authorities, reporting no correlation between these parameters (R = -0.05). Since similar geographical considerations apply with regard to tobacco smoking as to UV exposure, it is anticipated that, given the widespread distribution of postcode sectors within each radon band, geographical variations in smoking prevalence can be disregarded in the present analysis.

5.2.3 Physical Trauma

It has long been felt that physical trauma, particularly involving the spinal cord and/or the brain, could disrupt the blood–brain barrier, leading to the development of MS plaques in those who are already genetically at risk (Poser, 2000). In a recent meta-analysis (Lunny *et al.*, 2013) of 36 high-quality case–control studies and four cohort studies, the former indicated statistically significant association between premorbid head trauma and risk for developing MS. With one exception, where significant brain injury within the last six years was reported to double MS incidence (Kang *et al.*, 2012), this correlation was absent in the cohort studies. Although interactions of this nature were not sought in this study, it is anticipated that their incidence would be relatively low and will not significantly influence the results.

5.2.4 Ethnicity and Social Deprivation

Although Ramagopalan *et al.* (2010) noted that studies controlling for confounding factors, e.g. the US Veterans series (Kurtzke *et al.*, 1979), showed lower MS prevalence in a number of non-Caucasian races/nationalities, recent studies in the USA (Langer-Gould *et al.*, 2013) question the widely accepted assertion that black males have a lower risk of MS than whites. In England and Wales, immigrant non-Caucasian ethnic groups have historically concentrated in cities where, as already noted, radon levels are generally low (Bands 0 and 1), where the 50-measurement criterion excludes many postcode sectors from analysis (Band 0), and where genetic disposition to MS is below average (Hedstrom *et al.*, 2013). Ramagopalan *et al.* (2011) observe that the pattern of UV-B and MS is confounded in large metropolitan areas (Merseyside, Manchester, Leeds, Birmingham and London), geographically-weighted regression showing these regions to be two standard deviations below the main trend.

The Database Managers report (Blak *et al.*, 2011) that THIN has a higher proportion of patients living in the most affluent areas than the national average, with 23.5% of its subjects resident in the least deprived Townsend quintile (Townsend *et al.*, 1988). This is likely to be related to deprivation in inner cities which, as discussed, tend to exhibit low radon levels and therefore contribute minimally to the results presented here.

No bias is therefore expected from either of these confounders.

5.2.5 Radon Band Allocation

While the Radon Atlas gave values for the average radon level in postcode sectors where 10 or more houses had been tested, the study protocol only collected data from postcode sectors where more than 50 houses had been tested. This ensured that the calculated average radon level for the postcode was more closely indicative of the actual average of the sector.

A consequence of the study protocol was that residents of homes where radon remediation had already been carried out, and where radon levels had consequently been reduced, could not be corrected for or excluded from consideration. The HPA confirm[8] that radon concentrations reported in the various Radon Atlases represent the first measurement from each house tested; in the vast majority of cases, these can therefore be assumed to represent the situation prior to any remediation that might have been carried out. Since remediated houses have lower radon concentrations than unremediated houses, the cumulative radon exposure for any radon band where some patients lived in remediated houses would therefore be expected to be less than that derived from calculating the exposure from the mean of the radon levels in each postcode sector.

However, response to successive campaigns to test and remediate homes has been modest, at best. Only 40% of householders in the original RAAs have had their homes tested, and of those finding radon levels exceeding the Action Level, only 15% have taken remedial action (Denman *et al.*, 2013). In Band 9, where 50% of homes exceed the Action Level, this represents just 3% of all houses, while for Band 8, it is 1.8%. For Bands 7 and below, the maximum percentage of houses remediated is below 1%. It is therefore unlikely that this effect will significantly influence the results.

5.2.6 Population Mobility

On average, during the period covered by the study data, 46% of the UK population lived in the same house for over 15 years and 25% for more than 30 years (DCLG, 2009). Conversely, 35% of the population moved house within five years, although 60% of movers stayed within a five-mile radius of their last property and 23% moved less than one mile. Even this restricted mobility, however, can potentially confound the analysis since, as noted above, the causative exposure for radon-induced lung-cancer could be up to five years before disease onset. The study population was therefore restricted to patients registered at their GP practice for at least five years prior to the commencement of the analysis period. While this condition necessarily impacts patient numbers in the more-mobile 20 – 30 year age group, population standardisation effectively compensates for this. It should be noted that this criterion does not exclude patients who moved home, but remained registered with their original GP.

The similarity of this study's estimate of overall MS incidence to those of previous UK studies (Alonso *et al.*, 2007; Mackenzie *et al*., 2014) (c.f. Table 4) suggests that using a population subset with lower mobility has not introduced any bias.

6 Conclusions

Although attention has hitherto been focussed on environmental radon gas in the context of its causative role in lung-cancer, a growing body of evidence suggests that radon may be implicated in the initiation of other conditions, recent studies indicating a possible causative link between elevated levels of environmental (particularly domestic) radon gas and increased MS incidence. To test this hypothesis, a retrospective study was performed of MS incidence among the population of

[8] Private communication to CJGK, 2005

England and Wales resident in those areas of elevated domestic radon concentration classified as Radon Affected Areas (RAAs), using the clinical extraction database maintained by The Health Improvement Network (THIN). This contains the electronic medical records of 12.4 million patients (3.6 million active patients) equivalent to 75.6 million patient years of data collected from 587 general practices in the UK, covering 5.7% of the UK population.

The study population, 20,140,498 person-years of clinical monitoring, represents a mean annual population over the eight-year study period of around 2.5 million individuals, equally divided between males and females. During this period, 1,512 new MS cases were diagnosed, females (1,065 cases) outnumbering males (441 cases) by nearly 2.5 times, equivalent to raw incidence rates of 7.51, 10.61 and 4.40 per 10^5 person-years respectively, comparable to previous studies.

Of the 1,512 new cases, 115 were reliably allocated to one of the radon bands representing areas located in RAAs. Standardising raw data to the 2010 England and Wales age profile, ERR figures for MS were calculated for each radon band, using the mean MS incidence for the full population as normalising parameter. No simple monotonic relationship is apparent between MS incidence and radon concentration and the data exhibit wide scatter ($R^2 = 0.25$). Linear regression of ERR against mean band radon concentration shows a positive gradient of 0.22 per 100 $Bq \cdot m^{-3}$ when forced to the origin (representing linear-no-threshold response), comparable to that reported for lung-cancer (0.16 per 100 $Bq \cdot m^{-3}$ (Darby *et al.*, 2005) and hinting at a possible common mechanism for the triggering process. Most of the plotted points fall between the 95% Confidence Limits for the linear fit, as also do the null hypothesis represented by the x-axis ($y = 0.0$) and the linear increase expected for radon-induced lung-cancer, and although a trend of increasing MS incidence with increasing radon concentration has been identified, the correlation is not statistically significant.

On the basis of the evidence available, and despite the geographical spread of postcode sectors within each radon band, the relatively low and non-uniform patient coverage by THIN renders insufficient data available for a statistically significant conclusion to be drawn, and the hypothesis that mean radon concentration in a RAA is a predictor of the incidence of MS is consequently not proven. It is anticipated that the forthcoming *Care.Data* service, linking GP and hospital records with universal scope, will provide a future opportunity to repeat this study with a database significantly larger than that explored here, with correspondingly enhanced statistical power.

As noted above, the definitive demonstration of association between radon and MS incidence would comprise a longitudinal case-control study, measuring radon in the homes of individual MS patients and controls. This might need to be international in scope and collaboration to recruit sufficient participants. Our study may not have generated a sufficiently interesting result to justify such a major investigation, but it does justify further repeat investigations, either using a larger UK patient database, or considering regions with higher indoor radon levels.

Numerous campaigns to monitor domestic radon levels, and to encourage remediation where high levels are discovered, have been undertaken, the prime motivation being the reduction in the overall population risk of lung-cancer. However, the response to these campaigns to date has been moderate, with positive action being generally greatest among the sections of the population least at risk of lung-cancer. Recognition of the linkage between radon and other conditions contributing significantly to the overall health burden has the potential to bring additional, hitherto unrecognised, health benefits, with the associated publicity potentially increasing the likelihood of the public taking action to reduce domestic radon levels and making remediation campaigns correspondingly more cost-effective.

Finally, although a limited number of ecological studies on MS have been reported, no similar investigations appear yet to have been undertaken on the other neurological conditions in which

radon has previously been incriminated, viz. Alzheimer's and Parkinson's diseases and motor neurone disease. With radon concentration data for England, Wales, Northern Ireland and much of Scotland now becoming available at increasing geographical resolution, and with the increasing availability of integrated clinical data record systems such as THIN, CPRD and, imminently, *Care.Data*, the opportunity now presents itself to initiate further studies of this nature.

7 Ethics

Ethical approval for the present study, under the title "*Is Naturally Occurring Radon Gas an Environmental Risk Factor for Multiple Sclerosis? – A Pilot Study*", Ref Number R13-024, was granted by THIN Scientific Review Committee on 17th September 2013.

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9 Conflicting Interests

There are no conflicting interests.

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11 Tables

Table 1: Definition of radon Bands 1 - 9, with corresponding numbers of postcode sectors and included homes, with arithmetic (AM) and geometric (GM) mean indoor radon levels, calculated from Green *et al.* (2002).

Band	Postcode Sectors	Homes		THIN Population 2005-2012 [person-years]	Weighted Mean Radon [Bq·m^{-3}]		Homes projected to exceed Action Level		
		Total	Tested		AM	GM	Total	Definition % > A.L.	Actual % > AL
1	202	638390	55282	505522	36	27	224	<=1.0	0.41
2	93	263070	33281	157275	47	32	515	1.1 - 2.0	1.55
3	133	355960	67067	267162	58	39	2282	2.1 - 5.0	3.40
4	115	278270	70689	192725	80	52	5286	5.1 - 10.0	7.48
5	74	179990	52337	119988	106	66	6567	10.1 - 15.0	12.55
6	39	97890	31672	83356	127	80	5428	15.1 - 20.0	17.14
7	46	103770	32468	46983	160	99	7790	20.1 - 30.0	23.99
8	27	53990	18980	43639	218	127	6554	30.1 - 40.0	34.53
9	14	26530	9080	14	312	201	4790	>40.0	52.75
Band 1-9	743	1997860	370856	1416650	73	63	39436		10.63

Table 2: Read Codes used in data extraction

Read Code	Description
666A.00	Multiple sclerosis review
666B.00	Multiple sclerosis multidisciplinary review
8CS1.00	Multiple sclerosis care plan agreed
9kG..00	Special Services for patient with multiple sclerosis – enhanced service administration
F20..00	Multiple sclerosis
F20..11	Disseminated sclerosis
F200.00	Multiple sclerosis of the brain stem
F201.00	Multiple sclerosis of the spinal cord
F202.00	Generalised multiple sclerosis
F203.00	Exacerbation of multiple sclerosis
F20z.00	Multiple sclerosis NOS
ZRVE.00	Kurtzke multiple sclerosis rating scale
ZRVE.11	Kurtzke multiple sclerosis scale

Table 3: Raw extracted data and calculated incidence rate per 10^5person-years for England and Wales combined, in standard age-bands

(a): Full population (Bands 0 – 9)

	MS Cases			Person-Years			MS Incidence [10^{-5}]		
Age	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**
0–14	3	1	4	1,109,208	1,173,131	2,282,339	0.27	0.09	0.18
15–19	15	7	22	591,476	675,608	1,267,084	2.54	1.04	1.74
20–24	27	23	50	438,921	564,489	1003,410	6.15	4.07	4.98
25–29	58	23	81	405,197	498,611	903,808	14.31	4.61	8.96
30–34	91	36	127	486,577	522,709	1,009,286	18.70	6.89	12.58
35–39	150	53	203	667,870	673,230	1,341,100	22.46	7.87	15.14
40–44	169	77	246	832,750	830,303	1,663,053	20.29	9.27	14.79
45–49	178	63	241	851,240	858,599	1,709,839	20.91	7.34	14.09
50–54	135	52	187	771,590	788,267	1,559,857	17.50	6.60	11.99
55–59	102	36	138	750,967	760,526	1,511,493	13.58	4.73	9.13
60–64	78	38	116	749,137	747,803	1,496,940	10.41	5.08	7.75
65–69	36	17	53	627,071	604,729	1,231,800	5.74	2.81	4.30
70–74	13	6	19	538,073	491,167	1,029,240	2.42	1.22	1.85
75–79	8	6	14	473,091	392,496	865,587	1.69	1.53	1.62
80–84	4	3	7	381,095	270,477	651,572	1.05	1.11	1.07
85+	3	1	4	409,607	204,483	614,090	0.73	0.49	0.65
Total	1070	442	1512	10,083,870	10,056,628	20,140,498	10.61	4.40	7.51

(b): Validated residents of Bands 1 - 8

	MS Cases			Person-Years			MS Incidence [10^{-5}]		
Age	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**
0–14	0	0	0	79,613	84,366	163,979	0.00	0.00	0.00
15–19	1	0	1	42,529	49,719	92,248	2.35	0.00	1.08
20–24	3	1	4	30,017	40,699	70,716	9.99	2.46	5.66
25–29	4	4	8	25,502	33,565	59,067	15.69	11.92	13.54
30–34	4	0	4	30,709	34,374	65,083	13.03	0.00	6.15
35–39	13	5	18	42,379	43,943	86,322	30.68	11.38	20.85
40–44	15	6	21	55,939	57,832	113,771	26.81	10.37	18.46
45–49	13	5	18	59,637	62,271	121,908	21.80	8.03	14.77
50–54	10	2	12	54,070	56,834	110,904	18.49	3.52	10.82
55–59	8	6	14	51,743	53,290	105,033	15.46	11.26	13.33
60–64	5	3	8	54,313	54,836	109,149	9.21	5.47	7.33
65–69	4	1	5	47,369	46,941	94,310	8.44	2.13	5.30
70–74	0	1	1	38,348	35,943	74,291	0.00	2.78	1.35
75–79	0	0	0	32,657	28,012	60,669	0.00	0.00	0.00
80–84	0	1	1	26,164	19,241	45,405	0.00	5.20	2.20
85+	0	0	0	28,955	14,840	43,795	0.00	0.00	0.00
Total	80	35	115	699,944	716,706	1,416,650	11.30	4.67	7.89

Table 4: MS incidence (this study and recent UK Studies) for the catchment population.

Study	Geographical Scope	Time Frame	MS Cases	MS Incidence [10^{-5}]		
				Female	Male	Both
This study	England & Wales [Raw]	2005 - 2012	1512	10.61	4.40	7.51
	England & Wales [UK 2010]			11.43	4.88	8.12
	England & Wales [World 1960]			11.80	4.77	8.12
Mackenzie *et al.* (2014)	UK	1990 - 2010	1320	11.52	4.84	9.64
Alonso *et al.* (2007)	UK [Raw]	1993 - 2000	642	7.42	3.44	5.47
	UK [World 1960]			7.16	3.07	5.10

Table 5: Radon bands – population and coverage. Assumes household size 2.47

Radon Band	Mean Band Radon	MS Cases (2005-2012)	THIN Population (2005-2012) [person-years]	2002 Radon Atlas Population	Coverage
1	36	44	505,522	1,589,173	3.98%
2	47	10	157,275	658,675	2.98%
3	58	19	267,162	880,802	3.79%
4	80	13	192,725	684,610	3.52%
5	106	8	119,988	450,503	3.33%
6	127	11	83,356	241,788	4.31%
7	160	7	46,983	249,396	2.35%
8	218	3	43,639	149,410	3.65%
9	312	0	14	56,390	0.00%
Total (1 – 9)	73	*115*	*1,416,650*	*4,960,747*	
0		*1397*	*18,152,817*	*Not included in radon analysis*	
All		1512	19,569,467	49,662,100	5.07%

Table 6: MS incidence by radon band for England and Wales:
(a) Raw incidence
(b) Incidence standardised to England and Wales 2010 population (ONS, 2011)
(c) Incidence standardised to World Standard Population (Bray, 2002)

Radon Band	Mean Radon Level [Bq·m^{-3}]	Female		Male		Both	
		Cases	Incidence 10^{-5}	Cases	Incidence 10^{-5}	Cases	Incidence 10^{-5}
(a)	**Raw Incidence**						
1	36	31	12.33	13	5.12	44	8.70
2	47	6	7.72	4	5.03	10	6.36
3	58	10	7.64	9	6.61	19	7.11
4	80	9	9.39	4	4.13	13	6.75
5	106	7	11.95	1	1.63	8	6.67
6	127	8	19.53	3	7.08	11	13.20
7	160	7	30.34	0	0.00	7	14.90
8	218	2	9.36	1	4.49	3	6.87
9	312	0	0.00	0	0.00	0	0.00
1-9	73	80		35		115	
0-9	124	1070	10.60	442	4.40	1512	7.50
(b)	**Standardised to England and Wales 2010 Population (Bray, 2002)**						
1	36		12.39		4.47		8.85
2	47		8.31		6.76		6.36
3	58		6.36		7.63		6.32
4	80		9.58		3.93		6.44
5	106		10.74		1.40		5.87
6	127		19.99		11.33		12.54
7	160		30.25		0.00		14.40
8	218		14.47		16.05		9.17
9	312		0.00		0.00		0.00
0-9	73		10.24		4.16		7.17
(c)	**Standardised to World Standard Population (Segi, 1960)**						
1	36		11.11		4.94		8.00
2	47		7.59		3.75		5.47
3	58		4.95		4.92		4.98
4	80		8.54		2.56		5.39
5	106		8.67		0.88		4.65
6	127		18.09		4.82		10.70
7	160		27.09		0.00		12.52
8	218		15.86		5.31		9.12
9	312		0.00		0.00		0.00
0-9	73		8.97		3.55		6.06