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Ageing and Dementia

Residential distance from high-voltage overhead power lines and risk of Alzheimer's dementia and Parkinson's disease: a population-based case-control study in a metropolitan area of Northern Italy

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Abstract

Background: The association between the extremely low-frequency magnetic field generated by overhead power lines and neurodegenerative disease is still a matter of debate.
Methods: A population-based case-control study was carried out on the residents in the Milan metropolitan area between 2011 and 2016 to evaluate the possible association between exposure to extremely low-frequency magnetic fields generated by high-voltage overhead power lines and Alzheimer's dementia and Parkinson's disease. A statistical analysis was performed on cases and controls matched by sex, year of birth and municipality of residence (with a case to controls ratio of 1 : 4) using conditional logistic regression models adjusted for socio-economic deprivation and distance from the major road network as potential confounders.
Results: Odds ratios for residents <50 m from the source of exposure compared with residents at ≥ 600 m turned out to be 1.11 (95% confidence interval: 0.95–1.30) for Alzheimer's dementia and 1.09 (95% confidence interval: 0.92–1.30) for Parkinson's disease.
Conclusions: The finding of a weak association between exposure to the extremely low-frequency magnetic field and neurodegenerative diseases suggests the continuation of research on this topic. Moreover, the low consistency between the results of the already existing studies emphasises the importance of increasingly refined study designs.

Key words: ELF-MF, logistic models, electromagnetic fields (adverse effects), electric power supplies (adverse effects), case-control studies, Alzheimer dementia (epidemiology), Parkinson disease (epidemiology), residence characteristics

Key Messages

- The risk for Alzheimer's dementia and Parkinson's disease tends to be higher in residents living <50 m from high-voltage overhead power lines compared with those resident at >600 m.
- This case-control study benefited from a population-based design, an accurate selection of cases and controls and adjustment for potential confounders. Conversely, the lack of a longitudinal approach represents an open limit.
- The scarcity and the low consistency of the results so far existing in literature suggest that research on this topic should continue focusing, in particular, on the refinement of study designs.

Background

The possible health effects related to exposure to magnetic fields have been the subject of numerous studies and currently extremely low-frequency magnetic fields (ELF-MFs) have been classified by the International Agency for Research on Cancer as possible carcinogens for humans, based on limited available evidence, exclusively for paediatric leukaemia.[1]

The effect of the ELF-MF generated by power lines on the health of subjects residing in areas close to them was studied for the first time in 1979, suggesting the hypothesis that exposure promotes the onset of cancer in humans.[2] In the following decades, numerous studies have been conducted that have confirmed the excess in cancer risk in the paediatric population,[3–9] for which an explanatory hypothesis has recently been made.[10] Other studies have assessed the effects of occupational exposure to ELF-MF on health, producing specific evidence on cancer-like outcomes.[11–13]

Over the years, further evidence has been accumulated regarding the association of ELF-MF exposure and neurodegenerative diseases. The first assessment of the association between residential exposure to ELF-MF and neurodegenerative diseases was carried out by Huss *et al.*[14] on a residential cohort of 4.7 million inhabitants. This work highlighted an excess of mortality from Alzheimer's dementia that was double in residents living <50 m from the high-voltage lines for at least 15 years and modest increases for amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis. Recently, the literature has highlighted an association between amyotrophic lateral sclerosis and occupational exposure,[15,16] but not with residential exposure,[17,18] to ELF-MF. Parkinson's disease has also been the subject of a recent meta-analysis that highlights an association with occupational exposures to ELF-MF.[19] The systematic review of 20 studies evaluating the association between Alzheimer's dementia and ELF-MF suggests an increase in the risk for occupational exposures, highlighting, however, a high heterogeneity between the studies and between the residential cohort and case-control approaches.[20]

The aim of this study, conducted on a population of over 2 million residents using a case-control approach and a methodology based entirely on current health flows, is to estimate the association between proximity of residence to high-voltage overhead power lines, to be intended as a proxy for exposure to ELF-MF, and the onset of Alzheimer's dementia and Parkinson's disease.

Methods

The study has used all current health data available from 2010 from the Agency for Health Protection of Milan (ATS) relating to hospital admissions, exemptions from the payment of the minimum fee (ticket) and prescriptions of drugs for residents in the metropolitan city of Milan and in the province of Lodi. The following assumptions for data extraction were used. First, that in the Italian Health System the diagnoses of Alzheimer's dementia and Parkinson's disease are made by expert physicians (neurologists, geriatricians, and psychiatrists); these diagnoses are those found on hospital admissions (as ICD-9 or ICD-10 codes) and on exemptions (as Health System exemption codes). In the second place, regarding the prescriptions of drugs, antidementia drugs (acetylcholinesterase inhibitors and memantine) are reimbursed, i.e. are paid by the Public Health System only to patients diagnosed with Alzheimer's dementia, not to people affected by other forms of dementia, whereas levodopa is reimbursed only to patients diagnosed with Parkinson's disease.

The database that was used is georeferenced to the address of residence, and only for 3.97% of the population are the geographical coordinates of the residence not available. All subjects with a new diagnosis of Alzheimer's dementia or Parkinson's disease in the period 1 January 2011 to 31 December 2016 were identified using a validated algorithm,[21–23] which is based on the aforementioned assumptions and reported in Supplementary Material 1, available as Supplementary data at *IJE* online. Cases were defined as subjects with specific diagnoses who had unchanged geographical coordinates of residence from 1 January 2011 until at least the diagnosis date; all subjects

without a diagnosis of Alzheimer's dementia or Parkinson's disease who had unchanged geographical coordinates of residence for the entire duration of the time-frame 1 January 2011 to 31 December 2016 have been identified as controls. It is plausible that the potential effect of ELF-MF on health emerges after years (even decades) of residential exposure. Therefore, the purpose of selecting only subjects with unchanged residence was to exclude people for whom the exposure was known to have been changing over time. Analogously, those subjects living in nursing homes at diagnosis are excluded from the analysis: usually people don't reside in these facilities for more than months or a few years, thus considering the nursing home as the reference point for quantifying the exposure of these subjects would have been misleading (subjects diagnosed with Alzheimer's dementia or Parkinson's disease before they took up residence in a nursing home are, of course, included). The age groups for which Alzheimer's dementia and Parkinson's disease aetiology are likely to be genetic ($\leq$65 years for Alzheimer's dementia and $\leq$45 years for Parkinson's disease[24,25]) have been excluded also.

Information on the location of the power lines in the territory of the ATS and on the road network have been obtained from open data of the region of Lombardy.[26]

Since there are no overhead power lines in the municipality of Milan (population 1.3 million), as all power lines are underground, all the residents of this city have been excluded from the study both as cases and as controls.

For each subject in the study, the co-ordinates of the address of residence have been used to determine the distance from the nearest high-voltage (>30 kV[27]) overhead power line as a proxy for exposure to ELF-MF and the distance from the nearest high-traffic road considered as a possible confounding factor. The distance from the residence to the border of the ATS has also been calculated to exclude subjects for whom this distance was shorter than the distance between their residence and the nearest high-voltage overhead power line or the nearest high-traffic road inside the ATS. We also considered the distance from the residence to the ATS border for all subjects classified as 'not exposed' to power lines and high-traffic roads within ATS area. If this distance was less than 600 meters these subjects were excluded as, due to the lack of information on power lines and roads beyond the border of the ATS, their classification as 'not exposed' could have been fallacious (see Supplementary Material 2, available as Supplementary data at *IJE* online, for graphical representations of the georeferencing process, and Supplementary Material 3, available as Supplementary data at *IJE* online, for a summary of the whole selection process).

Each case was matched with four controls by sex, year of birth, and municipality of residence.[28] The distance between the residence address and the power grid has been categorized into 4 classes: <50, 50–199, 200–599, $\geq$600 m.[14,29] The Italian socio-economic deprivation index, standardized on the ATS distribution as a measure of socio-economic status calculated for small census sections (each section includes on average, considering the entire national territory, 169 inhabitants distributed over 0.6 km^2), has also been considered as a possible confounder. It is an aggregate indicator calculated as the sum of the standardized values of five variables: the percentage of people who got at most a primary school degree, the percentage of economically active people who are unemployed or seeking a first job, the percentage of rented residences, the percentage of single-parent families, and the population density (in inhabitants per 100 m^2). This index has been categorized in 5 levels, corresponding to the quintiles of the distribution of values of individual census sections: the higher value of the index corresponds to the more deprived sections.[30] Another considered covariate is the distance from the high-traffic road network, categorized into five classes: <50, 50–99, 100–199, 200–300, $\geq$300 m.[31]

To test the validity of the entire experimental design, a further group of cases and controls has been introduced to study the association between ELF-MF exposure and diabetes mellitus, for which there is currently no evidence in the literature.

The analysis has been performed by means of conditional regression models, estimating the odds ratio (OR) of disease and the corresponding 95% confidence intervals (95% CI). The models included the distance from the nearest high-voltage overhead power line, the deprivation index and the distance from the nearest high-traffic road as independent variables.

All analyses have been performed using SAS 9.4 (SAS Institute, Cary, NC, USA), whereas for the management of georeferenced data and the calculation of the distances the software ArcGIS 10.5 (ESRI, Redlands, CA, USA) has been used.

Results

Table 1 shows the results of the control case study for Alzheimer's dementia: 9835 cases and 39 340 controls have been included. The mean age of those with Alzheimer's dementia was 78.5 years (min-max: 65–103). The OR of Alzheimer's dementia has been found, for residents <50 m from high-voltage overhead power lines compared with residents at a distance $\geq$600 m, to be 1.11 (95% CI: 0.95, 1.30). There was no association between Alzheimer's dementia and socio-economic deprivation or proximity to the high-traffic road network.

Table 2 shows the results for Parkinson's disease: 6810 cases and 27 240 controls have been identified. The mean

Table 1. Distribution of cases (at diagnosis) with Alzheimer's dementia and matched[a] controls and odds ratios for disease according to residential distance from the high-voltage overhead power grid, Italian deprivation index and residential distance from the high-traffic road network, metropolitan area of Milan, Italy, 2011–2016

		No. of cases (%)	No. of controls (%)	OR[b]	95% CI
Sex					
	Females	6496 (66.05%)	25 984 (66.05%)		
	Males	3339 (33.95%)	13 356 (33.95%)		
Age group (years)					
	66–75	3358 (34.14%)	13 425 (34.13%)		
	76 – 85	4943 (50.26%)	19 852 (50.46%)		
	>85	1534 (15.60%)	6063 (15.41%)		
Deprivation index[c]					
	1	527 (5.36%)	2051 (5.21%)	1.00	Referent
	2	1364 (13.87%)	5567 (14.15%)	0.95	0.85, 1.07
	3	2859 (29.07%)	11 849 (30.12%)	0.93	0.83, 1.05
	4	3156 (32.09%)	12 425 (31.58%)	0.99	0.89, 1.11
	5	1929 (19.61%)	7448 (18.93%)	1.02	0.91, 1.15
Distance from roads (m)					
	<50	704 (7.16%)	2709 (6.89%)	1.05	0.95, 1.15
	50–99	569 (5.79%)	2426 (6.17%)	0.94	0.85, 1.05
	100–199	1227 (12.48%)	4766 (12.11%)	1.04	0.96, 1.12
	200–299	1001 (10.18%)	4002 (10.17%)	1.00	0.93, 1.09
	≥300	6334 (64.40%)	25 437 (64.66%)	1.00	Referent
Distance from power lines (m)					
	<50	241 (2.45%)	875 (2.22%)	1.11	0.95, 1.30
	50–199	1076 (10.94%)	4325 (10.99%)	1.00	0.92, 1.09
	200–599	3767 (38.30%)	15 059 (38.28%)	1.01	0.95, 1.07
	≥600	4751 (48.31%)	19 081 (48.50%)	1.00	Referent
Total					
		9835 (100.00%)	39 340 (100.00%)		

[a]Each case was matched with four controls by sex, year of birth, and municipality of residence.

[b]Odds ratios and corresponding 95% confidence intervals were calculated from a conditional multivariate logistic model including the distance from the nearest high-voltage overhead power line, the distance from the nearest high-traffic road and the deprivation index as independent variables.

[c]The 'referent' level (1) is the least deprived one.

CI, confidence interval; OR, odds ratio.

age of those with Parkinson's disease was 72.9 years (min-max: 45–100). The estimated OR of Parkinson's disease has been found, for residents <50 m from high-voltage overhead power lines compared with residents at a distance ≥600 m, to be 1.09 (95% CI: 0.92, 1.30). For Parkinson's disease as well, there were no obvious associations with the proximity to high-traffic roads, whereas there was a clear linear association between the increase in deprivation level and the risk of illness.

Table 3 shows the results of the study on 6751 subjects diagnosed with diabetes mellitus and 27 004 controls. The mean age of those with diabetes mellitus was 49.1 years (min-max: 0–95). There was no evidence of an association between ELF-MF exposure and diabetes mellitus, whereas there was an association between diabetes mellitus and socio-economic deprivation, with an OR of 1.32 (95% CI: 1.12, 1.55) for the fifth quintile (which covers the most deprived subjects) compared with the first quintile (which covers the least deprived subjects). There was also an increase in the risk for residences near the major roads: for the ranges 50–99 and <50 m compared with the range ≥300 m the ORs were 1.11 (95% CI: 0.99, 1.25) and 1.17 (95% CI: 1.05, 1.31), respectively.

Discussion

This work shows a modest increase in risk for Alzheimer's dementia and Parkinson's disease in subjects residing <50 m from high-voltage overhead power lines compared with those resident at >600 m. This result, although not conclusive with respect to the discussion on the association between ELF-MF and neurodegenerative diseases, suggests the need for further studies to explore this matter in depth through study designs aimed at the control of possible confounders and better estimates of the duration and/or intensity of exposure. Of extreme interest is the lack of any

Table 2. Distribution of cases (at diagnosis) with Parkinson's disease and matched[a] controls and odds ratios for disease according to residential distance from the high-voltage overhead power grid, Italian deprivation index and residential distance from the high-traffic road network, metropolitan area of Milan, Italy, 2011–2016

		No. of cases (%)	No. of controls (%)	OR[b]	95% CI
Sex					
	Females	3465 (50.88%)	13 860 (50.88%)		
	Males	3345 (49.12%)	13 380 (49.12%)		
Age group (years)					
	46–55	499 (7.33%)	2012 (7.39%)		
	56–65	911 (13.38%)	3677 (13.50%)		
	66–75	2316 (34.01%)	9210 (33.81%)		
	76–85	2572 (37.77%)	10 283 (37.75%)		
	>85	512 (7.52%)	2058 (7.56%)		
Deprivation index[c]					
	1	338 (4.96%)	1439 (5.28%)	1.00	Referent
	2	944 (13.86%)	3902 (14.32%)	1.04	0.90, 1.21
	3	1996 (29.31%)	8210 (30.14%)	1.05	0.91, 1.21
	4	2240 (32.89%)	8695 (31.92%)	1.13	0.98, 1.30
	5	1292 (18.97%)	4994 (18.33%)	1.14	0.98, 1.32
Distance from roads (m)					
	<50	505 (7.42%)	1956 (7.18%)	1.04	0.92, 1.16
	50–99	446 (6.55%)	1702 (6.25%)	1.05	0.93, 1.18
	100–199	840 (12.33%)	3429 (12.59%)	0.98	0.90, 1.07
	200–299	691 (10.15%)	2804 (10.29%)	0.99	0.90, 1.08
	≥300	4328 (63.55%)	17 349 (63.69%)	1.00	Referent
Distance from power lines (m)					
	<50	189 (2.78%)	704 (2.58%)	1.09	0.92, 1.30
	50–199	834 (12.25%)	3277 (12.03%)	1.03	0.93, 1.13
	200–599	2662 (39.09%)	10 720 (39.35%)	1.00	0.93, 1.07
	≥600	3125 (45.89%)	12 539 (46.03%)	1.00	Referent
Total					
		6810 (100.00%)	27 240 (100.00%)		

[a]Each case was matched with four controls by sex, year of birth, and municipality of residence.

[b]Odds ratios and corresponding 95% confidence intervals were calculated from a conditional multivariate logistic model including the distance from the nearest high-voltage overhead power line, the distance from the nearest high-traffic road and the deprivation index as independent variables.

[c]The 'referent' level (1) is the least deprived one.

CI, confidence interval; OR, odds ratio.

association between exposure and diabetes mellitus, which instead emphasises the absence of residual confounding on the highlighted excesses of risk.

Comparison with previous studies

To date, two works have evaluated the association between residential exposure to ELF-MF and the onset of neurodegenerative diseases. The first, a Swiss longitudinal cohort study,[14] has shown an excess risk of Alzheimer's dementia with the reduction of the distance between residence and the high-voltage power grid (in the higher exposure range, i.e. <50 m, the risk was particularly increased, to a greater extent for the subjects residing at the same address for at least 15 years); however, no association with Parkinson's disease was found. The second work, a Danish case-control study,[29] has found no association between exposure to ELF-MF and Alzheimer's dementia or Parkinson's disease.

All the studies conducted on ELF-MF residential exposure and onset of neurodegenerative diseases have used the residence distance of the study subjects from the power lines as a proxy for exposure to ELF-MF. The results and the size of the population investigated are comparable, as well as the estimated risk excesses. In this study the average age of Parkinson's disease onset is seemingly high (72.9 years) compared with that reported in the literature (about 60 years); the latter value, however, is most likely affected by selection bias in the cases studied.[32] In fact, considering that the cases of age ≤45 years have been excluded, the result of this study is comparable with that of a recent review on the topic that has shown a real median age of onset of around 70 years.[32]

Table 3. Distribution of cases (at diagnosis) with diabetes mellitus and matched[a] controls and odds ratios for disease according to residential distance from the high-voltage overhead power grid, Italian deprivation index and residential distance from the high-traffic road network, metropolitan area of Milan, Italy, 2011–2016

		No. of cases (%)	No. of controls (%)	OR[b]	95% CI
Sex					
	Females	3392 (50.24%)	13 568 (50.24%)		
	Males	3359 (49.76%)	13 436 (49.76%)		
Age group (years)					
	≤15	170 (2.52%)	680 (2.52%)		
	16–25	154 (2.28%)	615 (2.28%)		
	26–35	1007 (14.92%)	4035 (14.94%)		
	36–45	1369 (20.28%)	5468 (20.25%)		
	46–55	1571 (23.27%)	6294 (23.31%)		
	56–65	1499 (22.20%)	5992 (22.19%)		
	66–75	780 (11.55%)	3116 (11.54%)		
	76–85	175 (2.59%)	702 (2.60%)		
	>85	26 (0.39%)	102 (0.38%)		
Deprivation index[c]					
	1	260 (3.85%)	1114 (4.13%)	1.00	Referent
	2	865 (12.81%)	3672 (13.60%)	1.01	0.86, 1.19
	3	1975 (29.25%)	8290 (30.70%)	1.02	0.87, 1.19
	4	2214 (32.80%)	8985 (33.27%)	1.07	0.92, 1.25
	5	1437 (21.29%)	4943 (18.30%)	1.32	1.12, 1.55
Distance from roads (m)					
	<50	555 (8.22%)	1956 (7.24%)	1.17	1.05, 1.31
	50–99	448 (6.64%)	1665 (6.17%)	1.11	0.99, 1.25
	100–199	883 (13.08%)	3623 (13.42%)	1.00	0.92, 1.09
	200–299	796 (11.79%)	3170 (11.74%)	1.02	0.93, 1.12
	≥ 300	4069 (60.27%)	16 590 (61.44%)	1.00	Referent
Distance from power lines (m)					
	<50	170 (2.52%)	694 (2.57%)	0.98	0.82, 1.18
	50–199	874 (12.95%)	3631 (13.45%)	0.97	0.88, 1.07
	200–599	2791 (41.34%)	10 904 (40.38%)	1.04	0.97, 1.11
	≥600	2916 (43.19%)	11 775 (43.60%)	1.00	Referent
Total					
		6751 (100.00%)	27 004 (100.00%)		

[a]Each case was matched with four controls by sex, year of birth, and municipality of residence.

[b]Odds ratios and corresponding 95% confidence intervals were calculated from a conditional multivariate logistic model including the distance from the nearest high-voltage overhead power line, the distance from the nearest high-traffic road and the deprivation index as independent variables.

[c]The 'referent' level (1) is the least deprived one.

CI, confidence interval; OR, odds ratio.

Strengths and limitations

The strengths of this study are the size of the population investigated and the high quality of information available from the ATS data warehouse. Personal data, which provide monthly updated information on each resident, have made it possible to trace the population in a comprehensive manner. In the Swiss study death certificates determined the diagnosis of neurodegenerative disease, whereas in the Danish case-control study hospital admissions were used: both studies have therefore produced an important case selection, due to under-reporting of neurodegenerative diseases in the death certificates in the first case and to the severity of the disease in the second. In this study, the use of three different and independent sources of information has maximized the ability to discriminate cases and controls within the population (it should be noted that both in the Danish study and in this study the included cases are incident, whereas the Swiss study focused on mortality from the diseases). The selection process had only a minor effect on the distribution of cases for sex, age class, and socio-economic deprivation (see Supplementary Material 4, available as Supplementary data at *IJE* online, for a comparison between all cases and those selected for the final analysis).

On the other hand, an important limitation of this study is represented by the short duration of exposure due to unavailability of data necessary to establish the level of exposure for times comparable with those of the two previous studies (15–20 years): this has prevented an analysis of the long-term effect of the exposure on the incidence of diseases. The advancing integration of scattered data in usable databases may permit, in the near future, analyses to be carried out on a dataset covering a longer span of time in the past with a time-dependent approach and, consequently, investigation of the long-term effect of exposure in a meticulous fashion; moreover, this would remove the residual bias due the strictness of the selection of subjects based on continuity of residence.

The determination of the distance of residence of the study subjects from the sources of exposure has been very precise because in the consulted health flows the residence is georeferenced, i.e. the exact geographical coordinates are available. This is, of course, an approximation of the real exposure to the ELF-MF which has been necessary in the absence of a method to precisely estimate the exposure level based on the effective intensity of the electric current, on the size and shape of the magnetic field that this current generates and on the variations over time of the quantities considered. The approximation reduces the ability to accurately estimate the exposure level of the study subjects even when knowing their location with respect to the power grid; this is a limitation that this study shares with the two most similar existing studies.[14,29] Modelling of the magnetic field that the power lines generate is indeed necessary for the progression of research on this topic; as well as the time-based approach, this might be possible in the near future with closer cooperation between the Agency for Health Protection and the Regional Environmental Protection Agency (which has already proved to be fruitful in a study on paediatric leukaemia performed in Emilia-Romagna, another region of Northern Italy[4]).

A supplementary strength is the inclusion in the analyses of important confounders, specifically socio-economic deprivation and the distance from the residence to the high-traffic road network. The standardization of the Italian deprivation index on the ATS average, and not on the national average as usual, has made it possible to obtain values that take into account the specificity of the studied territory; however, it must be pointed out that this index remains an aggregate, and not an individual, indicator. Whereas no clear association between deprivation and Alzheimer's dementia has emerged, the risk of Parkinson's disease was found to be increased in the more deprived classes compared with the less deprived ones (the association is particularly strong in the two most deprived quintiles). These results recall those of a work by Lix *et al.* published in 2010 that showed a higher prevalence and incidence of Parkinson's disease in the lower income quintile compared with the highest income quintile[33] in a Canadian urban population, although other studies have not confirmed this relationship[34] or have even highlighted an increased risk of Parkinson's disease in the less deprived sections.[35–37]

The fact that no association has emerged between the distance of residence from the high-traffic road network and Alzheimer's dementia and Parkinson's disease is partially at odds with the results of a recent Canadian study[31] that highlighted an association between the proximity of residence to a network of large roads and the onset of dementia (but not of Parkinson's disease). In this case the generalization of the results is particularly difficult due to the lack of an unequivocal definition of 'large road', even in the same country: in Italy, for example, there are two distinct systems of classification of roads, one administrative and the other technical (both of them were considered in this study).

The overlap of the results obtained in relation to diabetes mellitus compared with those already reported in the literature (no association with ELF-MF exposure and strong association with socio-economic deprivation[38–40]) confirms the overall soundness of the experimental design used. Interesting, and so far not reported in the literature, is the finding of an increase in the risk of diabetes mellitus in residents within 50 m from the nearest high-traffic road compared with those living at least 300 m away.

Conclusion and perspectives

The results of this study do not disprove the hypothesis that the ELF-MF generated by high-voltage overhead power lines can increase the risk of Alzheimer's dementia and, to a lesser extent, Parkinson's disease. The repeated suggestions regarding the existence of an association between ELF-MF and neurodegenerative diseases, both for residential exposures and for occupational exposures,[41] constitute an incentive to continue the evaluation through the planning of specific studies. The lack of univocal and definitive results emphasises, however, the need to adopt, for this specific field of investigation, increasingly rigorous experimental designs, with particular reference to the selection of study subjects, the quantification of exposure and the definition of confounders.

Considering the complexity of the experimental design applied in this study and the relatively limited amount of resources with which it was possible to implement it, it is to be hoped that this design may be adopted, and improved, for similar investigations in other Italian or foreign geographical areas.

Supplementary Data

Supplementary data are available at *IJE* online.

Conflict of interest: None declared.

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