



Spatial Clusters and Non-spatial Predictors of Tick-Borne Disease Diagnosis in Indiana

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Published online: 3 July 2019
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Abstract

The purpose of this study was two-fold. First, we sought to identify spatial clusters of self-reported tick-borne disease (TBD) diagnosis in Indiana. Secondly, we determined the significant predictors of self-reported TBD diagnosis in a sample of Indiana residents. Study participants were selected from existing online panels maintained by Qualtrics and completed a cross-sectional survey ($n = 3003$). Our primary outcome of interest was self-reported TBD diagnosis (Yes/No). Cases and background population were aggregated to the county level. We used a purely spatial discrete Poisson model in SatScan® to determine significant clusters of high-risk TBD diagnosis counties. We also used X^2 tests in bivariate analyses, to identify potential predictor variables for inclusion in an initial model, and backward elimination selection method to identify the final model. Two clusters of counties with significant high relative risk of self-reported TBD diagnosis in the southeast and southwest of Indiana were detected. Males in Indiana were more likely to self-report TBD diagnosis compared to females. Study participants who conducted a thorough tick check after being outdoors were significantly less likely to report TBD diagnosis compared to those who did not. Increased positive perceptions of TBD personal protective measures were associated with reduced self-reported TBD diagnosis. Older study participants were less likely to self-report TBD diagnosis compared to younger participants. The identification of two clusters of TBD diagnosis in southern Indiana is consistent with a northern spread of TBDs and suggests a need for continued surveillance of the counties in the vicinity of the observed clusters. Future studies should be designed to identify risk factors for TBD diagnosis in the affected counties of Indiana.

Keywords Self-report · Tick-borne disease diagnosis · Spatial clusters · Indiana · Personal protective measures

Introduction

The United States Centers for Disease Control and Prevention (CDC) and other national agencies charged with gathering population-level data have long recognized the validity of self-reported information in the estimation of a variety of health indicators and risk behaviors [1, 2]. Questions such as “Has a doctor, nurse, or other health professional EVER told

you that you had any of the following [list of health conditions]” have formed part of the behavioral risk factor surveillance system (BRFSS)—the United States premier system of health-related surveillance collected through widespread telephone surveying. Responses to these questions are especially useful for exploratory research, issue selection, and identifying population health indicators in the absence of more objective measures. In relation to tick-borne diseases (TBD) diagnosis, where the evidence suggests significant under-reporting, [3] self-reported measures are invaluable in assessing prevalence as a prelude to resource allocation. Additionally, these reports can corroborate data obtained from active surveillance.

As the geographical distribution of TBD vectors in the United States have spread farther north, [4] and to broader regions of the Eastern Seaboard and upper Midwest, [5] multiple studies have begun to identify clusters of TBD prevalence in the United States. For example, Kugeler, Farley [6] identified specific counties across the U.S that

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10900-019-00691-0>) contains supplementary material, which is available to authorized users.

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where within a spatial cluster of elevated incidence of Lyme Disease (LD). Adjemian, Krebs [7] identified clusters of TBD-related deaths and cases of moderate severity respectively. TBD predictors that have been previously investigated include pet ownership [8], personal and peri-domestic protective behaviors [9–12], spending time outdoors [13], TBD risk perception and exposure to ticks [14–16], knowledge [15, 17, 18], perceived efficacy of preventive measures [18], feelings of concern (because of LD) [16], education [19], and knowing someone who had LD [16]. To our knowledge, no previous documentation of TBD diagnosis clusters based on self-reporting exists in Indiana. Furthermore, few studies have investigated predictors of TBD diagnosis. It is critical to identify clusters of TBD diagnosis and predictors in Indiana given that, (a) many TBDs are now endemic to Indiana, (b) ticks' distribution varies dramatically across different areas, [4, 5] (c) susceptibility of the population to TBD and the magnitude and direction of TBD risk factors may vary with respect to state or even county, [20] and (d) clusters of TBD diagnosis or infection can reveal underlying risk patterns [21, 22].

The purpose of this study is two-fold. First, we will identify spatial clusters of self-reported TBD diagnosis in Indiana. Secondly, we will determine significant predictors of self-reported TBD diagnosis in a sample of Indiana residents. The spatial distribution of TBDs and the prevalence of TBD-associated risk and protective factors remains understudied in Indiana. Accordingly, we expect our study outcomes will contribute significantly to the identification of counties with a greater risk of TBD diagnosis. This information will be useful for the design and development of risk-reduction interventions including policy formulation, control measures and public health education efforts for particularly at-risk counties.

Method

Participant Recruitment

Study participants were selected from existing online panels maintained by Qualtrics to participate in a cross-sectional survey [23.] Our target population were adults age 18 years or older, who had lived in Indiana State for at least 6 months prior to study participation. To ensure representativeness of the target population, we used the following quota for panel selection; gender (Female 50%, Male 50%), Age (17–34 [33%], 35–54 [33%], 55 years or older [33%]). Study data were collected over a 14-day period (June/July) in 2018. This study was approved by the Indiana University IRB (protocol #: 1806808759).

Key Variables

Our primary outcome of interest was self-reported TBD diagnosis. This was based on study participant's response to the question; "Have you EVER been told by a health practitioner that you have a TBD, such as Lyme?" Cases were participants who responded 'Yes' to the question. We used Chi square (X^2) cross tabulation to describe study participants sociodemographic characteristics based on self-reported TBD diagnosis (Yes/No) across the following categories; gender (female, male), age (> 44 and < 44 years), education (graduate degree, some college, high school or less), employment (employed by someone else, self-employed, not employed, other), income (low, high), and race (white, other). We used the median age as cut-off point for our dichotomous age categories.

Statistical Analysis

Spatial Model: Identifying TBD Clusters

We used a purely spatial discrete Poisson model in SatScan® to determine significant clusters of high-risk TBD diagnosis. SatScan® is a global clustering test, which applies a likelihood ratio test to evaluate and detect both the location of clusters as well as their statistical significance, while adjusting for multiple testing [24]. Significant cluster detection is based on results of Monte Carlo simulation, which compares the number of observed cases to the expected under conditions of the null hypothesis. The Poisson model calculates clusters based on risk for a background population [25].

Case Definition

Cases were participants who responded 'Yes' to TBD diagnosis ($n = 142$), while all study participants ($N = 2927$) were used to represent the background population at risk [25]. Cases and the corresponding background population were aggregated to the county level. We set maximum spatial cluster size to 25% of the background population and number of Monte Carlo replications at 9999 random permutations, with significant p value ≤ 0.05 . We geographically visualized the shapefile output from SatScan® cluster detection using the Environmental Systems Research Institute (ESRI) ArcGIS software (version 10.6). A county boundary map of Indiana was used as the background for all map projections (WGS 1984).

Logistic Regression Model: Predicting TBD Diagnosis

Based on evidence in the published literature, [15, 16] we also used X^2 tests in bivariate analyses, to identify potential predictor variables that were significantly associated with self-reported TBD diagnosis. These comprised twenty-five tick-exposure risk related variables, 7 recommended personal protective measures (PPMs), and four interaction terms. (See Appendix for a full list of the tick-exposure risk related variables). The list of recommended PPMs are; (1) wearing light-colored clothing for easy identification and removal of ticks when outdoors (Yes vs. No), (2) walking on established trails and avoiding contact with adjacent vegetation (Yes vs. No), (3) tucking shirt into pants, and the pants into socks when outdoors (Yes vs. No), (4) using bug spray on exposed skin when outdoors (Yes vs. No), (5) treating outdoor clothing with special bug spray (Yes vs. No), (6) conducting a thorough check of clothing and the body soon after returning from the outdoors (Yes vs. No), and (7) showering immediately after returning from the outdoors (Yes vs. No). The following interaction terms were also tested; (1) TBD knowledge and TBD risk, (2) TBD knowledge and pet ownership, (3) TBD knowledge

and perceptions of TBD PPMs, and (4) TBD risk and perceptions of TBD PPMs. Next, we included the significant predictor from bivariate analysis in an initial model. We used a backward elimination selection method to identify the final model. The p-value to remove covariates from the model was ≥ 0.05 . The final model was checked for Goodness-of-Fit (GOF) with Hosmer and Lemeshow test and Tjur R^2 test [26]. We report odds ratios (ORs), 95% confidence intervals (Cis), and p-values of the variables in the final model. We used SAS 9.4 (Cary, NC) and SatScan® for statistical analysis.

Results

Results of *Chi square* cross tabulation of study participants' sociodemographic characteristics revealed significant differences ($p < 0.05$) in self-reported TBD diagnosis based on gender, age, education, employment status, and racial groupings (Table 1). Our results showed that male participants were significantly more likely to self-report TBD diagnosis compared to females. Participants who were less than 44 years of age were also significantly more likely to self-report TBD diagnosis compared to those older than 44 years. Study participants who had a high school or less

Table 1 Characteristics of the study population of (n = 2927)

	Total N	TBD diagnosis		p-value
		Yes N	No N	
Socio-demographic characteristics				
Gender				0.0002
Female	1491	50 (36%)	1441 (52%)	
Male	1429	90 (64%)	1339 (48%)	
Age				< 0.0001
Above 44	1451	25 (18%)	1426 (51%)	
Below 44	1469	115 (82%)	1354 (49%)	
Education				0.0027
Graduate degree	502	32 (23%)	470 (7%)	
Some college	717	18 (13%)	699 (5%)	
High School or less	1701	90 (64%)	1611 (58%)	
Employment				< 0.0001
Employed by someone else	1548	71 (51%)	1477 (53%)	
Self-employed	276	38 (27%)	238 (9%)	
Not employed	862	23 (16%)	839 (30%)	
Other	234	8 (6%)	226 (8%)	
Income				0.5068
Low	1401 (48%)	69 (49%)	1450 (52%)	
High	1519 (52%)	71 (51%)	1330 (48%)	
Race				0.0099
White	2544	112 (80%)	2432 (87%)	
Other	376	28 (20%)	348 (13%)	

p-values < 0.05 are given in bold

education where more likely to self-report TBD diagnosis compared to the college educated. Compared to other racial groups respondents who identified as white were more likely to self-report TBD diagnosis. No other sociodemographic differences in self-reported TBD diagnosis were observed.

Poisson cluster analysis detected ten geographic clusters, two of which were significant ($p \leq 0.05$). The relative risk of self-reported TBD diagnosis within a significant cluster compared to outside varied from 4.05 to 5.94, with significant cluster radius ranging from 18.65 to 23.85 miles (Table 2). Of the two significant clusters, seven counties were located in cluster 1 and 3 counties occurred in cluster 2.

Cluster locations are shown in Fig. 1. The two significant clusters were detected in the southern part of the state, occurring in the southeast and the southwest regions. Counties in in the first cluster include Switzerland, Ohio, Dearborn, Jefferson, Ripley, Decatur, and Jennings, while the second cluster contained the following counties: Knox, Daviess, and Martin.

Of the 32 variables and four interaction terms in the initial model, 11 variables and 1 interaction term remained in the final model. The Tjur R^2 was 0.32 and the Hosmer and Lemeshow GOF test resulted in a non-significant p-value (0.203), suggesting that the model acceptably fitted the data.

Participants who regularly spent time outdoors in summer months were 5.69 times more likely to self-report a TBD diagnosis in comparison with those who did not [OR (95% CI) 5.69 (1.41, 23.01)]. However, the number of outcomes for the subgroup who did not regularly spend time outdoors in summer was low ($n=3$), resulting in wide CIs. More specifically, those who spent time outdoors for leisure/recreation were 2.14 times more likely to self-report a TBD diagnosis, when compared to those who spent time outdoors for employment purposes (e.g. natural resource employment,

other outdoor related employment) [OR (95% CI) 2.14 (1.21, 3.8)]. Participants who had seen a tick in the past 12 months of survey were 2.03 times more likely to report TBD diagnosis, compared to those who had not seen any tick in that time interval [OR (95% CI) 2.03 (1.27, 3.22)] (Table 3).

Moreover, two of the protective behaviors remained in the final model. Participants who conducted a thorough body check after being outdoors were 52% less likely to self-report TBD diagnosis compared to those who did not practice this behavior [OR (95% CI) 0.48 (0.27, 0.85)]. However, showering after being outdoors was not found to be protective in this study population [OR (95% CI) 1.81 (1.09, 3.02)]. Further, those who had seen, heard, or read advertisements about TBD prevention were more likely to self-report a TBD outcome in comparison to those who had not been exposed to such advertisements [OR (95% CI) 3.58 (2.31, 5.54)]. Knowing anyone with TBD was another predictive factor for TBD outcome, suggesting that those who know someone with a TBD are fivefold more likely to report the TBD outcome, compared to those who did not know anyone with a TBD [OR (95% CI) 5.41 (3.47, 8.45)]. Avoiding being outdoors because of ticks was also found to have a point estimate above 1 [OR (95% CI) 1.74 (1.06, 2.85)]. Those who highly felt at risk because of ticks were more than 3 times more likely to report TBD outcome, versus those who felt at lower tick risk [OR (95% CI) 3.56 (2.22, 5.70)]. Female study participants were 58% less likely to self-report TBD diagnosis, compared to males [OR (95% CI) 0.42 (0.27, 0.66)]. Compared to participants with low TBD knowledge, those with high TBD knowledge were 73% less likely to report the TBD outcome, even though this was not significant [OR (95% CI) 0.27 (0.06, 1.22)]. For every unit increase in perceptions of TBD PPMs, our results showed a 26% reduction in the odds of self-reported TBD diagnosis

Table 2 Purely spatial Poisson model for cluster detection using self-reported TBD diagnosis as cases. The clusters are ranked according to their likelihood ratio test statistic

Cluster #	Cluster radius (miles)	County(ies) within cluster	Number of cases	Population	Expected cases	Observed/expected	Relative risk	Log likelihood-ratio	p-value
1	23.87	65, 66, 61, 71, 68, 73, 74	11	61	3.81	3.81	4.05	6.850084	0.0346*
2	18.65	77, 76, 75	7	26	1.23	5.69	5.94	6.524838	0.0430*
3	0	25	6	20	0.95	6.34	6.58	6.122778	0.0665
4	0	35	2	3	0.14	14.10	14.29	3.446231	0.5764
5	24.48	26, 33, 16	3	9	0.43	7.05	7.18	3.307908	0.6213
6	0	3	8	67	3.17	2.53	2.62	2.663552	0.8284
7	0	22	3	12	0.57	5.29	5.38	2.58421	0.8506
8	28.30	85, 80, 88, 86, 84, 79	8	70	3.31	2.42	2.50	2.450122	0.8883
9	16.07	19, 21, 20	6	58	2.74	2.19	2.24	1.478128	0.9979
10	0	20	3	20	0.95	3.17	3.22	1.424013	0.9982

p-values < 0.05 are given in bold

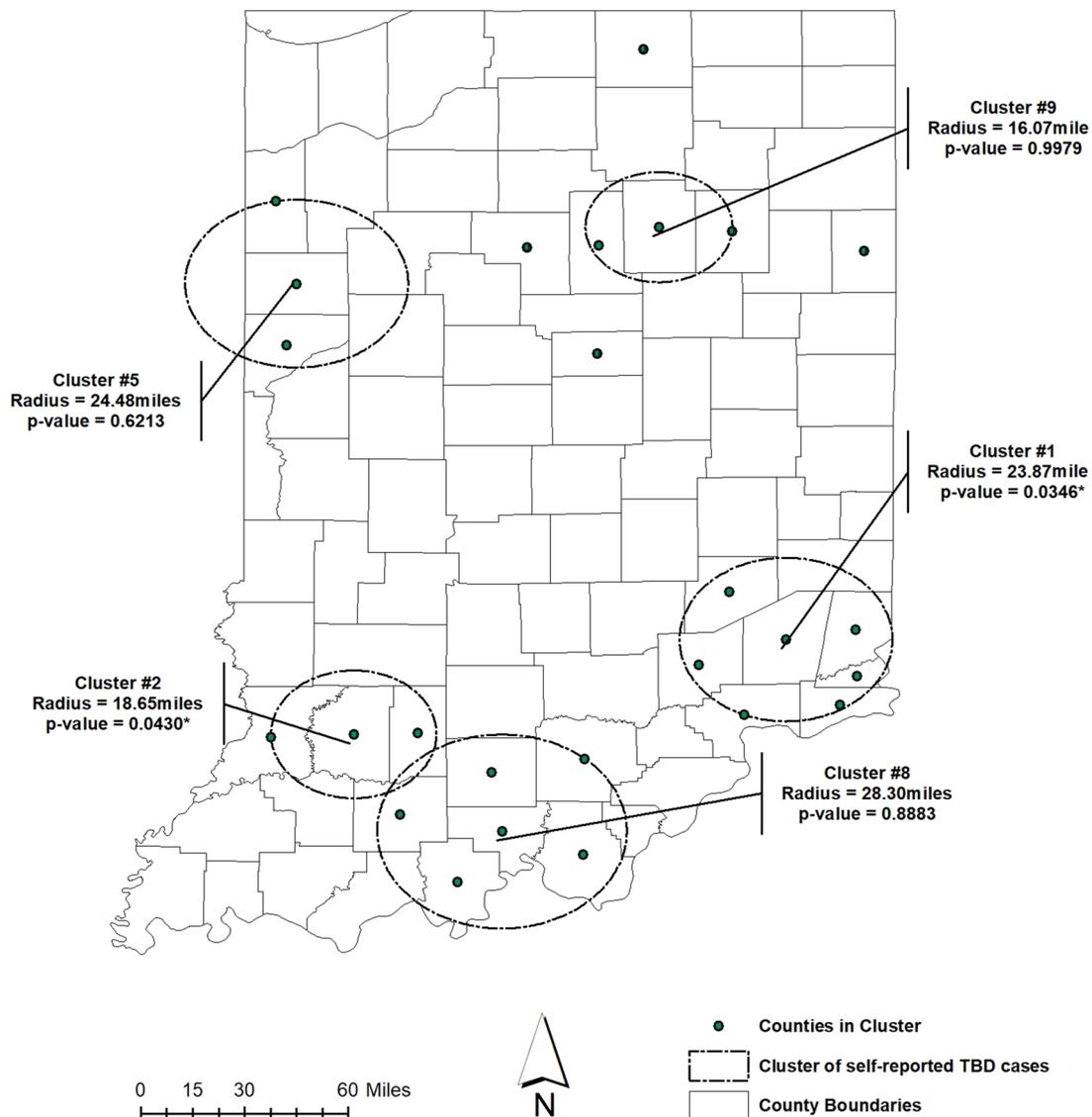


Fig. 1 Self-reported clusters of tick-borne disease cases in Indiana. Significant clusters have a p-value < 0.05

[OR (95% CI) 0.74 (0.66, 0.83)]. Lastly, participants older than 44 were 67% less likely to have the TBD outcome compared to those younger than 44 [OR (95% CI) 0.33 (0.20, 0.54)]. Hours spent outdoors was not predictive of the TBD outcome (Table 3).

Discussion

In this study, we were able to detect two clusters in the southeast and southwest of Indiana where the relative risk of self-reported TBD diagnosis was significantly higher for counties within the clusters compared to counties outside the clusters. Together, counties in both clusters include Switzerland, Ohio, Dearborn, Jefferson, Ripley, Decatur, Jennings,

Knox, Daviess, and Martin. A further look at the characteristics of these counties indicate that 80% are rural according to the Office of Management and Budget classification [27]. Given that tick exposure is the greatest risk factor for TBD diagnosis, and risk for tick exposure increases when there is a high number of tick vertebrate hosts and large areas of vegetation, it is not surprising that many of the counties in the observed high-risk clusters are rural as these risk factors are more likely to be seen in rural areas [28, 29].

We also observed that some TBD PPMs were more protective against TBD diagnosis than others. For example, study participants who conducted a thorough tick check after being outdoors were significantly less likely to report TBD diagnosis compared to those who did not. However, showering after being outdoors was not found to be protective

Table 3 Odds ratio estimates and 95% confidence intervals for predictors of self-reported TBD diagnosis in Indiana

Predictor variable	Point estimate	95% Wald confidence limits		p-value
Seen a tick in past 12 months				
No	1.000	1.235	3.075	0.0042
Yes	1.948			
TBD protective behavior, thorough body check				
No	1.000	0.291	0.880	0.0158
Yes	0.506			
TBD protective behavior, shower after being outdoors				
No	1.000	1.174	3.191	0.0096
Yes	1.935			
Recently seen, heard, or read ad(s) about TBD prevention				
No	1.000	2.157	5.079	<0.0001
Yes	3.310			
Know anyone with TBD				
No	1.000	3.428	8.225	<0.0001
Yes	5.310			
Avoid being outdoors because of ticks				
Low	1.000	1.177	3.046	0.0085
High	1.893			
Feel at risk because of TBD				
Low	1.000	2.319	5.841	<0.0001
High	3.680			
Gender				
Male	1.000	0.277	0.651	<0.0001
Female	0.425			
TBD knowledge				
Low	1.000	0.051	0.934	0.0401
High	0.219			
Positive perceptions of TBD PPMs				
Age				
≤44	1.000	0.198	0.535	<0.0001
≥44	0.325			

for self-reported TBD diagnosis among study participants. Multiple studies have reported on the effectiveness and frequency of adoption of tick checks in TBD prevention [11, 12, 30, 31]. Given that ticks must first attach and feed usually for several hours before infection occurs, finding and removing a tick before it attaches to the body for a blood meal will prevent infection. In this way conducting a tick check as a recommended TBD PPM works to prevent TBDs. On the other hand, several reasons may account for the lack of association between showering after being outdoors and TBD protection. First, ‘showering after being outdoors’ may not be consistently protective against tick bites. Most studies have not looked at this behavior in relation to TBD prevention [11, 12, 18]. Secondly, ‘showering after being outdoors’ is a behavior that people may engage in for other reasons than for tick bite prevention. Individuals may engage in this behavior after spending time in various non-tick exposure

related outdoor pursuits, such as after jogging, post-outdoor exposure to toxic chemicals, [32] and other events. As such, it may be that risk exposure is independent of this behavior.

Study participants who knew someone with a TBD were more likely to report a TBD diagnosis. This association may be explained by them sharing a common exposure source. Female study participants were less likely to self-report TBD diagnosis, compared to males. Older study participants were less likely to self-report TBD diagnosis compared to younger participants. A U.S. Centers for Disease Control and Prevention [CDC] [33] report indicates that TBD occurs more among males and in people over 40 years of age. Multiple studies have reported that females tend to be more risk averse and therefore more likely to adopt recommended PPMs [12, 34]. Our study however contradicted the CDC report on the association between increasing age and TBD incidence. Finally, we found that increased positive

perceptions of TBD PPMs were associated with reduced self-reported TBD diagnosis.

Some findings in this study are not consistent with what we might expect given the transmission dynamics of TBDs and deserve particular mention. Specifically, unique categories of study participants were more likely to self-report TBD diagnosis. These included, (1) individuals who felt more at risk because of ticks, (2) those who recently said they saw, heard, and read about TBD prevention, (3) those with high TBD knowledge and, (4) those who said they avoid being outdoors because of ticks. According to Slovic and Peters [35], humans perceive risk either as ‘feelings’ or ‘analysis’. Risk as feelings refer to the reactions of an individual to danger that is based on instinct and intuition. Under such conditions reactions to perceived risk is handled quickly and automatically, based on prior experience. Risk as analysis, however, refers to an individual’s reaction to danger that is based on logical reasoning. Risk as feelings coupled with risk as analysis may partly explain these unique categories of findings. In the first instance, subjects who have prior experience with tick exposure leading to TBD, may feel more at risk. This will in turn lead to information search, which might explain why they’ve reported having seen, heard or read about TBD prevention, together with high TBD knowledge. Although avoidance of the outdoors is supposed to confer protection against TBD, the avoidance observed in our study population may be a secondary response to prior TBD in association with outdoor exposure rather than a pro-active, primary prevention measure. A meta-analytic review of published research support this analysis, [36] describing how individuals perceive and evaluate risk in ways that sometimes are outside rational reasoning. Particularly, as this combination of experiential mode of thinking and logic has not been investigated in relation to TBD risk, this interpretation if true has important implications for TBD risk assessment.

Limitations

Given the cross-sectional study design, we are unable to ascertain that the discussed identified predictors are temporally before the TBD outcome. This limitation would be solved with a longitudinal study design. Another limitation of the current study is measurement error. Since the data was collected subjectively via a self-reported web-based survey, the predictors and the TBD outcome might be erroneously measured. This potential error could be due to recall bias and/or social desirability bias. Both bias types can change the magnitude of the measure of association in either directions. However, unlike the predictor variables, TBD outcome is less prone to recall bias because it is a notable and to some extent unforgettable event in one’s life. Generalizability of

study findings may also be a problem if the sampling frame (Indiana adult residents with internet access) are significantly different in some respect from the target population (all Indiana adult residents). Lastly, we looked at all the variables in one model, assuming they share common confounders. Further, there might be other unmeasured confounders that were not included in the model. To better understand the associations between different predictors and the outcome, it is best to evaluate each predictor individually. Nonetheless, the aim was to understand the associations in the sample, and not the causal effects.

Conclusion

Active disease surveillance can be costly and time-intensive, especially when empirical data is limited. Our findings indicate that some counties in southern Indiana have a higher prevalence of self-reported TBD diagnosis than would be expected if TBD diagnosis were randomly distributed. This may point to the presence of more risk factors for tick exposure and TBD diagnosis in these counties. Whether these risk factors are the same as those reported in our predictive model remain to be seen. It is also possible that over-diagnosis of TBDs may be responsible for the observed results in some of the affected counties. The finding of clusters of self-reported TBD diagnosis in the south is consistent with the increasing northern spread of TBDs that has been reported severally [4, 5].

It is worth mentioning too, that because spatial scan statistics only provides an approximate location and size of the clusters, the exact borders of the clusters are uncertain. This implies that for any given cluster, there may be areas within the cluster that do not have an excess risk of self-reported TBD diagnosis, and areas outside the cluster that could have an excess risk. Nonetheless, communities in the counties with high relative risk of self-report TBD diagnosis, along with neighboring counties, can use the findings of this study to advocate for more investigation into the reasons behind the significant findings. Results can also be used to garner support for tick exposure and TBD awareness initiatives among government agencies, community organizations, policy makers and members of the public in the affected counties. This study shows that self-reported TBD diagnosis data provides important clues for identifying geographic foci of TBD. These findings can inform more efficient targeted surveillance strategies, monitoring of the possible geographic expansion of TBDs, and an improved understanding of the spatial epidemiology of TBDs in Indiana. The identification of two clusters of TBD diagnosis suggests a need for continued surveillance and monitoring of the counties observed within these clusters. Future studies

should be designed to identify risk factors for TBD diagnosis in the affected counties of Indiana.

Acknowledgements This project was supported by the Environmental Resilience Institute (ERI), funded by Indiana University's Prepared for Environmental Change (PfEC) Grand Challenge initiative.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest to declare.

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