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Abstract
Lyme borreliosis cases have been reported from Lombardy in northern Italy, where *Ixodes ricinus* is the main vector of *Borrelia burgdorferi* sensu lato. However, spatial and temporal variation in the incidence of Lyme borreliosis is not well understood. In the present study, based on new notified cases of Lyme borreliosis from 2000 to 2015, an average of 1.24 new cases per million residents per year was documented. New cases, georeferenced at the municipal level, were analyzed by retrospective space-time analysis (using SaTScan v. 9.3.1); and land cover, extrapolated from a Corine Land Cover dataset (using QGIS 2.8.1), was used to implement an environmental risk factor analysis. Firstly, a temporal high-risk cluster was detected in Lombardy: the relative risk of Lyme borreliosis was 3.73 times higher during 2008-2015 compared with the entire study period. Moreover, in a spatiotemporal high-risk cluster with a circular base, land cover consisting of wildland-urban interface, meadow, forest and meadow-forest transition were significantly higher compared to low-risk areas. Results of the present study demonstrate that the incidence of Lyme borreliosis is increasing in Lombardy and that environmental conditions are suitable for *I. ricinus* ticks infected with *B. burgdorferi* s.l.: citizens and health systems should be aware of Lyme borreliosis to reduce tick bites with personal protective behaviors and to avoid misdiagnosis, particularly within the area including the observed high-risk cluster. Economic resources should be invested to inform about methods to prevent tick bites, how to check people and pets after frequenting risk areas, and ways of removing the biting ticks when they are found.

Keywords Lyme borreliosis incidence, Spatial analysis, Environmental risk factors, *Borrelia burgdorferi* sensu lato, Epidemiology.

1. Introduction
The *Borrelia burgdorferi* sensu lato (s.l.) complex includes several causative agents of Lyme borreliosis in western Europe, where the hard tick *Ixodes ricinus* is the main vector. The incidence of tick-borne diseases is increasing worldwide, and this trend has been widely documented for Lyme borreliosis (Rizzoli et al., 2011; Kugeler et al., 2015). Lyme borreliosis eco-epidemiology is complex as it depends on: tick development and survival; abundance of vertebrates serving as spirochete reservoirs; hosts that contribute to the spread of the tick; and human exposure to tick-bites (Kilpatrick et al., 2017). All these factors are linked to environmental features, and geospatial analysis tools have proved to be helpful in the understanding of tick-borne disease epidemiology (Svec et al., 2013).

In Italy, the first case of Lyme borreliosis was recorded in northern Italy in 1983 (Crovato et al., 1985) and since then most new cases have been observed in the Liguria, Friuli-Venezia Giulia,
and Trentino-Alto Adige regions (Cimmino et al., 1992; Pavan et al., 2000; Nazzi et al., 2010). At present, these northern regions have higher incidence of Lyme borreliosis compared to central and southern Italy, where Lyme borreliosis appears to be hypoendemic (Santino et al., 1995; Santino et al., 1996; Fazii and Riario Sforza, 1999). Some regions of northern Italy, such as Piedmont and Lombardy, also have low incidence or report only sporadic cases (Orani and Sala, 1994; Casbaiana et al., 1996). Following the increase of diagnosed cases since 1983, the Ministry of Health included Lyme borreliosis in the list of notifiable diseases in 1992. In Lombardy, the most populous region of Italy, *I. ricinus* has long been known to be present and *B. burgdorferi* s.l. spirochetes have been detected in this tick (Scali et al., 2001; Pistone et al., 2010; Olivieri et al., 2010). Despite this, the epidemiology and spatial distribution of Lyme borreliosis cases are poorly understood, and the regional trend of disease incidence has not been described. To fill these knowledge gaps, the present study aimed to evaluate i) the incidence of Lyme borreliosis in the resident population of Lombardy from 2000 to 2015; ii) the distribution of new cases with a retrospective spatiotemporal analysis; and iii) the existence of environmental predictors for disease incidence. To address these research questions, new cases of Lyme borreliosis, georeferenced at the municipal level, were analyzed by space-time scan statistic (Kulldorff, 1997) followed by an environmental risk factors analysis based on a Corine Land Cover dataset.

2. Materials and Methods

2.1. Study area and data sources.

Lombardy is a region of northern Italy (Latitude: 45°40’ N; Longitude: 9°30’ E), covering 23,863.7 km² and divided into 12 provinces (Figure 1). It is the most populous region of Italy, with a population density of 419.7 inhabitants per km². The health care system is regionally managed in Italy, and notifiable diseases are recorded at the regional level. For the study, new notified cases of Lyme borreliosis in the resident population from 2000 (January the 1st) to 2015 (December the 31st) were obtained from the Rare Disease Register of the Lombardy Region. Age, sex, municipality of residence and date of notification were collected for each case. We verified that notifications were always done in the same year as the appearance of symptoms, so in the annual based statistical analysis, no bias was introduced due to the time lag between diagnosis and notification. Sporadic information about travel-associated cases was recorded only for non-residents, and these were not included in the present study. Annual demographic data for the Lombardy resident population were obtained from the National Institute of Statistic (Istituto Nazionale di Statistica, ISTAT, http://demo.istat.it/) at the municipal level. For each year and municipality, the age of the resident population (male or female) was grouped in 5-yr age classes, ranging from one (0-4 years old) to 19
Also, the shapefile of administrative areas was downloaded from the ISTAT website (http://www.istat.it/it/archivio/104317); using QGIS 2.8.1 (Quantum GIS Development Team, www.qgis.org), centroids of municipal areas were determined, and their geographical coordinates were exported. Lyme borreliosis cases were coupled with their municipalities of residence. Annual incidences were determined for the study period and mean provincial annual incidences were also calculated. Eleven provincial incidences were determined, although Lombardy Region is currently composed of twelve provinces. The Monza-Brianza province was created during the study period (in 2009) so demographic data for municipalities in the Monza-Brianza and Milan provinces were merged and considered as single province for incidence calculation.

2.2. Retrospective space-time analysis.

To evaluate whether or not there was a higher than expected Lyme borreliosis incidence in some areas within the Lombardy Region and during different time periods, retrospective space-time analysis was performed using SaTScan v. 9.3.1 (Kulldorff et al., 1998). The space-time scan statistic is defined by a cylindrical window with a circular or elliptic geographic base and with the height corresponding to time. The window imposed on the map is in turn centered on each of several possible grid points positioned throughout the study region. For each grid point, the radius of the window varies continuously in size from zero; an upper limit of 50 percent of the population at risk was specified. In this way, the circular or elliptic window is flexible in both location and size. In total, the method creates an infinite number of distinct geographical windows with different sets of neighboring data locations within them. Each circle or ellipse is a possible candidate cluster, while the height reflects the period of potential clusters; the minimum (1 yr) and maximum (50 percent of the study period) temporal cluster size were specified (Kulldorff, 1997). Population file uploaded in SaTScan for scan statistic with discrete Poisson model contained census data for each municipality at each January the 1st of the period 2001-2015, divided into the 19 age classes of male and female residents. The same categorical covariates were introduced in the case file, so an adjustment for age class and sex was included in the space-time analysis. The coordinates file incorporated municipal UTM zone 32N coordinates on the WGS84 Datum to create both circular and elliptic windows.

To evaluate the temporal trend of Lyme borreliosis incidence through the study period, Kendall’s tau-b correlation was used.

2.3. Explanatory spatial analysis.

To separate associations between environmental features and Lyme borreliosis incidence in Lombardy Region, data on land cover classes and their spatial proportion in each municipality were obtained from the Corine Land Cover (CLC) dataset of the National Environmental Information
System (Sistema Informativo Ambientale Nazionale, http://www.sinanet.isprambiente.it/it/sia-ispra/download-mais/corine-land-cover/). Fifty-five classes of land cover were categorized in this dataset. The CLC nomenclature for levels I, II, III was the one described by Bossard et al. (2000) and Heymann et al. (1994). Averge altitude (in meters above sea level, m a.s.l.) for each municipality was obtained from ISTAT (http://www.istat.it/it/archivio/156224).

Municipalities with centroids located inside or outside the cylindrical high-risk spatiotemporal cluster(s) were tested for environmental differences by a generalized linear model (GLM) with binary logistic regression. The percentages of municipal area covered by each of the CLC land cover classes and the altitude were considered independent variables; CLC classes that covered less than 0.2% of area both inside and outside the cluster(s) were excluded. Location of a municipal centroid inside versus outside the cluster(s) was the dependent variable. Independent variables were tested for multicollinearity by tolerance and variance inflation factor (VIF); the final model was obtained by backward elimination of not significant independent variable and Akaike Information Criterion (AIC). Statistical analyses were performed using SPSS ver. 20 (IBM, Chicago, IL, U.S.A.).

The analysis workflow of the present study is schematized in the block diagram presented in the supplementary material (Fig. S1).

3. Results

In the 16 years from 2000 to 2015, 189 new cases of Lyme borreliosis were recorded in the resident population of the Lombardy Region (11.8 new cases/year). The resident population amounted to 9,523,648 people: an average of 1.24 new cases per million of residents per year was observed. The spatial distribution of municipalities in which these cases were recorded is shown in Figure 2. The annual incidence across the study period varied from 0.3 (minimum, observed in 2005) to 2.6 (maximum, observed in 2014) new cases per million of residents; and the provincial incidence varied from 0.3 to 7.6 new cases per year recorded in Lodi and Sondrio provinces respectively (Figure 3).

3.1. Retrospective spatiotemporal analysis.

The retrospective spatiotemporal analysis of Lyme borreliosis incidence produced both a purely temporal and a spatiotemporal high-risk significant cluster. The temporally significant cluster covered an eight-year period (from 2008, January the 1st to 2015, December the 31st) and all municipal centroids were included (relative risk=3.73; p-value<0.001). During this period, under the space-time scan statistic’s null hypothesis of homogeneous distribution of incidence, the number of expected new cases of Lyme borreliosis in the Lombardy Region resident population was 97.5. However, the actual number of observed new cases was 151 (observed/expected ratio=1.55), with an
average of 1.98 new cases per million of residents per year (Figure 4). Further, a strong positive
correlation was detected between year and Lyme borreliosis incidence in the resident population by
Kendall’s tau-b correlation ($\tau_B = 0.633$; $p<0.001$).

The high-risk spatiotemporal cluster presented a circular base (relative risk=14.01; $p$-
value<0.001); it covered the same time period as the previously described temporal cluster (Figure
5). The latitude and longitude of its center were 46°9'58.55"N and 9°26'40.47"E, respectively, and its
radius length measured 42.33 km. Throughout the study period, the risk of Lyme borreliosis was 14.0
times higher for residents in this space-time cylinder than for people residing outside it. Out of 1,530
locations (total municipal centroids of Lombardy Region), 225 municipalities with 436,360 resident
people were situated inside this cluster. Municipalities situated inside the spatiotemporal cluster
belonged to Bergamo, Como, Lecco and Sondrio provinces. A mean municipal altitude of 991 m a.s.l.
(s.d. 466) was observed within the cluster, while the regional mean is 406 m a.s.l. (s.d. 458).
Moreover, within the cluster, expected and actual observed new cases of Lyme borreliosis were 4.4
and 47 respectively (observed/expected ratio=10.8), with an average of 13.5 new recorded cases per
million of residents per year. No spatiotemporal clusters presenting an elliptic base were detected.

3.2. Explanatory spatial analysis.

Fourteen CLC land cover classes, out of 36, each covered less than 0.2% of the surface both
inside and outside the cluster obtained with the retrospective spatial analysis: these were excluded in
the construction of the GLM. The coverage by the remaining 22 classes and municipality altitudes
were tested for multicollinearity: class 2111 of CLC (tolerance=0.041; VIF=24.602) and altitude
(tolerance=0.134; VIF=6.266) were excluded. The complete list of variables included and excluded
for statistical analysis are presented in Table S1 of the supplementary material. The backward
elimination of all non-significant independent variables required seven steps, but the best AIC was
obtained after six steps; so, class 332 (“Bare rocks”) remained in the final model despite the $p$-
value>0.05. Overall, percentages of area covered by 12 different classes of CLC (112, 231, 243, 311,
312, 313, 321, 322. 324, 333, 511, 512) were significant positive predictors of being inside the high-
risk cluster of Lyme borreliosis incidence (Table S2 and S3). The listed type of land cover positively
associated with Lyme borreliosis incidence are classified as “Artificial surfaces” (class 112, odds
ratio: 1.051), “Agricultural areas” (classes 231 and 243; odds ratios: 1.078 and 1.068, respectively),
"Forest and semi-natural areas" (classes 311, 312, 313, 321, 322. 324 and 333; odds ratios: 1.075,
1.091, 1.089, 1.127, 1.106, 1.072 and 1.117, respectively), and “Water courses” (classes 511 and 512;
odds ratios: 1.083 and 1.116, respectively).

4. Discussion
According to Sykes and Makiello (2017), the incidence of Lyme borreliosis in Italy during 2001-2015 was 0.01 new cases per million of resident population/year, but the disease is probably underdiagnosed and underreported. During our study period (2000-2015), 1.24 new cases per million residents/year were observed in Lombardy. Noticeable differences were documented both between years and between provinces (Figure 3): the annual incidence for 2014 was 2.61, more than twice the average for 2001-2015, and the mean annual incidence for Sondrio, the northernmost province, was 7.63, more than six times the regional average.

4.1. Retrospective spatiotemporal analysis.

The scan statistic showed the incidence of Lyme borreliosis in Lombardy to be heterogeneous both in space and time. Firstly, the detected temporally significant cluster demonstrated that the incidence of Lyme borreliosis is increasing over time in Lombardy. Attention towards the disease has grown over the years and the observed increasing incidence is probably partially due to growing awareness of clinicians and demand for testing (Mavin et al., 2015). Nevertheless, a real increase of Lyme borreliosis incidence likely occurred in Lombardy Region, similar to other European and North American studies reporting an increase of ticks, tick bites and Lyme borreliosis (Rizzoli et al., 2011; Vandenesch et al., 2014; Kugeler et al., 2015). This phenomenon could be due to several factors, such as those influencing vectors, reservoir hosts and human-tick encounters (Lindgren and Jaenson, 2006). The present study showed that about 15% of regional municipalities (225/1530) and 5% of the regional resident population (436,360/9,523,648) were located inside the detected high-risk space-time cluster of Lyme borreliosis. From 2008-2015, the annual incidence of Lyme borreliosis in the resident population within the cluster was about eleven times greater than the regional average in the whole study period (13.5 new cases per million of resident people per year versus 1.2). Possible bias of our spatiotemporal retrospective analysis could lie in the low incidence of Lyme borreliosis registered in Lombardy: different attitudes in notifying the disease in certain health structures could lead to errors. However, we must consider that the overall spatial distribution of cases concerns the whole region (Figure 2), thus making us assume that this error was contained. Furthermore, the results of the explanatory spatial analysis discussed below seemed to confirm that the identified high-risk area presented environmental characteristics suitable for the spread of Lyme borreliosis. Finally, the spatiotemporal analysis, taking into account the population density and the population structure at a highly detailed level, minimizes the possible errors related to specific segments of the population exposed to the disease (Li et al., 2014), so the existence of this cluster can be considered reliable.

4.2. Explanatory spatial analysis.

Environmental differences were detected between municipalities situated inside and outside the regional high-risk space-time cluster of Lyme borreliosis incidence: municipal area percentages
for 13 different land cover classes were predictors of being located within the cluster (Table S3). Class 112 ("Discontinuous urban fabric") was positively related to high risk for Lyme borreliosis incidence. It could be hypothesized that the "Discontinuous urban fabric" land cover class is positively associated with human-tick encounters. Previously, the ‘emergence’ of Lyme borreliosis cases registered in the Czech Republic in the 1990–2000s was solely attributable to disease exposure at or near (<5 km) patients' homes and human risk for Lyme borreliosis appear to be peridomestic, at least in the northeastern United States (Diuk-Wasser et al., 2012; Zeman et al., 2013). Further, Larsen et al. (2014) observed those counties with high Lyme borreliosis incidence tended to have a large share of its population residing in the wildland-urban interface. According to these authors, the high percentage of municipal area covered by "Discontinuous urban fabric" within the high risk-cluster could determine a high exposure to tick bites at or near resident people's home. Mixes of anthropized and natural environment inside the high-risk cluster also involved agricultural activities, as evidenced by the presence as a predictor in the final model of the 243 class ("Land principally occupied by agriculture, with significant areas of natural vegetation").

The risk of being situated inside the high-risk cluster was also positively related to the percentage of municipal area occupied by seven CLC classes in which land cover varied from meadow (classes 231 and 321) to forest (classes 311, 312 and 313), and meadow-forest transition (classes 322 and 324). These results agree with observations made elsewhere in Europe, in which *I. ricinus* samples were collected in localities characterized by deciduous or mixed deciduous/coniferous woodland or eco-tones between woodland and open, meadow-like areas (Jaenson et al., 2009). We also found that the percentage of municipal area covered by coniferous forests was a positive predictor of being within the high-risk cluster; then, not only broadleaf/mixed forests but also specific types of coniferous forests can probably produce a layer of decaying vegetation on the ground providing sufficient humidity for the development and survival of ticks and supporting a range of potential vertebrate reservoir hosts (Stanek et al., 2012). Higher percentage of municipal area covered by classes 231, 321, 311, 312, 313, 322 and 324 inside the high-risk cluster seem to be also consistent with previous studies that underlined, mainly in North America, the importance of forest fragmentation and forest-herbaceous edge for Lyme borreliosis incidence (Jackson et al., 2006; Horobik et al., 2006). European Lyme borreliosis studies have focused more on climate and less on local site-specific or landscape characteristics, so possibilities for comparisons are scarce (Killilea et al., 2008). In Central France, Halos et al. (2010) observed that the rate of *B. burgdorferi* s.l. infection in *I. ricinus* was higher in questing ticks collected both from the forest and the fragmented forest than those from pastures. Moreover, in the sub-sample from pastures, the infection rate of ticks was higher when forests surrounded pastures with low perimeter length/surface
area ratios and having a high percentage of shrubs on the perimeter. Further, in habitats characterized by forest, pasture and hedgerow/ecnones, rodents and birds, suitable hosts for younger stages of *I. ricinus*, were particularly concentrated in the shrubby vegetation around pastures; rodents were more often captured near hedgerows between pasture and woodland than inside pastures and forest (Boyard et al., 2008; Vourc’h et al., 2008). Apparently, in Central France, the spatial distribution of both small hosts and ticks infected by *B. burgdorferi* s.l., grossly fitted with the twelve cited explanatory variables of the final model obtained in the present study. Nevertheless, a relation between infection rates in vectors and Lyme borreliosis in humans has not been verified; more often Lyme borreliosis appeared linked to density of infected ticks and tick density, which probably is mainly affected by host availability (Nazzi et al., 2010; Sonnleitner et al., 2015; Randolph, 2001). The association of Lyme borreliosis cases with certain land cover classes could be related to the presence of hosts required by *I. ricinus* for its life cycle. Hofmesteer et al. (2016) quantified the relative importance of host groups providing blood meals for different life stages of *I. ricinus*. Rodents, birds (thrushes and other small birds) and ungulates played the main role in maintaining and disseminating tick populations. Inside the high-risk cluster of Lyme borreliosis incidence, observed typologies of cultivated and natural areas favor all the listed host groups. Particularly, vegetation within the cluster seemed highly suitable for some ungulates. In Lombardy, the highest population density of roe deer (*Capreolus capreolus*) was observed inside the high-risk cluster (Carnevali et al., 2009). Moreover, in northern Italy, Manfredi et al. (1999) observed that higher frequency of tick-bites was recorded in municipalities with higher roe deer density. As regards red deer (*Cervus elaphus*) living in the mountain forest of Lombardy, its population density inside the Lyme borreliosis high-risk cluster is lower than that of roe deer, and it does not differ from surrounding areas. Further, the regional population density of Alpine chamois (*Rupicapra rupicapra*) peaks within the high-risk cluster, but probably it is less relevant for the dissemination of ticks: *I. ricinus* infestation prevalence is higher in roe deer than in chamois living in the same areas (Hoby et al., 2009). Presence of wild boar (*Sus scrofa*) and ibex (*Capra ibex*) within the cluster is scarce or sparse (Carnevali et al., 2009).

5. Conclusions

In conclusion, the results presented in this study showed that the incidence of Lyme borreliosis in Lombardy is higher than the estimates previously proposed for Italy (Sykes and Makiello, 2017). Increasing incidence of Lyme borreliosis must be taken into account by healthcare practitioners, who should always consider a differential diagnosis with Lyme borreliosis in patients with compatible clinical symptoms. Further, medical staff should always be encouraged to report cases of the disease, and the resident population should also be aware of this situation. Finally, information campaigns should be put into practice on behaviors to reduce the risk and duration of tick bites, particularly
within the identified high-risk cluster. The social and economic costs of Lyme borreliosis should push investments primarily in the direction of prevention and, when necessary, early treatment of the disease, with appropriate training for health personnel and population exposed to the risk of transmission (Rizzoli et al., 2011; Lohr et al 2015; Mac et al. 2019). Implementation of local efficient and cost-effective vector monitoring should also be considered (Capelli et al., 2012).

Conflict of interest
The authors declare no competing interests

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Figures captions.

Fig. 1. Lombardy (dark grey) and its 12 provinces (BG: Bergamo; BS: Brescia; CR: Cremona; CO: Como; LC: Lecco; LO: Lodi; MB: Monza Brianza; MI: Milano; MN: Mantova; PV: Pavia; SO: Sondrio; VA: Varese; dotted area: Italy)

Fig. 2. Spatial distribution and number of Lyme borreliosis cases (a) and incidence of Lyme borreliosis (b) in the resident population of Lombardy at the municipal level (2000-2015)

Fig. 3. Mean provincial annual incidence of Lyme borreliosis (a) and annual incidence (dark grey bars; left vertical scale) and case number (light grey bars; right vertical scale) (b). Dashed lines indicate the mean regional annual incidence (a, b).

Fig 4. Annual incidence (columns) and time period of the temporal high-risk significant cluster of Lyme borreliosis (black bar); dashed line is the mean regional annual incidence.

Fig. 5. Spatiotemporal high-risk significant cluster of Lyme borreliosis incidence in Lombardy (2000-2015)
### Table S1

Variables included or excluded in the construction of the generalized linear model with binary logistic regression

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<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>333 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>335 (%)</td>
<td>x</td>
<td>&lt;0.2%</td>
<td></td>
</tr>
<tr>
<td>311 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>312 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>313 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>321 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>411 (%)</td>
<td>x</td>
<td>&lt;0.2%</td>
<td></td>
</tr>
<tr>
<td>412 (%)</td>
<td>x</td>
<td>&lt;0.2%</td>
<td></td>
</tr>
<tr>
<td>511 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>512 (%)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Altitude x Multicollinearity

(%) = percentage of municipal soil covered by the indicated CLC class

<0.2% = the CLC class covered less than 0.2% of soil
Table S2
Selection of final model by backward elimination and best AIC.
The removal of all terms with p-values ≥ 0.05 required 7 steps; final model according to AIC and backward elimination was obtained at step 6.

<table>
<thead>
<tr>
<th>Step of backward elimination</th>
<th>Eliminated variable</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>--</td>
<td>797.828</td>
</tr>
<tr>
<td>Step 1</td>
<td>213</td>
<td>802.754</td>
</tr>
<tr>
<td>Step 2</td>
<td>121</td>
<td>800.770</td>
</tr>
<tr>
<td>Step 3</td>
<td>221</td>
<td>799.404</td>
</tr>
<tr>
<td>Step 4</td>
<td>111</td>
<td>798.415</td>
</tr>
<tr>
<td>Step 5</td>
<td>242</td>
<td>797.381</td>
</tr>
<tr>
<td>Step 6</td>
<td>131</td>
<td>796.042</td>
</tr>
<tr>
<td>Step 7</td>
<td>332</td>
<td>797.103</td>
</tr>
</tbody>
</table>

Table S3
Generalized linear model with binary logistic regression: final model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description of Corine Land Cover classes</th>
<th>B ±s.e.</th>
<th>Wald Chi-Square test</th>
<th>O.R. (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>112</td>
<td>Discontinuous urban fabric</td>
<td>0.049 ±0.010</td>
<td>23,192</td>
<td>1.051 (1.030-1.072)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>231</td>
<td>Pastures</td>
<td>0.075 ±0.011</td>
<td>50,300</td>
<td>1.078 (1.056-1.100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>243</td>
<td>Land principally occupied by agriculture, with significant areas of natural vegetation</td>
<td>0.066 ±0.009</td>
<td>49,910</td>
<td>1.068 (1.049-1.088)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>311</td>
<td>Broad-leaved forests</td>
<td>0.072 ±0.009</td>
<td>66,791</td>
<td>1.075 (1.056-1.094)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>312</td>
<td>Coniferous forests</td>
<td>0.087 ±0.012</td>
<td>56,856</td>
<td>1.091 (1.066-1.116)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>313</td>
<td>Mixed forests</td>
<td>0.085 ±0.009</td>
<td>85,996</td>
<td>1.089 (1.069-1.109)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>321</td>
<td>Natural grassland</td>
<td>0.120 ±0.012</td>
<td>102,506</td>
<td>1.127 (1.102-1.154)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>322</td>
<td>Moors and heathland</td>
<td>0.101 ±0.023</td>
<td>19,206</td>
<td>1.106 (1.057-1.157)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>324</td>
<td>Transitional woodland/shrub</td>
<td>0.070 ±0.011</td>
<td>38,594</td>
<td>1.072 (1.049-1.096)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>332</td>
<td>Bare rocks</td>
<td>0.047 ±0.026</td>
<td>3,257</td>
<td>1.049 (0.996-1.104)</td>
<td>0.071</td>
</tr>
<tr>
<td>333</td>
<td>Sparsely vegetated areas</td>
<td>0.111 ±0.017</td>
<td>41,937</td>
<td>1.117 (1.080-1.155)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>511</td>
<td>Water courses</td>
<td>0.080 ±0.017</td>
<td>22,626</td>
<td>1.083 (1.048-1.119)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>512</td>
<td>Water bodies</td>
<td>0.110 ±0.013</td>
<td>70,293</td>
<td>1.116 (1.088-1.145)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

B: unstandardized coefficient; s.e.: standard error; O.R.: odds ratio; 95% CI: 95% confidence interval.
Fig. S1. The block diagram of the analysis workflow (LB: Lyme borreliosis; ISTAT: National Institute of Statistic; CLC: Corine Land Cover; SINANET: National Environmental Information System; GLM: generalized linear model; AIC: Akaike Information Criterion).