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Living near waterbodies as a proxy of cyanobacteria exposure and risk of amyotrophic lateral sclerosis: a population based case-control study

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ABSTRACT

Background: Epidemiological studies highlighted the possibility that exposure to cyanotoxins leads to the development of the neurodegenerative disease amyotrophic lateral sclerosis (ALS).
Methods: We devised a population-based case-control study in two Italian populations. We used residential proximity of the residence to water bodies as a measure of possible exposure to cyanotoxins.
Results: Based on 703 newly-diagnosed ALS cases and 2737 controls, we calculated an ALS odds ratio (OR) of 1.41 (95% CI: 0.72–2.74) for current residence in the vicinity of water bodies, and a slightly lower estimate for historical residence (OR: 1.31; 95% CI: 0.57–2.99). Subjects <65 years and people living in the Northern Italy province of Modena had higher ORs, especially when historical residence was considered.
Conclusions: Overall, despite some risk of bias due to exposure misclassification and unmeasured confounding, our results appear to support the hypothesis that cyanotoxin exposure may increase ALS risk.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of the upper and lower motor neurons, which leads to muscle weakness and eventual paralysis (Couratier et al., 2016; Kiernan et al., 2011; Salameh et al., 2015; Zufiría et al., 2016). ALS is classified into familial and sporadic forms: according to Masseret et al. the former represents 4–8% of total ALS cases (Masseret et al., 2013); the latter is much more common and its incidence in Europe is 2–3 cases per 100.000 person-years, with heterogeneous distribution worldwide (Couratier et al., 2016; Marin et al., 2017).

In the last decades, the incidence of ALS has increased in Western countries (Al-Chalabi and Hardiman, 2013; Couratier et al., 2016), including Italy (Bonvicini et al., 2008; Georgoulopoulou et al., 2011; Nicoletti et al., 2016; Scialò et al., 2016; Tesauro et al., 2017). While the association of genetic factors involved in ALS etiology has been determined, the role of environmental factors is still largely unknown (Couratier et al., 2016; Factor-Litvak et al., 2013; Ingre et al., 2015; Riancho et al., 2018; Rooney et al., 2016; M. Vinceti et al., 2012).

Several environmental risk factors are thought to be associated with ALS onset, especially intense physical activity, trauma, exposure to pesticides, heavy metals and selenium (Filippini et al., 2020; Ingre et al., 2015; Schwartz et al., 2017; Marco Vinceti et al., 2012a; M.

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Vinceti et al., 2012; Vinceti et al., 2019, 2017c, 2017a; Zufiría et al., 2016). Moreover, a group of substances has been suggested as an important environmental risk factor for ALS development: cyanotoxins (Spencer et al., 1987c, 1987b, 1987a, Banack et al., 2007; Cox et al., 2005; Cox et al., 2018; Murch et al., 2004). These toxins are produced as a secondary metabolite by cyanobacteria, and they have been associated with ALS/Parkinson's Dementia Complex (ALS/PDC) and other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (Cox et al., 2016; Lemere et al., 2004; Rodgers et al., 2018). In the last few years, the role of the cyanotoxin β-Methylamino-L-Alanine (BMAA) as a potential contributing factor for ALS has been in-depth investigated, and evidence supporting a causal relation with the disease onset was observed (Banack et al., 2015; Caller et al., 2018; Cox et al., 2018; Delcourt et al., 2018; Masseret et al., 2013; Tan et al., 2018a; Bradley et al., 2018; Torbick et al., 2018; Davis et al., 2020). This association was first observed in the island of Guam (Pacific Ocean), in local Chamorro people, as a result of BMAA accumulation in the food chain from seeds and fruits of cycad tree with cyanobacterial root symbionts (Cox et al., 2005). Consumption of flying foxes and other feral animals feeding on cycad seeds by the local population has been proposed as the main mechanism of exposure (Cox et al., 2003; Cox and Sacks, 2002). BMAA exposure has been also correlated to an increase of incidences of ALS/PDC in the Kii peninsula of Japan and in the Irian Jaya of New Guinea (Spencer et al., 1987c, 1987b; 1987a). Moreover, trace amounts of BMAA were found in post-mortem brain samples from patients who had been diagnosed with ALS/PDC (Murch et al., 2004) and have been detected in human cerebrospinal fluid samples from both ALS and controls (Berntzon et al., 2015).

The purpose of this study was to investigate the association between cyanotoxins exposure and ALS risk in two Italian populations.

2. Materials and methods

2.1. Study population

After receiving the approval by the Ethics Committees of the Modena and the Catania provinces, we carried out a population-based case-control study to examine the role of environmental risk factors in ALS etiology, whose methodology has already been described in detail [(Vinceti et al., 2017a, 2017b). Briefly, we attempted to identify all newly-diagnosed cases of ALS in the period between 1998 and 2011 among residents in the provinces of Parma, Reggio-Emilia and Modena, of the Emilia-Romagna region in Northern Italy, and in the province of Catania, of the Sicily region in Southern Italy. These provinces include an overall population of approximately 3,000,000. We used several administrative data sources to identify newly-diagnosed patients in these provinces (Mandrioli et al., 2014; Nicoletti et al., 2016): the ALS Emilia-Romagna Registry (established in 2009), and for both the Emilia-Romagna and Sicily regions the hospital discharge directory, the drug prescription directory and the death certificates. We included in the study only “definite” and “probable” ALS cases, as determined by using El Escorial revised criteria (Brooks et al., 2000).

For each enrolled patient, we randomly selected four controls from the database of Local Health Authority Registries, which includes all Italian residents. Every control was individually matched to patients by sex, year of birth and province of residence and wherever possible calendar year of resident directory.

2.2. Exposure assessment

We obtained data regarding location and geocoding of water bodies in the Catania province from the Department of Urban Planning - Territorial Information Systems and Cartography of the Sicily Region and from the Department of Agriculture of the Emilia-Romagna Region. We included all water bodies with the exception of the saline ones in the Catania area, because no subjects were living in their proximity, and the ones smaller than 10 m^2. We defined “water bodies density” as the presence of water bodies within a circular 100 m zone around each participant's residence.

We inserted these geocoded data into a GIS (*Geographic Information System*) along with georeferenced subjects' residences, using the ARC-GIS software (version 10, ESRI, Redlands, CA, 2010).

We used the proxy variable of land use and specifically water bodies density close to the subject's home assuming that cyanotoxins drift and their aerial spreading may lead to residential exposure (Bradley et al., 2018; Stommel et al., 2013).

We ascertained the residential address of cases at date of diagnosis and of their matched controls, in addition to their oldest demonstrable residence for which exposure data were also available (“historical residence”), as long as the aforementioned residence was consequently stable for at least two years. If this was not the case, the subject was excluded from the historical analysis. To obtain this historical residence, we used the Ministry of Finance Revenue Agency database, starting from December 1979 for the Modena, Reggio Emilia and Parma residents, and from December 1989 for Catania.

Participants' addresses were geocoded using the database available at the Province Authorities of Modena, Reggio Emilia, Parma and Catania (Malagoli et al., 2010; Marco Vinceti et al., 2012b; Vinceti et al., 2017a). For geographic coordinates that could not be found in these databases (around 10%), we geocoded using Google Earth, and for the few participants for whom the geographic coordinates could still not be found (N = 120), we directly geocoded them *in loco* using a portable GPS device (Garmin GPSmap 60CSx, Garmin Int. Corp., Olathe, KS). We included all geocoded information into the GIS.

2.3. Data analysis

We used crude and multivariable-adjusted logistic regression models to estimate odds ratios (ORs) with their 95% confidence intervals (CIs) of ALS according to current exposure at diagnosis and historical exposure to estimated cyanotoxin drift from water bodies. Adjustments were done for age, sex, province and total agricultural land use. Moreover, we carried out stratified analyses for sex, age, and residence area. We used Stata Software (v16.1, Stata Corp, TX, 2019) for data analysis. As regards to age category, we set a 65 years cut-off, the median age of onset for sporadic ALS (Chiò et al., 2013) in order to differentiate cases possibly carrying gene mutations that increased ALS susceptibility and characterized by an earlier age of onset (Zufiría et al., 2016).

3. Results

Data concerning study population are shown in Fig. 1. Ultimately, 703 cases and 2737 controls were included in the study. During the study period, 537 cases and 2049 controls were found to be resident in the study area since 1976 for the Emilia-Romagna region and 1989 for Sicily, so they could be maintained in the historical analysis.

The distribution of age, sex and province of residence of study participants is reported in Table 1.

Exposed controls are slightly older than exposed cases. More than half of non-exposed cases are older than 65 years. Fifty-two percent of patients were male and the majority of them (97.8%) were born in Italy.

The relative risk of ALS related to the presence of water bodies in the proximity of subjects' residence at diagnosis, as estimated through the OR, is reported in Table 2. Considering age, there was a statistically imprecise increased risk in subjects aged less than 65 years, especially in model 2 (OR = 1.64; 95% CI = 0.62–4.36). The analysis by province of residence at the time of diagnosis shows an increased risk associated to water bodies in the vicinity of residence for people living in Emilia-Romagna (OR 1.53; 95% CI 0.58–4.04), especially in the province of Modena and particularly in the most adjusted model.

The distribution of age, sex and province of residence of study

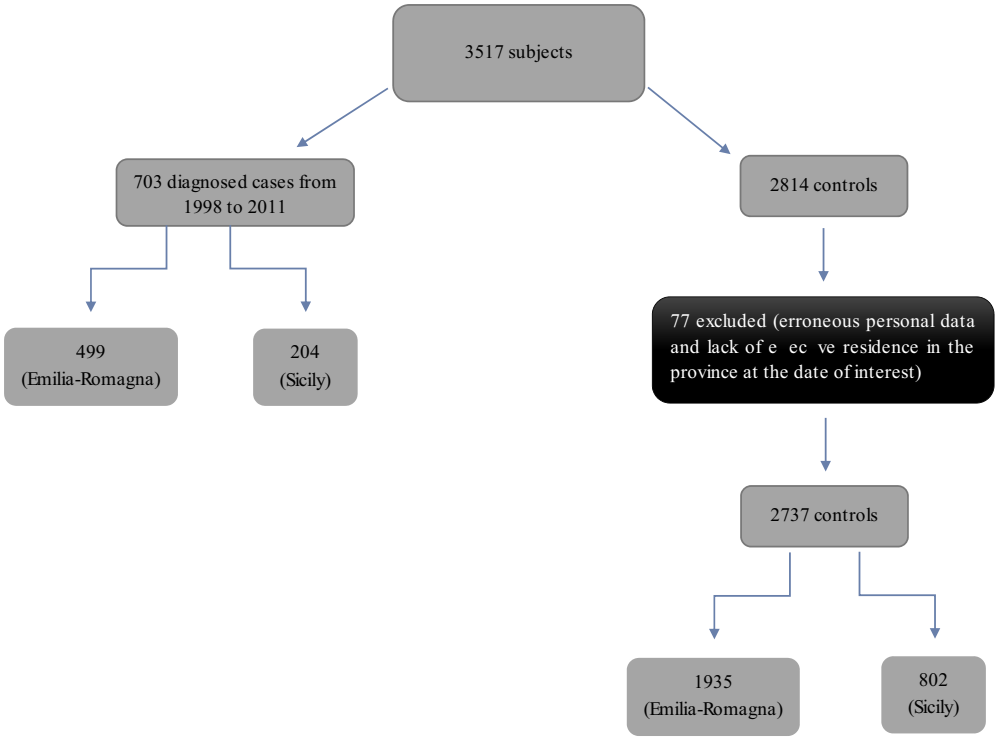

Fig. 1. Flowchart of the study participants.

participants for historical exposure is reported in Table 3.

When considering historical exposure, age less than 65 years was confirmed as a risk factor. The risk of ALS related to residential proximity to water bodies in the previous 30 years is reported in Table 4. Similarly to Table 2, adjusted estimates were not substantially different from crude ones. Proximity to water bodies in subjects <65 years was associated to a much higher excess ALS risk compared with the analysis based on current exposure, especially in the adjusted models. The province of Modena has the highest risk of ALS associated with historical residence near water bodies compared to the others.

4. Discussion

The present study was devised to assess the hypothesis that residence near water bodies, likely associated to an increased exposure to cyanotoxins, may be associated with an increased risk of ALS. Our results showed an increased risk of ALS in subjects residing within 100 m from water bodies, both for historical and concurrent exposure at the time of diagnosis. The risk seems to be modified by sex, age and province of residence. On the other hand, when considering historical residence, women presented a higher risk of ALS compared to men. It's difficult to explain such opposite results. Possible misclassification using either current or historical residence cannot entirely be ruled out. In particular, when using historical residence for exposure assessment, we hypothesize that the during the less recent period, women were most likely to work at home/housewives compared to men most frequently used to work outside their home, thus affecting the real exposure for this latter category. Unfortunately, information about occupational exposure of study subjects was not available, due to the study design, avoiding direct contact with participants, and due to the unavailability of data from the National Social Insurance Agency. In addition, the limited number of exposed subjects suggests caution in the interpretation of such sex-specific results.

The increased risk in subjects aged less than 65 is of interest, and is

Table 1
Characteristics of study participants for exposure at diagnosis.

	Cases			Controls		
	Overall	Exposed	Non-exposed	Overall	Exposed	Non-exposed
All participants	703 (100)	12 (1.71)	691 (98.29)	2737 (100)	33 (1.21)	2704 (98.79)
Sex						
Men	365 (51.92)	6 (0.85)	359 (51.07)	1413 (51.63)	14 (0.51)	1399 (51.11)
Women	338 (48.08)	6 (0.85)	332 (47.23)	1324 (48.37)	19 (0.69)	1305 (47.68)
Median (IQR)	67 (59–75)	63 (53–68)	67 (59–75)	67 (59–75)	67 (53–71)	67 (59–75)
Age categories						
<65 years	281 (39.97)	6 (0.85)	275 (39.12)	1088 (39.75)	15 (0.55)	1073 (39.20)
≥65 years	422 (60.03)	6 (0.85)	416 (59.17)	1649 (60.25)	18 (0.66)	1631 (59.59)
Area						
Emilia-Romagna	499 (70.98)	6 (0.85)	493 (70.13)	1935 (70.70)	15 (0.55)	1920 (70.15)
Modena	235 (33.43)	5 (0.71)	230 (32.72)	905 (33.07)	8 (0.29)	897 (32.77)
Reggio Emilia	152 (21.62)	1 (0.14)	151 (21.48)	599 (21.89)	5 (0.18)	594 (21.70)
Parma	112 (15.93)	0 (0.00)	112 (15.93)	431 (15.75)	2 (0.07)	429 (15.67)
Sicily/Catania	204 (29.04)	6 (0.85)	198 (28.17)	802 (29.30)	18 (0.66)	784 (28.64)

Table 2
Risk of ALS related to water bodies density within 100 m from subjects' residence at the time of diagnosis.

	Model 1			Model 2			Model 3		
At diagnosis (buffer 100m)	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
All participants	1.41	(0-72-2.74)	0.318	1.40	(0.72–2.73)	0.322	1.39	(0.71–2.73)	0.337
Sex									
Men	1.62	(0.61–4.32)	0.333	1.68	(0.63–4.50)	0.305	1.61	(0.59–4.35)	0.350
Women	1.25	(0.50–3.13)	0.637	1.25	(0.50–3.13)	0.637	1.29	(0.51–3.27)	0.586
Age categories									
<65 years	1.56	(0.59–4.11)	0.369	1.64	(0.62–4.36)	0.320	1.56	(0.59–4.17)	0.372
≥65 years	1.28	(0.51–3.24)	0.597	1.28	(0.51–3.24)	0.596	1.36	(0.53–3.46)	0.525
By province									
Emilia-Romagna	1.54	(0.58–4.05)	0.385	1.53	(0.58–4.04)	0.386	1.65	(0.62–4.40)	0.315
Modena	2.49	(0.77–8.00)	0.126	2.48	(0.77–7.99)	0.127	2.91	(0.88–9.62)	0.080
Reggio Emilia	0.76	(0.09–6.51)	0.802	0.76	(0.09–6.52)	0.803	0.63	(0.07–5.60)	0.679
Parma	-			–			–		
Sicily/Catania	1.30	(0.52–3.28)	0.578	1.38	(0.54–3.49)	0.502	1.08	(0.41–2.82)	0.875

Model 1: crude model, matched by sex and province.
Model 2: adjusted for age (continuous) and matching variables.
Model 3: further adjusted for total agricultural land use (continuous).

Table 3
Characteristics of study participants for historical exposure.

	Cases			Controls		
	Overall	Exposed	Non-exposed	Overall	Exposed	Non-exposed
All participants	537 (100)	8 (1.49%)	529 (98.51%)	2049 (100)	21 (1.02%)	2028 (98.98%)
Sex						
Men	289 (53.82)	4 (0.74)	285 (53.07)	1117 (54.51)	11 (0.54)	1106 (53.98)
Women	248 (46.18)	4 (0.74)	244 (45.44)	932 (45.49)	10 (0.49)	922 (45.00)
Median (IQR)	68 (60–75)	64 (52–69)	68 (60–75)	68 (60–75)	67 (64–73)	68 (60–75)
Age categories						
<65 years	207 (38.55)	4 (0.74)	203 (37.80)	762 (37.19)	7 (0.34)	755 (36.85)
≥65 years	330 (60.71)	4 (0.74)	326 (60.71)	1287 (62.81)	14 (0.68)	1273 (62.13)
Area						
Emilia-Romagna	349 (64.99)	3 (0.56)	346 (64.43)	1307 (63.79)	10 (0.49)	1297 (63.30)
Modena	161 (29.98)	2 (0.37)	159 (29.61)	617 (30.11)	3 (0.15)	614 (29.97)
Reggio Emilia	112 (20.86)	1 (0.19)	111 (20.67)	418 (20.40)	6 (0.29)	412 (20.11)
Parma	76 (14.16)	0 (0.00)	76 (14.15)	272 (13.27)	1 (0.05)	271 (13.23)
Sicily/Catania	188 (35.01)	5 (0.93)	183 (34.08)	742 (36.21)	11 (0.54)	731 (35.68)

worth further investigation. It is possible that younger subjects are more susceptible to environmental risk factors such as cyanobacterial toxins, while older patients could be more likely to develop the disease as a result of age-related degenerative metabolic pathway. A higher risk at younger age could also suggest an interaction with genetic factors, and therefore a higher susceptibility of this age group, Our results are consistent with a few previous studies, which found a higher ALS risk in subjects living in the proximity of lakes containing algal blooms (Caller et al., 2009; Mello et al., 2018; Torbick et al., 2018, 2014).However, in the above-mentioned studies no stratified analysis according to age and sex was performed (Caller et al., 2009).

The mechanism underlying the possible association between

Table 4
Risk of ALS related to water bodies density within 100 m from subjects' residence in the former 30 years.

	Model 1			Model 2			Model 3		
Previous 30 years (buffer 100m)	OR	(95% CI)	P	OR	(95% CI)	P	OR	(95% CI)	P
All participants	1.31	(0.57–2.99)	0.521	1.30	(0.57–2.96)	0.538	1.30	(0.57–2.97)	0.534
Sex									
Men	1.20	(0.38–3.80)	0.752	1.26	(0.39–4.00)	0.700	1.24	(0.39–3.95)	0.720
Women	1.44	(0.44–4.74)	0.548	1.44	(0.44–4.74)	0.549	1.50	(0.45–4.97)	0.504
Age categories									
<65 years	2.08	(0.58–7.47)	0.260	2.26	(0.61–8.31)	0.221	2.26	(0.61–8.34)	0.220
≥65 years	0.96	(0.32–2.94)	0.948	0.96	(0.31–2.94)	0.946	0.96	(0.32–2.95)	0.949
Area									
Emilia-Romagna	0.95	(0.26–3.48)	0.939	0.95	(0.26–3.48)	0.938	0.96	(0.26–3.51)	0.945
Modena	2.51	(0.42–15.09)	0.313	2.51	(0.42–15.09)	0.313	2.96	(0.48–18.13)	0.241
Reggio Emilia	0.46	(0.05–3.81)	0.468	0.46	(0.05–3.81)	0.468	0.43	(0.05–3.65)	0.441
Parma	-			–			–		
Sicily/Catania	1.69	(0.57–4.98)	0.343	1.89	(0.63–5.70)	0.257	1.89	(0.63–5.70)	0.257

Model 1: crude model, matched by sex and province.
Model 2: adjusted for age (continuous) and matching variables.
Model 3: further adjusted for total agricultural land use (continuous).

cyanotoxin exposure and ALS has not been identified yet, but it could occur through ingestion of water (Caller et al., 2009; Torbick et al., 2018), consumption of contaminated food (Brand et al., 2010; Dunlop and Guillemin, 2019; Field et al., 2013; Jonasson et al., 2010; Masseret et al., 2013; Mondo et al., 2012) or inhalation through aerosolization (Stommel et al., 2013). The majority of the studies analysing the correlation between cyanotoxins and health effects did not unfortunately consider biomonitoring data. Torbick et al. verified that an increased risk of ALS was associated with ever having lived full-time within 3 km of a waterbody (OR = 1.59; 95% CI: 1.05–2.42). The link between vicinity to waterbodies and ALS risk could be due to exposure to cyanobacterial harmful algal blooms and specifically to its cyanotoxin β-Methylamino-L-Alanine (BMAA) (Bishop et al., 2018; Torbick et al., 2018). In the environment, the amino acid BMAA is released by cyanobacteria and was found in marine areas with cyanobacterial blooms in different countries of Europe, North America, Middle-East and Eastern Australia (Brand et al., 2010; Caller et al., 2009; Chatziefthimiou et al., 2018; Jonasson et al., 2010; Violi et al., 2019); for this reason, recent studies have related seafood consumption (e.g., bivalves and crustacean) to the development of several neurodegenerative pathologies (Banack et al., 2014).

Several recent studies have shown that BMAA has neurotoxic effects in animal models, as well as in vitro culture studies. It has been associated with different neurotoxic mechanisms, such as glutamate excitotoxicity (Brownson et al., 2002; Chiu et al., 2012; Lobner et al., 2007), endoplasmic reticulum stress (Okle et al., 2013), mitochondrial dysfunction (Chiu et al., 2012), oxidative damage (Laugeray et al., 2018; Okle et al., 2013; Rao et al., 2006) and toxic protein aggregation (Dunlop et al., 2013). All these mechanisms result in motor deficits, neuronal degeneration and somatic death (Duncan et al., 1992; Karlsson et al., 2015; Lewis et al., 1990; Weiss et al., 1989). In vivo, neuronal cells depend on support from glial cells and neurotrophic factors to function efficiently. A damage to glial cells from BMAA exposure results in the so-called “non-cell autonomous death”, which leads to an increased vulnerability of neurons to excitotoxic stress agents (Boillée et al., 2006). Any alteration of these neuronal support cells contributes to the development and progression of neural degeneration (Boillée et al., 2006; Cory et al., 1991; Tan et al., 2018b).

Some limitations of our study need to be acknowledged. First, the small sample size has affected the statistical precision of the risk estimates. Moreover, we did not collect biomonitoring data or water samples to validate the presence of contamination, thus hampering further assessment of the correlation between cyanotoxins and ALS risk. In addition, to locate study participants we used the “official” home address, which in some though likely few cases may differ from the actual address of residence. It might also be worth investigating a higher distance from water bodies to test the hypothesis of an effect of cyanobacterial toxin exposure on ALS risk, i.e. exposure distances grater than 100 m, under the hypothesis that toxin spread may go well beyond this cutpoint particularly in some meteorological conditions. Besides exposure misclassification, which however should have been non-differential and therefore should not have substantially biased the results, the study may have been affected by unmeasured confounding. For instance, water bodies may be the source of other contaminants of potential interest to ALS etiology, such as the neutoxic forms of selenium (Vinceti et al., 2014, 2019). The elimination of residual confounding was complicated by the limited knowledge concerning potential environmental, lifestyle, and genetic risk factors of the dissease, especially of its sporadic form. On the other hand, there was evidence that the variables used in our study for control sampling and data analyses were not important confounders (Vinceti et al., 2017a).

A major strength of this study is its population-based design; controls were recruited from the general population by randomly extracting them from Local Health Authority registries, thus limiting the occurrence of selection bias. In addition, the area covered by the study included provinces located both in the Northern and the Southern part of the country, characterized by different lifestyle, environmental exposures and probably genetic background, thus allowing us to assess factors potentially influencing disease susceptibility. Moreover, residential mobility in Italy is much lower than some other countries, thus reducing the risk of exposure misclassification compared with studies carried out in other countries (Hanada et al., 2013). Our study also considered long-term antecedent exposure to waterbodies, thus strengthening the validity of exposure assessment taking into account the nature of ALS and its likely long period of induction and latency.

5. Conclusion

Overall, using an index of environmental exposure to cyanotoxins based on proximity of residence to waterbodies in two areas of Northern and Southern Italy, we found some evidence of an association with excess ALS risk, though generally limited to youngest subjects and stronger in females, and very heterogeneous according to the province of residence. However, the interpretation of our findings is limited by the limited statistical precision of the risk estimates and some concerns about exposure assessment, thus highlighting the need for further studies on this issue.

For future policy, the implementation of environmental monitoring system in the proximity of water bodies to evaluate cyanotoxins exposure of the resident population should also be considered, making such monitoring data available for health risk assessment studies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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