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Residential exposure to ultra high frequency electromagnetic fields emitted by Global System for Mobile (GSM) antennas and amyotrophic lateral sclerosis incidence: A geo-epidemiological population-based study

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease of unknown etiology. Mobile communication antennas have increased over the last few decades. Consequently, there has been a steady increase in environmental exposure to ultra high frequency electromagnetic fields (UHF-EMFs) emitted by Global System for Mobile (GSM) communication antennas, which raises concerns about possible health risks in the general population. We aimed to evaluate the relationship between residential exposure to UHF-EMFs generated by GSM antennas and the risk of ALS in general population. A geo-epidemiological population-based study was performed in Limousin (France). ALS incident cases were identified through a register (FRALim, 2000–2012 period). A model to estimate UHF-EMF exposure was developed based on the distance and the power of GSM antennas. Exposure to multiple emissions from multiple directions was considered. A non-cumulative and a cumulative model were established. A geographic information system integrated the raster model of exposure, and the residential distribution of observed and expected cases. A generalized linear model was performed to test the association. Overall, 312 ALS cases were included. We estimated exposures below 1.72 V/m in urban areas and below 1.23 V/m in rural areas for 90% of the population. A gradient effect between UHF-EMF exposure and ALS incidence was apparent with a statistically significant trend. A significant increased risk of ALS was observed between the non-exposure category and the highest exposure category, with a relative risk of 1.78 (95% CI: 1.28–2.48) in the non-cumulative model and 1.83 (95% CI: 1.32–2.54) in the cumulative model. Our results suggest a possible association between residential UHF-EMF exposure and ALS. Ecological studies are a means of generating hypotheses. Further studies are needed to clarify the potential role of EMFs on neurodegeneration.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease involving the upper and lower motor neurons that leads to respiratory compromise with a fatal outcome within 15–20 months of diagnosis (Marin et al., 2016). Disease onset represents the initial symptoms reported by the patient. The onset is categorized as either spinal or bulbar depending on the affected muscle territories and related clinical symptom. Diagnosis is based on the clinical signs and electromyography evidence of acute denervation according to the Airlie House criteria (Brooks et al., 2000).

ALS is predominantly a sporadic disease with an unknown etiology. Various environmental factors have been postulated to play a role in the occurrence of ALS (Gil et al., 2007; Luna et al., 2017) including electromagnetic fields (EMFs). EMFs occur in nature and thus have always been present on earth (World Health Organization, 2002). However, environmental exposure has increased and is related to the expansion of EMF sources. Global System for Mobile (GSM) communication antennas are a common source of ultra-high frequency-EMFs (UHF-EMFs) and have recently experienced rapid growth in operation worldwide.

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The potential effects of UHF-EMFs are still unknown, which has raised concerns about possible health risks in the general population (International Commission on Non-Ionizing Radiation Protection ICNIRP, 1998). Several neurological effects have been reported for exposure to electromagnetic radiation from mobile communications systems, such as changes in sleep patterns and cognitive functions, modification of neuronal electrical activity, and disturbance of neurotransmitter release (Consales et al., 2012; Hossmann and Hermann, 2003). In addition, researchers have reported that increased exposure to EMF can modify the cellular balance by generating reactive oxygen species (Consales et al., 2012; Simkó, 2007). However, the evidence is still controversial.

In this context, it is essential to understand the role of UHF-EMFs on ALS occurrence as it could be a potential modifiable component of risk. We aimed to evaluate the relationship between residential exposure to UHF-EMFs generated by GSM antennas and the risk of ALS in population-based settings.

2. Methods

2.1. Study population

The study was performed in the Limousin region, a mostly rural area in central France covering 747 towns, with an area of 16,942 km^2. Over the study period, the total population increased from 714,012 in 2000 to 738,766 in 2012 according to the French National Institute of Statistics (Insee).

2.2. Case ascertainment

Patients were identified through the ALS French register in Limousin (FRALim), the first population-based ALS register using multiple sources of case ascertainment in France. The FRALim methodology has been described in detail in a previous publication (Marin et al., 2014). The crude incidence of ALS in Limousin was estimated at 3.19/100,000 person-years of follow-up (PYFU; 95% CI: 2.81–3.56). The exhaustiveness of the register was estimated at 98.4% (95% CI: 95.6–99.4) by capture–recapture analysis (Hook and Regal, 1995). We included all incident cases (2000–2012 period) of persons living in Limousin at the time of diagnosis, i.e., definite, probable, probable laboratory-supported or possible ALS cases according to Airlie House criteria (Brooks et al., 2000).

2.3. Data collection

2.3.1. Demographic and clinical characteristics of ALS cases

The following data were extracted from the FRALim register: age at time of diagnosis, sex, date of onset, date of diagnosis, residential address at time of diagnosis, type of onset, Airlie House criteria, and date of death.

2.3.2. General population demographics and residential buildings

The French National Institute of Statistics (Insee) provided the number of inhabitants by age and sex in each town for each year of the study period. Residential building and cartographic information were provided by the French National Institute of Geography (IGN) to establish the spatial distribution of the population in each town in any given year. BD TOPO® software (BDTOPO® | IGN - Espace professionnel) was used, providing a vector description of the territory and its infrastructure with a metric precision ranging from 1:5000 to 1:50,000.

2.3.3. Global System for Mobile (GSM) antennas

Data on GSM antennas were collected from the French National Agency of Radio Frequencies (ANFR), available from 1991 (first antenna installation) onwards. ANFR is a public administrative institution with the mission to control radiofrequency equipment and to verify compliance with regulatory conditions. Data were collected for each antenna in the area, including installation date, operational period, geolocalization, orientation, frequency, and technical information.

2.4. Statistical analysis

2.4.1. Descriptive and comparative analysis

We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Vandenbroucke et al., 2007) guidelines in this study. Quantitative variables were expressed as medians with interquartile ranges (IQRs) and qualitative variables as frequencies and percentages. Percentages were compared using the X^2 test and means using the Kruskal–Wallis test.

Crude incidence per 100,000 PYFU was calculated and a normal distribution was assumed for calculation of the 95% confidence interval (CI). Direct age and sex standardized incidence was calculated based on the 2010 French population (Insee) and the 2010 US population (US Census Bureau, 2010).

Survival analysis was conducted from the date of onset and the date of diagnosis until the date of death or censoring. The Kaplan–Meier method and Cox's proportional hazards modelling were employed. A p-value of < 0.05 was considered to be statistically significant. All missing data were reported.

2.4.2. Estimation of the expected number of cases

We calculated the annual expected number of ALS cases for each town, considering age and sex distributions of the yearly estimations of the population provided by Insee, and the ALS incidence rate previously estimated in Limousin (internal reference rate) (Marin et al., 2014). Calculations were based on a homogeneous distribution and a Poisson distribution was assumed. The standardized incidence ratios (SIR) with associated 95% CIs were calculated to estimate whether the number of observed cases was higher or lower than expected in the population.

2.4.3. Estimation of the exposure to electromagnetic fields

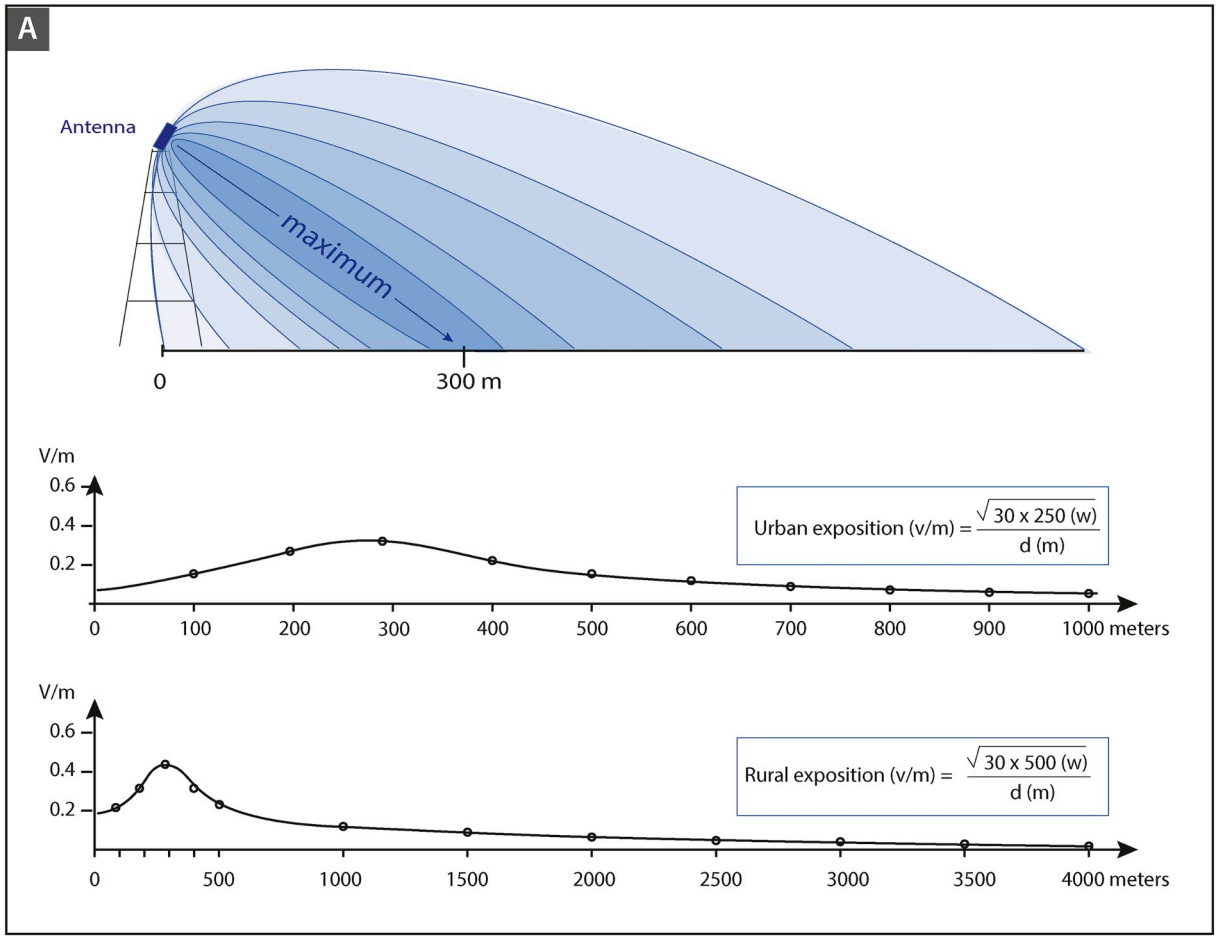
GSM antennas emit EMFs at UHFs (900–2600 MHz) that propagate around the source in the form of electromagnetic waves (Aniołczyk, 1999). EMF exposure at a given point depends on the distance from the antenna and the intensity of radiation in a specific direction. The exposure is inversely proportional to the distance from the source, and proportional to the power of the antenna, which is assessed in terms of equivalent isotropically radiated power (*EIRP*). *EIRP* is the product of the power supplied to the antenna and the maximum antenna gain relative to an isotropic antenna (Singh, 2012).

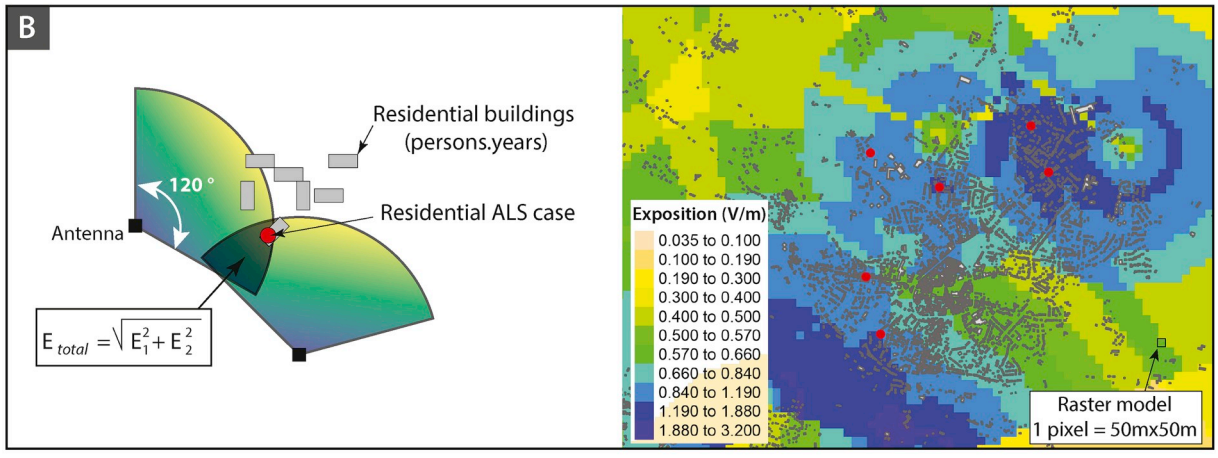
The technical parameters used in the model were based on the French National Agency of Radio Frequencies technical guide (2009): modelling radioelectric sites and safety perimeters for the public (Agence nationale des fréquences, 2009). Depending on the geographic distribution of antennas, the EIRP was estimated at 250 W in urban areas (high antenna distribution density) and 500 W in rural areas (lower antenna distribution density). The maximum exposure was estimated at 300 meters (m) from the GSM antenna, and it was estimated that the maximum emission distance of antennas was 1000 m in urban areas and 4000 m in rural areas (Fig. 1a).

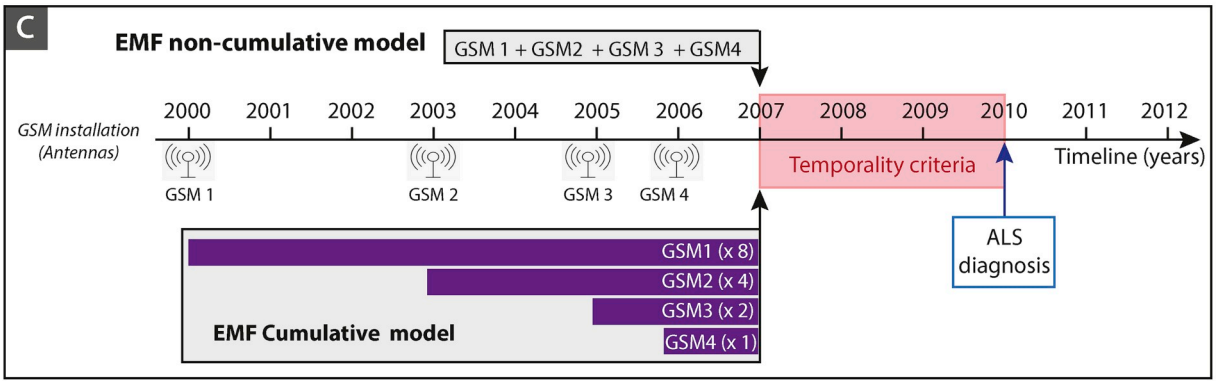
2.4.4. Geostatistical analysis

All analysis was performed using R software (version 3.1.2). Kulldorff's scan statistic was used for the detection of spatiotemporal and spatial clusters of disease (Kulldorff, 1997, 1999). Significance was determined under the null hypothesis via Monte Carlo simulations.

A raster data model was developed based on the Geographic Information System (GIS) using the following R packages: Geographic Data Analysis and Modelling (raster) (Hijmans et al., 2017), Bindings for the Geospatial Data (rgdal) (Bivand et al., 2018), and Classes and Methods for Spatial Data (sp) (Pebesma et al., 2018). The raster model consists of equally sized pixels measuring 50 m by 50 m, and each pixel







(caption on next page)

Fig. 1. Estimation of the exposure to electromagnetic fields (EMFs). 1a) Illustration of EMFs emitted by one Global System for Mobile (GSM) antenna in urban and rural areas (horizontal view); 1b) Illustration of superimposed EMF emissions from multiple antennas and the raster model in the geographic information system (GIS, vertical view); 1c) Illustration of EMF exposure in the non-cumulative and cumulative models.

carries a single exposure estimate. The exposure for each pixel was calculated using the distance from pixel to antenna, and the angle of emission (azimuth) with an opening angle in a horizontal level of 120° (Fig. 1b). The following exposure formula was used to calculate the electromagnetic field exposure (E), expressed in volts per meter (V/m), as a function of the power ($EIRP$) in watts and the distance (d) in meters.

Exposure formula:

$$E = \frac{\sqrt{30 \times EIRP}}{d}$$

The quadratic sum of the exposure (E_{Total}) was calculated to consider emissions from multiple antennas (superimposed UHF-EMF emissions) (Fig. 1b).

Quadratic sum formula:

$$E_{Total} = \sqrt{E_1^2 + E_2^2 + ...E_n^2}$$

We analyzed two theoretical models, namely, a non-cumulative model that measures the exposure in a specific time regardless of the past exposure (expressed as V/m), and a cumulative model that computes time-resolved exposure by considering the previous exposure per year (V/m per year). The exposure period was censored three years prior to the individual ALS diagnosis to ensure temporality (i.e., exposure precedes the outcome). Exposure was estimated for each ALS case individually in both models (Fig. 1c).

Geocoding was used to determine the residency of ALS cases through the French System of Coordinates (RGF93) (IGN). The number of annual expected cases per town was proportionally assigned to each residential building according to the surface area.

2.4.5. Association model

The geographic information system integrated three layers: the raster model of exposure to UHF-EMFs, the residential distribution of observed ALS cases, and the estimated residential distribution of expected ALS cases in the population. The analysis was carried out in each pixel (50 m by 50 m) of the GIS for each year. The level of UHF-EMF exposure was classified into five categories for this analysis. A non-exposure category was established for expected ALS cases, and then an equal distribution in the frequency of expected cases was used to decide the different exposure categories. SIRs with 95% CIs were estimated using an exact method for calculating the CI of a Poisson parameter. The relative risk (RR) with 95% CI was calculated by considering the number of observed ALS cases, and the number of PYFU non-exposed and exposed to EMF. A generalized linear model, specifically a Poisson regression, was performed to test the association between the number of incidence cases and exposure to UHF-EMFs. As the cumulative and non-cumulative models were non-nested, the Vuong test was used to compare their goodness of fit (Vuong, 1989).

2.5. Ethical considerations

The FRALim register was approved by the CNIL (Commission Nationale de l'Informatique et des Libertés) and an ethics review board (Comité de Protection des Personnes Sud-Ouest Outre Mer).

3. Results

3.1. ALS incidence

Overall, 312 ALS cases were included for the study period (Fig. 2). The crude ALS incidence per 100,000 PYFU for the Limousin region was 3.29 (95% CI: 2.92–3.65). The age-sex standardized incidence was 2.66 (95% CI: 2.36–2.96) based on the 2010 French population, and 2.30 (95% CI: 2.03–2.57) based on the 2010 US population.

3.2. Demographic and clinical characteristics of ALS cases

A slightly higher male proportion was observed with a male/female sex ratio of 1.31. The median age at onset was 69.0 years (IQR: 61.0–76.0 years). The median diagnosis delay was 8.0 months (IQR: 5.0–12.0 months), hence the median age at diagnosis was 70.0 years (IQR 62.0–76.7 years). Bulbar onset was found in 32.7% of cases. Most incident cases were probable ALS at the time of diagnosis (35.6%). The demographic and clinical characteristics of cases are shown in Table 1 (first column).

3.3. Spatiotemporal and spatial analyses of ALS cases

We have performed spatiotemporal and spatial analyses to assess potential clusters of ALS cases in the region with Kulldorff's scan statistic. There were no statistically significant clusters. The analyses are shown in the supplementary table e-1.

3.4. GSM antennas and UHF-EMF exposure

The number of GSM antennas increased sharply over the study period. After the first antenna installation in the region (1991), the number of GSM antennas increased to 8635 in 2009 (Fig. 2).

The estimated UHF-EMF exposure ranged from 0.00 to 2.81 V/m in the non-cumulative model and from 0.00 to 6.75 V/m/year in the cumulative model. The model estimated an exposure of below 1.72 and 1.23 V/m in urban and rural areas, respectively, for 90% of the population.

3.5. Association of ALS with electromagnetic fields

As shown in Fig. 3a, there was a progressive rise in the SIR with increases in the category of exposure in the non-cumulative model. A relative risk of 1.55 (95% CI: 1.20–2.01) was estimated for every 1 V/m increase in UHF-EMF exposure with a significant p-value for the trend ($p = 0.0008$). A gradient effect was apparent when exposure was categorized. ALS risk was significantly different in the non-exposed category compared to the three higher exposure categories. Subjects exposed to UHF-EMFs ranging from 0.63 to 2.81 V/m had a 78% (RR 95% CI: 1.28–2.48) increased risk as compared to those exposed to 0.0 V/m.

In the cumulative model, the SIR increased progressively and a gradient effect was also observed. A relative risk of 1.32 (95% CI: 1.13–1.54) was estimated for every 1 V/m/year increase in UHF-EMF exposure with a significant p-value for the trend ($p = 0.0005$). In the categorical analysis, a statistically significant risk was found after comparing the non-exposure category and higher exposure categories. Subjects exposed to UHF-EMFs ranging from 0.89 to 6.75 V/m/year had an 83% increased risk (RR 95% CI: 1.32–2.54) compared to those exposed to 0.0 V/m/year (Fig. 3b).

We did not observe over-dispersion in either the non-cumulative model ($\varphi = 1.42$) or the cumulative model ($\varphi = 1.28$). The adequate fit was not rejected in either of the two models (non-cumulative model, $p = 0.234$ and cumulative model, $p = 0.277$). There was not a significant difference between the two models (Vuong test, $p = 0.177$).

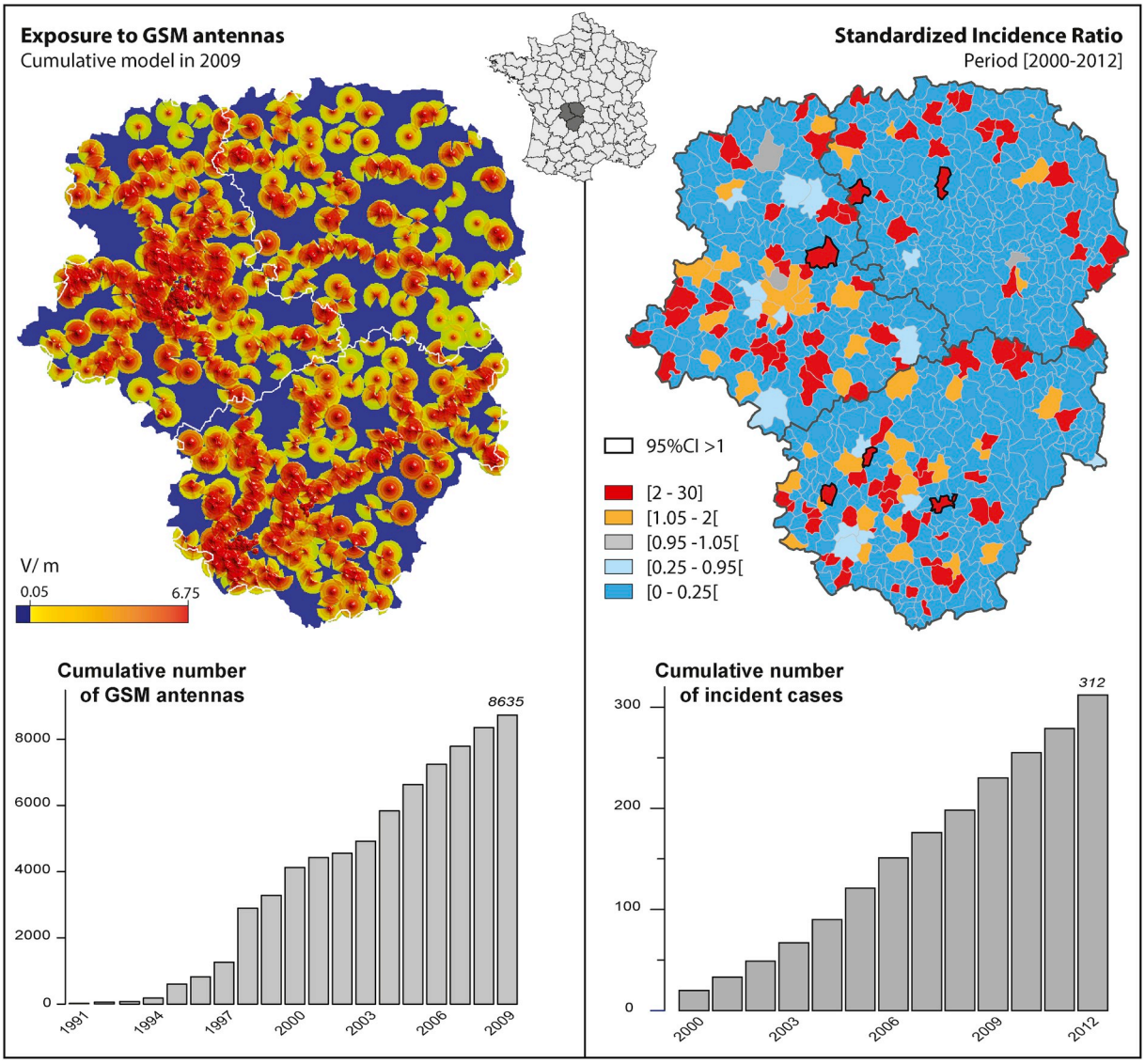


Fig. 2. Cumulative number of GSM antennas and amyotrophic lateral sclerosis (ALS) cases in the region.

3.6. ALS cases characteristics and survival in relation with UHF-EMF exposure

3.6.1. Demographic and clinical characteristics in relation with UHF-EMF exposure

There were no statistically significant differences between the residential UHF-EMF exposure categories (V/m) concerning demographic characteristics such as gender, age at onset and age at diagnosis. In the highest exposed category, a greater proportion of ALS cases were found in urban areas compared to rural areas, $p < 0.0001$ (Table 1a). No significant differences were found between the UHF-EMF exposure categories for the clinical features of ALS cases (i.e., onset site, Airlie House criteria, ALSFRS-R, and muscular testing; Table 1b).

3.6.2. Survival in relation with UHF-EMF exposure

A total of 253 ALS incidences were fatal cases. The crude mortality rate was 81 per 100 person-years. The median survival duration after onset was 26.0 months (95% CI: 22.6–29.4 months), while the median survival duration after diagnosis was 15.0 months (95% CI: 12.7–17.3 months). We found no statistically significant difference between the level of exposure to UHF-EMFs and survival times after onset (log rank $p = 0.690$, Breslow (Generalized Wilcoxon) $p = 0.430$, Tarone-Ware $p = 0.469$), and after diagnosis (log rank $p = 0.667$, Breslow (Generalized Wilcoxon) $p = 0.593$, Tarone-Ware $p = 0.594$). In the Cox proportional hazard model, exposure was not associated with survival duration after either onset ($p = 0.490$) or diagnosis ($p = 0.620$). Adjusted hazard ratios (on age, sex, and clinical characteristics) did not exhibit significant differences between the non-exposure category and the higher exposure categories (Table 1c).

4. Discussion

This study was conducted to assess the potential health risks of exposure to EMFs emitted by GSM antennas in the general population. Our study showed an association between ALS risk and residential exposure to UHF-EMFs. A gradient effect was observed with a statistically significant trend in both models. When we categorized the exposure, the differences in risk between the non-exposed category and the higher exposure categories were significant.

4.1. Exposure model

The French National Agency of Radio Frequencies technical guide (2009) was used as a reference to establish the parameters in the model

Table 1
Demographic, clinical and survival characteristics of ALS cases and their relationships with residential ultra-high frequency electromagnetic field (UHF-EMF) exposure.

	EMF exposure, V/m						
	Overall (n = 312)	Category 1 [0.0 V/m] (n = 72)	Category 2 [0.05–0.14 V/m] (n = 48)	Category 3 [0.14–0.31 V/m] (n = 60)	Category 4 [0.31–0.63 V/m] (n = 62)	Category 5 [0.63–2.81 V/m] (n = 70)	p-value
1a. Demographic characteristics							
Gender, n (%)							
Male	177 (56.7)	47 (65.3)	30 (62.5)	37 (61.7)	29 (468)	34 (48.6)	0.100 [a]
Female	135 (43.3)	25 (34.7)	18 (37.5)	23 (38.3)	33 (52.2)	36 (51.4)	
Sex Ratio, M/F	1.3	1.9	1.7	1.6	0.9	0.9	
Residential area, n (%)							
Urban	121 (38.8)	7 (9.7)	6 (12.5)	18 (30.0)	31 (50.0)	59 (84.3)	< 0.0001 [a]
Rural	191 (61.2)	65 (90.3)	42 (87.5)	42 (70.0)	31 (50.0)	11 (15.7)	
Age at onset, years[g]							
Median (IQR)	69.0 (61.0–76.0)	67.0 (58.0–76.0)	68.0 (62.0–74.0)	67.5 (59.0–76.0)	68.5 (60.5–75.7)	70.0 (63.0–77.7)	0.606 [b]
Age at diagnosis, years							
Median (IQR)	70.0 (62.0–76.7)	68.5 (59.2–77.0)	69.5 (62.5–75.0)	68.5 (61.2–76.7)	69.0 (62.0–76.0)	71.0 (64.0–78.0)	0.738 [b]
1b. Clinical characteristics							
Onset site, n (%)[g]							
Spinal	210 (67.3)	49 (68.1)	28 (58.3)	43 (71.6)	40 (64.5)	50 (71.4)	0.549 [a]
Bulbar	102 (32.7)	23 (31.9)	20 (41.7)	17 (28.3)	22 (35.5)	20 (28.6)	
Diagnostic delay, months[g]							
Median (IQR)	8.0 (5.0–12.0)	8 .0 (5.0–12.0)	8.0 (5.0–14.0)	7.0 (4.0–12.0)	9.0 (4.2–15.0)	8.0 (4.0–12.0)	0.853 [b]
Airlie House Criteria, n (%)							
Definite	53 (17.0)	15 (20.8)	8 (16.7)	7 (11.7)	12 (19.4)	11 (15.7)	0.840 [a]
Probable	111 (35.6)	22 (30.6)	22 (45.8)	24 (40.0)	20 (32.3)	23 (32.9)	
Probable with lab	49 (15.7)	12 (16.7)	7 (14.6)	7 (11.7)	11 (17.7)	12 (17.1)	
Possible	99 (31.7)	23 (31.9)	11 (22.9)	22 (36.6)	19 (30.6)	24 (34.3)	
ALSFRS-R[g]							
Median (IQR)	32.0 (27.7–35.0)	33.0 (24.0–35.0)	32.0 (27.7–36.0)	32.5 (28.7–36.0)	31.0 (28.0–35.0)	31.5 (28.0–34.0)	0.869 [b]
Muscular Testing[g]							
Median (IQR)	132.0 (116.0–143.2)	129.0 (116.2–142.0	135.0 (120.2–144.7)	132.0 (121.0–144.0)	135.0 (110.2–144.7)	134.0 (114.0–143.0)	0.806 [b]
1c. Survival characteristics							
Survival after onset, months[g]							
Median survival (95% CI)	26.0 (22.6–29.4)	33.0 (24.6–41.4)	27.0 (16.7–37.3)	32.0 (18.5–45.5)	24.0 (18.8–29.1)	23.0 (18.4–27.6)	0.690 [c]
							0.430 [d]
							0.469 [e]
aHR (95% CI)		1.00	1.21 (0.80–1.83)	1.14 (0.76–1.71)	0.94 (0.63–1.40)	1.29 (0.88–1.89)	0.490 [f]
Survival after diagnosis, months							
Median survival (95% CI)	15.0 (12.7–17.3)	16.0 (9.1–22.9)	14.0 (8.6–19.4)	18.0 (14.9–21.1)	13.0 (8.8–17.1)	13.0 (9.9–16.1)	0.667 [c]
							0.593 [d]
							0.594 [e]
aHR (95% CI)		1.00	1.15 (0.76–1.75)	1.13 (0.76–1.68)	1.11 (0.75–1.65)	1.36 (0.93–1.98)	0.620 [f]

AFSFRS-R, ALS Functional Rating Scale Revised; aHR, adjusted Hazard Ratio (adjusted by age, sex, onset site, and Airlie House criteria); IQR, interquartile range; M/F, male/female.

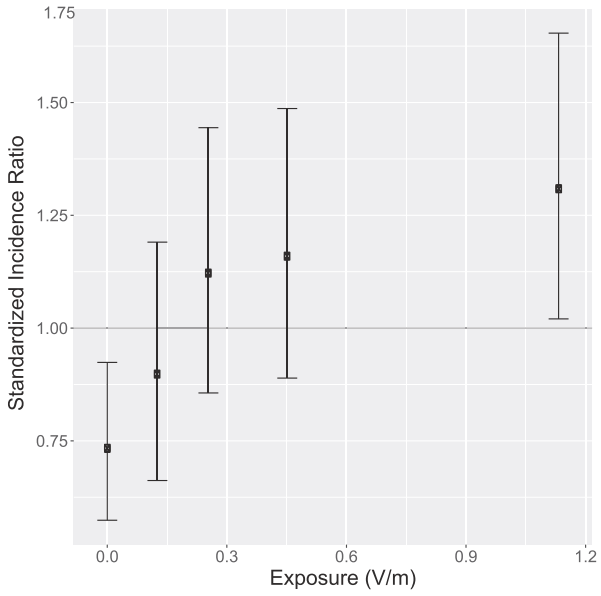
[a] Chi-square test.
[b] Kruskal Wallis.
[c] Log Rank test.
[d] Breslow (Generalized Wilcoxon).
[e] Tarone-Ware.
[f] Cox proportional-hazards model.
[g] Missing data: age at onset (n = 8), type of onset (n = 1), diagnostic delay (n = 8), ALSFRS-R (n = 154), muscular testing (n = 50).

(Agence nationale des fréquences, 2009). Our exposure estimations were consistent with an official report on electromagnetic waves emitted by mobile telephone base stations (Ministère de l'écologie, du développement durable et de l'énergie), published in 2013 by the French Department for the Prevention of Risks and the French National Agency of Radio Frequencies. This report predicted EMF exposures below 2.4 V/m in urban areas and 0.7 V/m in rural areas for 90% of the population, based on measurements and estimations of EMFs emitted by mobile antennas across the country. Our model estimated an exposure below 1.72 V/m in urban areas and 1.23 V/m in rural areas for 90% of the population. We hypothesize that the individual exposure to EMFs could be higher, for example through the individual use of mobile phones and other sources of UHF-EMFs and low frequency-EMFs (LF-EMFs) (television sets, Wi-Fi, microwave ovens, etc …).

The theoretical model assumes that the GSM antennas transmit at the same time, continuously and at full power, which could certainly overestimate the actual exposure. Nevertheless, our EMF estimations were extremely low compared to the regulatory limit values for frequencies used by GSM antennas in France, which are 41 V/m for GSM 900 and 58 V/m for GSM 1800, according to the National Institute for Industrial Environment and Risks (Ineris) (Service National d'Assistance sur les Champs Electromagnétiques SNA CEM).

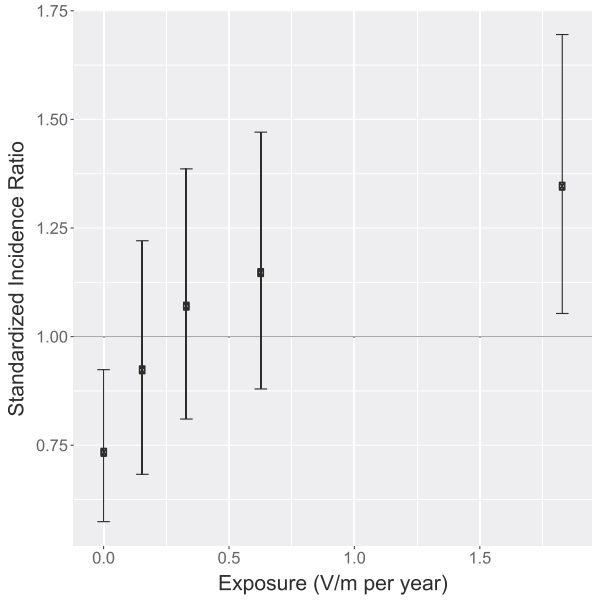
The residential exposure seemed to differ between urban and rural areas, which was related to the density and the power of the antennas in each area. We observed a higher proportion of ALS cases in the highest exposure category in urban areas. We verified that there was no

a)



Exposure (V/m)	Observed cases	Expected cases	SIR	(95% CI)	RR	(95% CI)
0.00	72	98.13	0.73	(0.57 – 0.92)	1.00	(0.72 – 1.39)
0.05 – 0.14	48	53.45	0.90	(0.66 – 1.19)	1.22	(0.85 – 1.76)
>0.14 – 0.31	60	53.48	1.12	(0.86 – 1.44)	1.53	(1.09 – 2.15)
>0.31 – 0.63	62	53.46	1.16	(0.89 – 1.49)	1.58	(1.13 – 2.22)
>0.63 – 2.81	70	53.48	1.31	(1.02 – 1.65)	1.78	(1.28 – 2.48)

b)



Exposure (V/m) per year	Observed cases	Expected cases	SIR	(95% CI)	RR	(95% CI)
0.00	72	98.13	0.73	(0.57 – 0.92)	1.00	(0.72 – 1.39)
0.05 – 0.19	49	53.07	0.92	(0.68 – 1.22)	1.26	(0.88 – 1.81)
>0.19 – 0.40	57	53.28	1.07	(0.81 – 1.39)	1.46	(1.03 – 2.06)
>0.40 – 0.89	62	54.04	1.15	(0.88 – 1.47)	1.56	(1.11 – 2.20)
>0.89 – 6.75	72	53.48	1.35	(1.05 – 1.70)	1.83	(1.32 – 2.54)

Fig. 3. Association between EMFs and ALS. a) Non-cumulative model; b) Cumulative model.

interaction between UHF-EMFs and location (urban/rural area) in both the non-cumulative ($p = 0.117$) and cumulative models ($p = 0.136$).

4.2. Studies on electromagnetic fields and neurodegenerative disorders

EMFs can be broadly divided into low frequency and high frequency magnetic fields. The main sources of LF-EMFs include power lines, household electrical appliances, and computers. Sources of high frequency EMFs include radar, radio, television broadcast facilities, and mobile telephones and their base stations (World Health Organization, 2002). Several studies have been performed to evaluate the potential associations between neurodegenerative disorders and extremely low frequency electromagnetic Fields (ELF-EMFs). On the other hand, UHF-EMFs have rarely been studied as a potential risk factor for neurodegeneration.

Studies have assessed residential exposure to extremely low frequency electromagnetic Fields (ELF-EMFs) from power lines and their potential associations with neurodegenerative diseases. There are conflicting results on this subject. A Swiss population study showed an increased risk of death from Alzheimer's disease and senile dementia for persons who lived within 50 m of a power line (Huss et al., 2009). Persons living within 50 m of a power line for at least five years had an adjusted hazard ratio of 1.51 (95% CI: 0.91–2.51), increasing to 1.78 (95% CI: 1.07–2.96) for > 10 years and to 2.00 (95% CI: 1.21–3.33) for > 15 years of residence in the vicinity of power lines. A Danish population study reported no increased risks of developing Alzheimer's disease (aHR 1.04, 95% CI: 0.69–1.56), Parkinson's disease (aHR 1.14, 95% CI: 0.79–1.64), multiple sclerosis (aHR 1.03 CI: 0.67–1.58), or motor neuron disease (aHR 0.80, 95% CI: 0.34–1.89) for persons living within close vicinity of a power line (< 50 m) in comparison to persons living further away (> 600 m) (Frei et al., 2013). A specific study was performed on ALS risk and residential exposure to ELF-EMFs from power lines in the Netherlands (Seelen et al., 2014). The researchers found no increased risk of ALS in persons living within close vicinity of a power line. An overall odds ratio of 0.90 (95% CI: 0.73–1.10) was estimated for subjects living < 200 m away in comparison to ≥200 m away from high voltage power lines. However, the number of participants living in close vicinity to power lines was low. Occupational exposure to ELF-EMFs has been associated with higher ALS risk. A recent meta-analysis supported a slightly increased ALS risk among occupational exposure to ELF-EMFs (RR = 1.29, 95% CI: 1.02–1.62) (Zhou et al., 2012), including electrical power engineers, electricians, and workers operating other electrical equipment such as welders, carpenters, or machinists.

ALS was first described by Jean-Martin Charcot in the 19th century, which implies that the disease was already present prior to modern telecommunications and, thus, EMF exposure from GSM antennas. Interestingly, several studies suggest increases in ALS incidence and mortality rate have occurred over the last few decades (Murphy et al., 2008; Seljeseth et al., 2000). In Norway, ALS mortality between 1951 and 2014 showed a statistically significant trend ($p < 0.001$) with a mean annual increase of 1.14% (Nakken et al., 2016). This phenomenon could be related to better case ascertainment or an escalation of potential environmental risk factors. EMFs might be a trigger for the development of ALS in persons with a predisposed genetic susceptibility. The increase in epidemiological indicators needs to be confirmed, including their potential relationships with changing environmental factors.

4.3. Causality criteria

To discuss the issue of a potential causal relationship, we have taken into account the Bradford Hill criteria (Höfler, 2005). First, a moderate association was found with a RRs of 1.55 and 1.32 for every 1 V/m EMF exposure increase in the non-cumulative and the cumulative models, respectively. Second, a dose-response effect was apparent between UHF-EMF exposure and ALS risk. The trend was statistically significant in both models. Third, we censored the EMF exposure three years prior to the individual ALS diagnoses to ensure temporality. Fourth, ALS is considered a complex disease that might be determined by multifaceted exposures and genetic interactions. Specificity criteria are not satisfied. If EMF plays a role in the occurrence of ALS, it does not seem to be the only contributing factor. Fifth, researchers have described several biological responses to EMF exposure that could play a role in ALS incidence rates, although the evidence is still controversial. High frequency (HF)-EMFs can induce thermal effects and non-thermal effects. The thermal effects occur through transfer of EMF energy to biological matter, leading to increases in average temperature through the vibration of atoms and molecules (Consales et al., 2012). The non-thermal effects include oxidative stress (Irmak et al., 2002; Kovacic and Somanathan, 2010), and alterations to the permeability of the blood-brain barrier (Stam, 2010). Further research is needed to clarify the effects and interactions of UHF-EMFs in biological systems. Sixth, it is difficult to establish coherence and consistency criteria after taking into account the conflicting evidence and the knowledge gaps surrounding the potential health consequences of EMFs. Seventh, there are no epidemiological studies assessing ALS risks after the cessation of EMF exposure, which may support the experimental criteria for a causal relationship. Eighth, evidence shows an increased risk for occupational exposure to ELF-EMFs and the occurrence of ALS. Based on analogous criteria, researchers should be more open to accepting evidence that a similar agent may cause a similar disease (Fedak et al., 2015). At this stage, it is difficult to conclude whether there is a causal relationship between EMF exposure and ALS.

4.4. Limits and strengths

There are some limitations to this study. First, it is difficult to estimate EMF exposure accurately. GSM antennas are continuously transmitting signals; however, EMF exposure may vary widely and is related to the number of calls made and the number of users connected. Furthermore, there are no reference parameters for modelling UHF-EMF exposure. In an effort to control these issues, we used the French National Agency of Radio Frequencies technical guide as a reference and the estimations in our study were consistent with an official report on UHF-EMF exposure in France. Second, a complete residential history of ALS cases was not available. For individual cases, we were not able to ensure that persons lived in the same place after diagnosis, which gives rise to concerns about whether individual exposure estimations were accurate if the patients did change their residency. Third, the model only took into account EMFs emitted by unidirectional antennas (i.e., omnidirectional antennas were not considered), which could result in the underestimation of EMF exposure in our models. Fourth, GSM antennas were considered as an overall network without distinction between 2G (Second Generation) and 3G (Third Generation) mobile networks. Lastly, our two-dimensional model was suitable for EMF emissions in a free field, which is likely to be the case in rural environments but much less so in urban environments. A 3D model of exposure, including a digital model of the ground, the elevation of the buildings, the height, and the tilt of the antennas, could improve the spatial estimation of EMF exposure. Additionally, a model considering different sources of EMFs and other environmental expositions could clarify the interactions of environmental factors on ALS incidence.

Our work relies on certain strengths. First, ALS case ascertainment was performed through a population-based register. Second, geocoding was used to determine the residency of ALS cases through geo-localization software. Third, the number of expected cases was calculated by taking into account age and sex of the population per year in each area. Fourth, the geographical modelling of expected cases was performed according to the age, sex, and spatial distribution of the population based on the coordinates of residential buildings. Fifth, we collected reliable data from official institutions in the country, including the

French National Agency of Radio Frequencies for GSM antenna data, the National Institute of Statistics for the population distribution, and the French National Institute of Geography for residential building and cartographic information. Sixth, our exposure estimates were consistent with an official French report on exposure to electromagnetic waves emitted by GSM antennas. Seventh, we censored the exposure to consider the temporality criteria. Lastly, exposure was calculated in a geographic region of 16,942 km^2 and divided into pixels (50 m by 50 m) that accounted for multiple emission sources, and population was assigned proportionally to the total surface area of the residential building areas in each town per year.

4.5. Public health implications and future research

The French Agency for Food, Environmental, and Occupational Health & Safety (ANSES) reported that there is insufficient evidence on the potential risk of radio frequencies in relation to neurological disorders such as ALS (ANSES, 2013). This study was developed as a public health response to assess the potential risk of UHF-EMFs. Here, we estimated the exposure risk over short and long time periods in a general population context.

A major knowledge gap needs to be filled, namely the potential health consequences of EMFs produced by mobile communications. It is essential to evaluate the potential risk of the entire EMF spectrum to ensure safe use of modern technologies. Ecological studies generate hypotheses rather than definitive evidence of association; hence, our results need careful interpretation. Given that ALS is a complex process of motor neuron degeneration that could result from genetic and environmental factors. It is difficult to assess the impact of potential confounding factors specially using an ecological approach. EMFs might trigger neurodegeneration in persons with genetic susceptibility. Further studies are needed to clarify the potential role of EMFs on neurodegeneration considering individual exposure and potential confounding factors.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethics committee approval

The FRALim register was approved by the CNIL (Commission Nationale de l'Informatique et des Libertés) and an ethics review board (Comité de Protection des Personnes Sud-Ouest Outre Mer).

CRediT authorship contribution statement

Jaime Luna: Formal analysis, Methodology, Writing - original draft, Writing - review & editing. **Jean-Philippe Leleu:** Conceptualization, Formal analysis, Methodology, Writing - review & editing. **Pierre-Marie Preux:** Supervision, Validation, Writing - review & editing. **Philippe Corcia:** Writing - review & editing. **Philippe Couratier:** Data curation, Writing - review & editing. **Benoit Marin:** Data curation, Formal analysis, Methodology, Validation, Writing - review & editing. **Farid Boumediene:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.108525.

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