Impact of prior and projected climate change on US Lyme disease incidence

Lisa I. Couper [1], Andrew J. MacDonald [2], Erin A. Mordecai [1]

Author affiliations:
1. Department of Biology, Stanford University, Stanford, California
2. Earth Research Institute, University of California, Santa Barbara, California

Corresponding author:
Lisa Couper
lcouper@stanford.edu
327 Campus Drive, Stanford, CA 94305

The authors declare they have no actual or potential competing financial interests.

Abstract

Background: Lyme disease is the most common vector-borne disease in temperate zones and a growing public health threat in the US. Tick life cycles and disease transmission are highly sensitive to climatic conditions but determining the impact of climate change on Lyme disease burden has been challenging due to the complex ecology of the disease and the presence of multiple, interacting drivers of transmission.

Objectives: We estimated the impact of prior temperature and precipitation conditions on US Lyme disease incidence and predicted the effect of future climate change on disease.

Methods: We incorporated 17 years of annual, county-level Lyme disease case data in a panel data statistical modeling approach to investigate prior effects of climate change on disease while controlling for other putative drivers. We then used these climate-disease relationships to forecast Lyme disease cases using CMIP5 global climate models and two potential climate scenarios (RCP 4.5 and RCP 8.5).

Results: We find that climate is a key driver of Lyme disease incidence across the US, but the relevant climate variables and their effect sizes vary strongly between regions, with larger effects apparent in the Northeast and Midwest where Lyme disease incidence has recently increased most substantially. In both of these regions, key climate predictors included winter temperatures, spring precipitation, dry summer weather, and temperature variability. Further, we predict that total US Lyme disease incidence will increase significantly by 2100 under a moderate emissions scenario, with nearly all of the additional cases occurring in the Northeast and Midwest.

Conclusions: Our results demonstrate a regionally-variable and nuanced relationship between climate change and Lyme disease and highlight the need for improved preparedness and public health interventions in endemic regions to minimize the impact of further climate change-induced increases in Lyme disease burden.

Introduction

Arthropod-transmitted pathogens and the diseases they cause pose a severe and growing threat to global public health (World Health Organization 2014). Because vector life cycles and disease transmission are highly sensitive to abiotic conditions (Mattingly 1969; Sonenshine and Roe 2013), climate change is expected to alter the magnitude and geographic distribution of vector-borne diseases (Kilpatrick and Randolph 2012; World Health Organization 2014). Climatic changes, in particular warming temperatures, have already facilitated expansion of several vector species (e.g., Purse et al. 2005; González et al. 2010; Roiz et al. 2011; Clow et al. 2017a), and have been associated with increased vector-borne disease incidence (e.g., Loevinsohn 1994; Subak 2003; Hii et al. 2009). Identifying areas of high risk for current and future vector-borne disease transmission under climate change is critical for mitigating disease burden. However, the presence of interacting drivers of disease transmission such as land use change and globalization, and the complex ecology of vector-borne disease make this effort challenging (Lafferty and Mordecai 2016; Mills et al. 2010; Ostfeld and Brunner 2015; Rogers and Randolph 2006; Tabachnick 2010).

This challenge is particularly apparent in the case of Lyme disease, the most common vector-borne disease in temperate zones (Kurtenbach et al. 2006; Rizzoli et al. 2011; Rosenberg et al. 2018), because transmission depends on a complex sequence of biotic interactions between vector and numerous host species that may respond differently to environmental change (Ostfeld 1997). In the US, Lyme disease is caused by the bacteria *Borrelia burgdorferi*, and is vectored by two tick species: *Ixodes scapularis* in the eastern and midwestern US and *Ixodes pacificus* in the western US. After hatching from eggs, both tick species have three developmental stages—larvae, nymph, and adult—during which they take a single blood meal from a wide range of vertebrate hosts before transitioning to the next developmental stage or reproducing (Sonenshine and Roe 2013). This life cycle takes 2-3 years to complete, 95% of which is spent at or below the ground surface in diapause, seeking a host, digesting a blood meal, or molting (Ostfeld and Brunner 2015; Sonenshine and Roe 2013).

Given their long life spans, inability to regulate their body temperature, and high degree of interaction with the physical environment, ticks are highly sensitive to changes in climatic and weather conditions (Sonenshine and Roe 2013). Prior research has demonstrated that temperature and moisture conditions at the ground surface strongly influence tick mortality, development, and host-seeking abilities (Ostfeld and Brunner 2015). In particular, high temperatures and low humidity decrease *I. scapularis* and *I. pacificus* survival (Bertrand and Wilson 1996; Nieto et al. 2010; Stafford 1994) and host-seeking activity (Lane et al. 1995; MacDonald et al. 2019b; Schulze et al. 2001; Vail and Smith 1998), while cold temperature extremes cause significant mortality (Lindsay et al. 1995; Vandyk et al. 1996). Accordingly, temperature and precipitation are important predictors of these tick species' latitudinal and altitudinal range limits (Berger et al. 2014a; Brownstein et al. 2003; Estrada-Peña 2002; Leighton et al. 2012; McEnroe 1977; Ogden et al. 2005), and changes in climatic conditions have been associated with northward range shifts of *I. scapularis* (Clow et al. 2017b, 2017a; Ogden et al. 2014a).

While the movement of vector species to higher latitudes suggests an associated impending increase in Lyme disease with further climate warming, the direct impacts of climate on Lyme disease cases are difficult to measure given the influence of many non-climate related factors (Kilpatrick et al. 2017). As a result, the few studies that have attempted to determine the impact of climate conditions on Lyme disease incidence have yielded conflicting results. For example, studies have found positive associations between incidence and each of the following: average spring precipitation (McCabe and Bunnell 2004), June moisture index in the region two years prior (Subak 2003), fewer dry summer days (Burtis et al. 2016), warmer winter temperatures in the prior year (Subak 2003), and increasing average annual temperature (Dumic and Severnini 2018; Robinson et al. 2015). However, others failed to detect an effect of temperature on incidence (McCabe and Bunnell 2004; Schauber et al. 2005), found the timing of climatic changes to be inconsistent with the timing of variation in Lyme disease cases (Randolph 2010), were limited in geographic scope (Burtis et al. 2016; Dumic and Severnini 2018; McCabe and Bunnell 2004; Robinson et al. 2015; Subak 2003) and/or used modeling techniques that did not account for confounding variables that might influence disease incidence (Subak 2003; McCabe and Bunnell 2004). Further, while the rise in Lyme disease cases in the US has occurred concurrently with climatic changes promoting tick suitability, demonstrating causal relationships is challenging (Ostfeld and Brunner 2015). This has led others to argue that climate change is merely the backdrop for rising tick-borne disease incidence (Randolph 2010), while other factors such as increasing physician awareness are the true drivers of increased disease burden (Morshed et al. 2006; Scott and Scott 2018). Nonetheless, a recent CDC study on vector-borne disease burden in the US showed a dramatic rise in Lyme disease (Rosenberg 2018), and much of the extensive media coverage of this report asserted the role of climate change. Despite this media attention, as well as strong known relationships between climate conditions and key features of vector ecology, the evidence for climate change as a driver of increasing Lyme disease incidence in the US remains equivocal.

In this study, we investigate the role of past climatic conditions on Lyme disease incidence across the US using a 17-year, county-level Lyme disease case reporting dataset and explicitly controlling for other drivers of disease burden. Specifically, we ask: How has interannual variation in climate conditions contributed to changes in Lyme disease incidence? We include climate variables capturing changes in temperature and precipitation conditions and investigate how relationships between climate and Lyme disease outcomes vary across different regions of the US. To avoid drawing spurious conclusions about the effects of climate, we analyze the effects of other known and potential drivers of disease incidence such as changing forest cover, public awareness of tick-borne disease, and health-seeking behavior, and use a statistical approach that explicitly accounts for unobserved heterogeneity in disease incidence between counties and years. We then use these modeled, regionally-specific relationships between climate and Lyme disease burden to ask: How is US Lyme disease incidence expected to change under future climate scenarios? We report the predicted change in Lyme disease incidence for individual US regions in 2040 – 2050 and 2090 – 2100 relative to hindcasted 2010 – 2020 levels under two potential climate scenarios: RCP 8.5, which reflects the upper range of the literature on emissions, and RCP 4.5, which reflects a moderate mitigation scenario (Hayhoe et al. 2017).

Methods

Lyme disease case data

We obtained annual, county-level reports of Lyme disease cases spanning 2000 to 2017 from the US Centers for Disease Control and Prevention (CDC) (Supplementary Methods). These disease case data provide the most spatially-resolved, publicly available surveillance data in the US. Raw case counts were converted to incidence—the number of cases per 100,000 people—for each year using annual county population sizes from the US Census Bureau (USCB).

Climate data

We calculated the following variables to capture climate conditions relevant for tick-borne disease transmission: average winter temperature lagged one year; average spring precipitation; the number of hot, dry days in May – July; cumulative average temperature; cumulative daily precipitation; temperature variance; and precipitation variance (Table 1). Details about how these variables were calculated and their biological relevance are listed in Table 1. For past climate conditions, we obtained daily, county-level average temperature and total precipitation data from the National Oceanic and Atmospheric Administration (NOAA) weather stations accessed via the CDC's Wide-ranging Online Data for Epidemiological Research (WONDER) database.

To estimate future climate variables, we used CMIP5 modeled temperature and precipitation data available from NASA Goddard Institute for Space Studies global climate models (Schmidt et al. 2014). Specifically, we obtained estimates of daily near-surface air temperature and precipitation through 2100 under the upper climate change scenario (RCP 8.5) and a moderate climate change scenario (RCP 4.5) (Taylor et al. 2012; van Vuuren et al. 2011). These climate scenarios are relatively similar in the radiative forcing levels assumed through 2050 but diverge substantially in the latter half of the century. Climate estimates from these two scenarios are provided at a 2° x 2.5° resolution; values were then ascribed to counties based on county latitude and longitude (Supplementary Methods). Mean values for hindcasted and forecasted climate variables for each region are listed in Supplementary Table 1.

Awareness data

We controlled for variation in public awareness of ticks and Lyme disease using data from Google trends on the frequency of “ticks” as a search term. We obtained data on “ticks” search frequency, normalized for a given location and year, for 2004 (the first year the data were available) to 2017. We also initially used “tick bite”, and “Lyme disease” as search terms, but found that these generated nearly identical coefficient estimates, thus we proceeded to use only the “ticks” search term as a predictor. Search frequency data were aggregated at the designated market area (DMA), the smallest spatial scale available. Search frequency values for a given DMA, which contained an average of 14 counties, were thus applied equally to all counties therein. We also calculated a 1-year lagged version of the tick search variable, as awareness of tick-borne disease is likely endogenous to disease reporting, and using predetermined values reduces endogeneity concerns (Bascle 2008).

Health-seeking behavior data

We explicitly controlled for variation in health-seeking behavior, previously posited as a driver of Lyme disease reporting (Armstrong et al. 2001; Wilking and Stark 2014) by including the following three variables: diabetes incidence, health insurance coverage, and poverty. Diabetes was selected as a healthcare-seeking proxy as the behavioral drivers of healthcare seeking that drive diabetes reporting are likely to be similar to those of Lyme disease. Namely, the early symptoms of diabetes are often vague (Harris and Eastman 2000) and an individual's ability and decision to seek healthcare plays a large role in whether their case is recorded, as reflected in the substantial underreporting of this disease (Anwar et al. 2011; Doshi et al. 2010; Harris and Eastman 2000). We obtained annual, county-level data for 2004 to 2015 on the percentage of adults aged 20+ years diagnosed with type 1 or type 2 diabetes from the CDC’s US Diabetes Surveillance System. To capture variation in healthcare access, we included the annual percentage of county residents with any form of health insurance coverage using data for 2005 to 2017 provided by the USCB’s Small Area Health Insurance Estimates (SAHIE) program. Lastly, we used data from the USCB to include the percentage of county residents living in poverty as a predictor, as poverty has been significantly negatively associated with healthcare-seeking behavior (Bourne 2009; Kirby and Kaneda 2005).

Land cover data

We included two land cover variables putatively associated with higher tick-borne disease risk: the percent forest in a given county and year, and the percent mixed development (Brownstein et al. 2005b; Dister and Fish 1997; Frank et al. 1998; Glass et al. 1995; Killilea et al. 2008; MacDonald et al. 2019a). We calculated these variables using 30-m resolution land cover data from the US Geological Survey (USGS) National Land Cover Database (NLCD) (Yang et al. 2018). Percent forest included any deciduous, evergreen, or mixed forest. Mixed development was defined as areas with a mixture of constructed materials and vegetation, including lawn grasses, parks, golf courses, and vegetation planted in developed settings. We calculated county-level values of these land cover variables for 2001, 2004, 2006, 2008, 2011, 2013, and 2016 as these are the only years the NLCD dataset is currently available.

To estimate future land cover variables, we used USGS land cover projections available through 2100 (Sohl et al. 2014). We used modeled land cover data from two land-use change scenarios corresponding to the Intergovernmental Panel on Climate Change (IPCC) Special Report on Emission Scenarios (SRES). We used scenario B1, which reflects lower urban development, to align with the moderate climate change scenario (RCP 4.5), and scenario A1B, which reflects higher urban development and forest clearing, to align with the upper climate change scenario (RCP 8.5) (Nakicenovic et al. 2000; Rogelj et al. 2012; Sohl et al. 2014). Using these data, we again calculated annual, county-level values of percent forest cover and mixed development. However, as the 'mixed development' land cover class was not included in the projected data, we instead used the 'mechanically disturbed' public or private land cover class (Supplementary Methods).

Regional divisions

Given the large variation in climatic conditions across the US, as well as variation in ecological dynamics of tick-borne disease such as tick species identity, tick densities, tick questing behavior, and host community composition (Eisen et al. 2016; Kilpatrick et al. 2017; Ostfeld 1997; Salkeld and Lane 2010), we examined regional differences in climate-disease relationships. We used the US Fish & Wildlife Service regional boundaries to divide the US into the following seven regions for analysis: Northeast, Midwest, Mountain Prairie, Pacific, Pacific Southwest, Southwest, and Southeast (Figure 1). These regional divisions were selected as they roughly correspond to genetic structuring of *I. scapularis* and *I. pacificus* (Humphrey et al. 2010; Kain et al. 1997, 1999) and are likely distinct in environmental conditions and resources (Ricketts et al. 1999; Smith et al. 2018). Further, each region contains only one vector species: *I. scapularis* in the Northeast, Midwest, Southeast, and Southwest, and *I. pacificus* in the Pacific and Pacific Southwest (Dennis et al. 1998). As neither species has an established presence in the Mountain Prairie, this region was removed from the analysis. Regional descriptions, including the population size (as of 2017), the number of counties, and the average climate conditions, are provided in Supplementary Table 2.

Statistical approach

We used a least squares dummy variable (termed "fixed-effects" in econometrics) regression approach to estimate changes in Lyme disease incidence using repeated observations of the same groups (counties) from 2000 – 2017 (Larsen et al. 2019). We included 'county' and 'year' as dummy variables to control for any unobserved heterogeneity that may influence reported Lyme disease burden in a particular county across all years (e.g., number of health care providers), or influence Lyme disease in all counties in a given year (e.g., changes in disease case definition). All counties (n = 2,232) for which there was complete data on Lyme disease cases, climate, and other predictors were included.

To account for regional variation in the predictors of tick-borne disease incidence (Raghavan et al. 2014; Wimberly et al. 2008), we ran separate models for each US region (see Methods: Regional divisions). We used stepwise variable selection, in which variables were added if they reduced model Akaike information criterion (AIC) by 2 or more, to identify the climate, land cover, and non-ecological predictors that best explained Lyme disease incidence in each region (Yamashita et al. 2007; Zhang 2016). We assessed the multicollinearity of these models by calculating the variance inflation factor (VIF). No predictors had VIF values greater than 10 after the stepwise variable selection procedure, thus we did not remove any variables from the final models due to high collinearity (Hair et al. 2014).

We accounted for spatial autocorrelation of observations by using cluster-robust standard errors. This nonparametric approach accounts for arbitrary forms of autocorrelation within a defined "cluster" to avoid misleadingly small standard errors and test statistics (Cameron and Miller 2015). We specified clusters as US Agricultural Statistics Districts (ASDs) as these districts contain contiguous counties grouped by similarities in soil type, terrain, and climate. When reporting on the significance of a predictor, we use standard errors and p-values calculated using this correction.

Lyme disease forecasting

We forecasted Lyme disease incidence using the climate and land cover variables included in the best model for each region as well as a county dummy variable. Non-ecological predictors were not included as projections for these variables are unavailable. Using these models, we obtained regional estimates for Lyme disease incidence under the upper and moderate climate change scenarios (RCP 8.5 and RCP 4.5) for 2040 – 2050 and 2090 – 2100. We calculated county-level changes in Lyme disease incidence by subtracting modeled incidence for 2010 – 2020 from forecasted incidence generated using the same modeled climate and land cover data sources. We converted predicted Lyme disease incidence to cases by assuming county population sizes remained the same as those in 2017. As the USCB projects a 75% increase in US population size by 2100 (under the most likely scenario regarding fertility, mortality, immigration, and emigration rates) (U.S. Census Bureau 2000), our estimates on the number of additional Lyme disease cases are conservative. To generate rough predictions of Lyme disease case counts under population growth, we provide estimates that assume a 75% increase in population size relative to 2017 within each county. We report point estimates and 95% prediction intervals when discussing predicted changes in Lyme disease case counts.

Model validation

We assessed predictive model accuracy by comparing hindcasted Lyme disease incidence under both emissions scenarios to observed values for 2008 – 2017 (Clark et al. 2001; Judge et al. 1985). We also compared model accuracy under varying model specifications. In the first specification, each regional model contained the predictors (climate, land cover, and non-ecological) determined through variable selection (see Methods: Statistical approach) as well as county and year dummy variables. In the second specification, each regional model contained all available predictors (7 climate predictors, 2 land cover predictors, and 4 non-ecological predictors) and the county and year dummy variables. Under the third specification, regional models contained all available predictors but no dummy variables. Under each of these specifications, we created models of Lyme disease incidence on a training dataset containing a randomly selected 75% subset of counties and years and used the withheld 25% of observations for validation (Caldwell et al. 2016; Hijmans 2012). To evaluate the performance of each model specification, we calculated the root-mean-square error and correlation coefficient between predicted and actual Lyme disease incidence for 2006 – 2013 (the years with complete data for all predictors) for each regional model.

To capture any non-linear relationships between climate predictors and Lyme disease incidence, we also generated models using quadratic versions of the climate predictors where applicable. Specifically, we used the stepwise variable selection approach starting with quadratic and linear versions of each climate variable to again determine the best model for each region. We then used these models to forecast Lyme disease incidence in 2090 - 2100 under both the upper and moderate climate change scenarios.

Results:

Climate and Lyme disease incidence

At least one climate variable was included in the best model of Lyme disease incidence for all US regions with vector species present (Table 2). However, the specific climate variables included in the model varied between regions. Variables capturing precipitation conditions, such as cumulative precipitation or average spring precipitation, were included in models of Lyme disease incidence in the Southwest, Southeast, and Pacific regions. Conversely, only average winter temperature was predictive of Lyme disease incidence in the Pacific Southwest. In the Northeast and Midwest, multiple temperature and precipitation variables such as the number of hot dry days, average spring precipitation, average winter temperature, and temperature variance were included. Further, cumulative temperature was included in the Northeast model while cumulative precipitation was included in the Midwest. Where included, average winter temperature and cumulative temperature were positive predictors of Lyme disease incidence, while average spring precipitation and precipitation variance were negative predictors. The effects of cumulative precipitation, temperature variance, and the number of hot, dry days varied between regions.

Non-climate predictors and Lyme disease incidence

For all regions, the best model of Lyme disease incidence included tick awareness, diabetes incidence, and a land cover variable (Table 2). Specifically, the 1-year lagged tick search frequency was included rather than the contemporary equivalent as it led to greater reductions in model AIC. This tick awareness variable was a positive predictor in all regions. County-level diabetes incidence was a negative predictor in the Northeast, Midwest, and Southeast, and a positive predictor in the Pacific, Pacific Southwest, and Southwest. The percent land cover classified as mixed development was included in the best model for the Northeast (negative predictor), and for the Pacific Southwest and Southwest (positive predictor), while the percent forest cover was included in the Midwest and Pacific (negative predictor), and in the Southeast (positive predictor). The other available non-climate predictors—county-level poverty and health insurance coverage—did not meet the criteria for inclusion in any regional models (see Methods: Statistical approach).

The above predictors were included in each regional model of incidence along with county and year dummy variables. A large portion of the variance in incidence for each region was explained by the county dummy variable (Table 2), indicating that unobserved county-level heterogeneity is a large driver of variable Lyme disease incidence.

Model Validation

Hindcasted Lyme disease incidence matched the observed values with reasonable accuracy overall, with greater correlation between estimated and observed values in higher incidence regions (Northeast and Midwest) than in lower incidence regions (Pacific, Pacific Southwest, Southwest, and Southeast) (Table 3 and Supplementary Figure 1). For all regions, total estimated Lyme disease incidence was within 8.9% of the observed total incidence. Further, the correlation between estimated Lyme disease incidence for a particular county and year and the observed values were 0.86 and 0.90 for the Northeast and Midwest, respectively. In the lower incidence regions, the correlation coefficients were 0.51, 0.34, 0.34, and 0.49 for the Pacific, Pacific Southwest, Southwest, and Southeast, respectively. While the point estimates for hindcasted Lyme disease incidence tended to closely match the observed values, the prediction intervals around these estimates were large, particularly for the lower incidence regions.

Predictive accuracy also varied across the three model specifications evaluated here. As expected, the model specification without county and year dummy variables had higher root-mean-square error or lower correlation coefficients for nearly all regions, indicating lower predictive accuracy (Supplementary Table 3). However, the two model specifications with county and year dummy variables—the main model specification in which predictors were determined through variable selection, and the alternative model specification containing all possible predictors—were very similar in their predictive accuracy. The simpler, variable selection-based model specification was thus selected for the remaining analysis to minimize overfitting and decrease transferability concerns (Allen and Fildes 2001; Wenger et al. 2011; Wenger and Olden 2012), but forecasting results from both model specifications are shown in Supplementary Table 4. Forecasting results from the alternative model specification with all ecological predictors suggest smaller changes and higher uncertainty in Lyme disease incidence for each region, compared to the main model specification.

Several regional models were improved through replacing linear climate predictors with quadratic climate predictors. Specifically, after repeating the variable selection approach including quadratic and linear climate terms, the Northeast incidence model now included quadratic terms for average spring precipitation and cumulative temperature; the Southwest models included quadratic terms for cumulative precipitation, average spring precipitation and precipitation variance; and the Midwest models included quadratic terms for hot dry days, average winter temperature, average spring precipitation, cumulative precipitation, and temperature variance. The Pacific, Pacific Southwest, and Southeast incidence models were not improved through the inclusion of quadratic climate predictors. Forecasting results from models including these non-linear climate variables are similar to those with linear predictors under the moderate climate change scenario, although with smaller predicted changes in incidence (Supplementary Table 5). Forecasting results differ more substantially under the upper climate change scenario, with non-significant decreases predicted for the Northeast and Southeast when quadratic climate predictors are included, but significant increases predicted for these regions under the original model. As the climate predictors used in this study were drawn from the prior literature on climate and Lyme disease cases (see Table 1), in which linear versions of climate predictors were used, we use output from the linear models when presenting forecasting results (but see Supplementary Table 5).

Forecasted Lyme disease incidence

Under the upper climate change scenario (RCP 8.5), the total number of Lyme disease cases in the US is predicted to increase by 17,672 [-13322, 48666] by 2040 – 2050 and 27,630 [-6468, 61727] by 2090 – 2100 (Figure 2, Table 4). These case changes are relative to hindcasted 2010 – 2020 case counts and are based on 2017 population sizes. For the moderate climate change scenario (RCP 4.5), the predicted increases in cases for 2040 – 2050 and 2090 – 2100 were 15,395 [-15493, 46284] and 34,183 [1124, 67243], respectively. These results indicate that substantial future increases in US Lyme disease burden are likely, although the prediction intervals around these estimates are large, and overlap zero except under the moderate climate change scenario for 2090 – 2100. Further, the expected change in incidence varies strongly by region (Figures 2-3). Significant increases in cases are predicted in the Northeast by 2090 – 2100 under both climate change scenarios (29,813 [8311, 51315] under RCP 8.5 and 25,565 [4697, 46434] under RCP 4.5) and for the Southeast under the upper climate change scenario only (1,248 [252, 2244]). Modest, non-significant increases or decreases are predicted for the Pacific, Pacific Southwest and Southwest under both scenarios. For the Midwest, an increase in cases is predicted under the moderate climate change scenario (8,872 [-66, 17810]) while a decrease is predicted under the upper scenario (-3,432 [-12688, 5823]. While both of these predictions were not statistically distinguishable from zero, these results suggest there may be nonlinear effects of climate change in this region.

These predicted changes in Lyme disease case counts are likely conservative as estimates are based on 2017 population sizes. By assuming equal population growth across the US, at levels predicted by the USCB, we find the total number of Lyme disease cases in the US may increase by 48,545 [-11365, 108455] by 2100 under the upper climate change scenario and 60,020 [1974, 118146] under the moderate scenario (Supplementary Table 6). However, as the degree of population growth is highly uncertain, and population growth will vary in magnitude and direction by county, this analysis was largely exploratory. Further, as with the predictions assuming no population growth, the large prediction intervals around the point estimates here indicate the future effects of climate change on Lyme disease incidence are highly uncertain.

Discussion

Vector-borne diseases are inherently sensitive to climatic conditions, making accurately estimating effects of climate change on disease burden a public health priority. We found that climate was a key predictor of Lyme disease incidence in all US regions with established vector species (Northeast, Midwest, Pacific, Pacific Southwest, Southwest, and Southeast) in the past 17 years. However, the specific climate variable(s) predictive of Lyme disease incidence varied between regions. In general, the climate variables predictive of disease incidence for a given region tended to reflect climate conditions within the region and known relationships between tick life cycles and climate (reviewed in Eisen et al. 2016). For instance, in the Southeast and Southwest regions, which have the warmest and driest conditions during the tick questing period (Supplementary Tables 1-2), climate variables capturing precipitation conditions (e.g., cumulative precipitation) were key predictors of Lyme disease incidence. In the colder and more thermally variable Northeast and Midwest regions, climate variables capturing limiting temperatures (e.g., average winter temperatures and temperature variance) were predictive of Lyme disease.

These regionally-specific climate and Lyme disease relationships are consistent with a large body of literature on the physiology and ecology of the US vectors of Lyme disease, *I. scapularis* and *I. pacificus.* In particular, many prior studies have demonstrated substantial decreases in tick survival and questing activity under low moisture conditions (Berger et al. 2014b, 2014a; Jones and Kitron 2000; Knülle and Rudolph 1982; Needham and Teel 1991; Rodgers et al. 2007; Stafford 1994). Thus, variation in precipitation may have a greater impact on Lyme disease incidence in drier regions, as observed in this study, through changes in tick abundance and tick-human contact rates. Also consistent with the results of this study, extensive prior research indicates that cold winter and annual temperatures are associated with longer development periods and/or higher tick mortality (Brownstein et al. 2003; Estrada-Peña 2002; Leighton et al. 2012; McEnroe 1977; Ogden et al. 2004), reduced host-seeking abilities of the adult life stage (Carroll and Kramer 2003; Clark 1995; Duffy and Campbell 1994), and reduced abundance of the white-footed mouse, a key reservoir host species (Wolff 1996). Similarly, studies have found that warming temperatures at high latitudes contribute to quicker tick development rates, increased survival, and range expansion (Brownstein et al. 2003; Clow et al. 2017a; Leighton et al. 2012; Lindsay et al. 1995; Ogden et al. 2004; Rand et al. 2004). These studies suggest that milder winters would be associated with increasing Lyme disease incidence, with the largest effects observed in cooler regions, as detected in this study.

In addition to supporting prior literature on climate and tick ecology, the effects of climate conditions on Lyme disease incidence were detected while controlling for non-climate predictors of disease. In particular, we explicitly controlled for variation in human awareness of ticks, land use, a proxy for health-seeking behavior, and other unobserved heterogeneity between US counties and years in our modeling approach. Increasing tick awareness, as determined by the frequency of tick-related Google searches, was generally positively associated with Lyme disease incidence, while land cover and health-seeking behavior predictors had regionally-variable relationships. By controlling for these effects, we provide strong evidence that the positive effect of warming temperatures on Lyme disease in colder regions is not simply driven by increasing human awareness of tick-borne disease, temporal trends, or other concurrent changes as has been previously suggested (Morshed et al. 2006; Randolph 2010; Scott and Scott 2018).

While our statistical models included both climate and non-climate predictors of Lyme disease incidence, model accuracy varied widely between regions. Most notably, model accuracy was substantially greater for endemic regions (Northeast and Midwest), compared to low incidence regions (Pacific, Pacific Southwest, Southwest, and Southeast) (Ciesielski et al. 1988). The relatively poor predictive accuracy in non-endemic regions may be due to higher misdiagnosis rates and/or higher travel-associated Lyme disease transmission (Eldin and Parola 2018; Parola and Paddock 2018) decoupling the relationship between local conditions and disease. However, evidence suggests that most Lyme disease transmission occurs in the peri-domestic environment, in which the county of transmission and reporting are likely to be the same (Connally et al. 2009; Falco and Fish 1988; Jackson et al. 2006; Maupin et al. 1991). The lower predictive accuracy in these regions more likely reflects a lack of sufficient annual variation in Lyme disease incidence needed to detect effects of climate in these regions, and/or weaker effects of climate conditions on Lyme disease transmission relative to confounding drivers not included in our model such as host movement and community composition. In contrast, the largest effect of climate on disease transmission is expected at the edges of the climate suitability for transmission (Githeko et al. 2000). As the Northeast and Midwest are near the *I. scapularis* northern range limit, the higher model accuracy here likely indicates stronger climate-Lyme disease relationships. Supporting this assertion, more climate variables were included as predictors after variable selection in these regions than in low incidence regions.

Our Lyme disease forecasts, made using regionally-specific incidence models and projected climate and land cover data, suggest that climate change may lead to substantial increases in incidence in coming decades, but that the magnitude of these effects is highly uncertain and depend on assumptions about the functional form of climate-disease relationships. Across the US, an estimated additional 34,183 cases [95% PI: 1124, 67243] are predicted by 2100 under a moderate climate change scenario (RCP 4.5), representing a 92% increase in Lyme disease burden relative to 2010 – 2020 levels. These estimates are likely to be conservative as they relied on 2017 county population sizes. Applying predicted US population growth rates to all counties equally increases this estimate to 60,020 [95% PI: 1974,118146] additional cases by 2100 under the moderate scenario. The overwhelming majority of this increase would be experienced in the Northeast and Midwest while minimal changes are expected elsewhere. Under the upper climate change scenario (RCP 8.5), Lyme disease incidence is predicted to increase in the Northeast and Southeast by 2100, while changes are not statistically distinguishable from zero in other regions and for the US as a whole. However, the large prediction intervals suggest high uncertainty in future Lyme disease incidence, which could include either increases or decreases that could be regionally-specific. Further, the forecasting results differ, particularly for the upper climate change scenario, when generated assuming non-linear climate-disease relationships. These results indicate that climate change will very likely impact future Lyme disease incidence, but that effects will vary strongly between regions, and will depend on the degree of climate change.

Our prediction of climate change-induced increases in Lyme disease burden, particularly at higher latitudes, is consistent with prior studies predicting or observing increasing *I. scapularis* habitat suitability and range expansion under climate warming (McPherson et al. 2017; Ogden et al. 2008, 2014b). Similar range expansions have also been predicted and observed for *Ixodes ricinus*, the European Lyme disease vector, under climate warming (Gray et al. 2009; Jaenson and Lindgren 2011; Lindgren et al. 2000; Porretta et al. 2013). Further, our finding that the predicted changes in incidence depend on the degree of future warming is also consistent with prior work. *I. scapularis* range expansion and population growth, and the proportion of Eastern Canadians at risk for Lyme disease, are predicted to be higher under upper climate change scenarios than under mitigation scenarios (Leighton et al. 2012;

McPherson et al. 2017). These results suggest that vector range expansions and future Lyme disease burdens depend in part on climate policy actions.

More generally, our results are consistent with expectations from vector thermal biology that suggest that warming temperatures generally increase transmission near the cold edge of a vector's range limit, but may decrease or have variable effects elsewhere (Lafferty and Mordecai 2016; Martens et al. 1995; Mordecai et al. 2019; Ogden and Lindsay 2016). For tick-borne disease, as for other vector-borne diseases, multiple temperature-sensitive traits combine to influence transmission, including survival, development rates, and host-seeking (questing) (Ogden et al. 2004; Ogden 2017; Randolph 2004; Randolph et al. 2002). Nonlinear effects of temperature on these traits typically leads to vector-borne disease transmission peaking at intermediate temperatures and declining to zero outside of lower and upper thermal limits (Mordecai et al. 2019). This suggests that climate warming would most strongly increase transmission near the lower thermal limits, such as in the Northeast and Midwest regions, as was observed here. This further suggests the effects of climate warming would differ in magnitude and direction depending on the extent of warming, as seen in the Midwest region where increases in incidence were predicted under moderate warming (RCP 4.5) and decreases in incidence were predicted with more severe warming (RCP 8.5). The theoretical expectations of nonlinear thermal responses therefore help to explain some of the context-dependent effects of temperature found empirically in this study

While our results match expectations from empirical and theoretical vector-borne disease biology, our Lyme disease forecasts should be interpreted with caution. The large prediction intervals around our point estimates indicate a wide range of potential disease outcomes under climate change. While significant increases were predicted for some regions, many other factors contribute to Lyme disease transmission including host movement and community composition, and human avoidance behaviors (Berry et al. 2018; Brinkerhoff et al. 2011; Brownstein et al. 2005b; Larsen et al. 2014; MacDonald et al. 2019a; Ogden et al. 2008; Ostfeld 1997). Accordingly, we found that unobserved county-level heterogeneity, which would encompass these factors, was a predominant driver of incidence in each of our regional models. Further, while we examined the effects of two potential climate scenarios, uncertainty in these climate change projections was not incorporated into our predictive models and would add additional uncertainty in our Lyme disease predictions. Lastly, as our forecasting models extrapolate from climate and disease relationships observed in the previous 17 years, we assume that these relationships can be extended to climate conditions not yet experienced. That is, we assume the relationship between cumulative temperature, for example, and Lyme disease incidence in a given region will remain the same even as cumulative temperatures exceed prior values. This could generate inaccurate predictions for regions near current tick upper thermal limits such as the Southeast and Southwest as further warming and drought here may reduce tick survival and host-seeking abilities (Berger et al. 2014a; Randolph and Storey 1999; Schulze et al. 2001; Vail and Smith 1998). Generating more accurate predictions for these regions would require experiments investigating effects of future temperatures on aspects of tick-borne disease transmission.

Despite these limitations, our results are consistent with a growing body of evidence linking increased Lyme disease risk with climate warming (Brownstein et al. 2005a; Burtis et al. 2016; Clow et al. 2017b; Dumic and Severnini 2018; Kilpatrick et al. 2017; Leighton et al. 2012; Ogden et al. 2008, 2014b; Robinson et al. 2015; Subak 2003; Tuite et al. 2013). We demonstrate that climate is a key driver of Lyme disease incidence across the US, independently of other drivers of disease risk. We predict that future climate change could substantially increase Lyme disease burden, but the predicted effects are highly uncertain and regionally-specific. The largest changes in incidence are likely to be experienced in the Northeast and Midwest, where current climate-disease relationships are strongest and Lyme disease incidence has recently increased most substantially (Rosenberg 2018). Our predictions provide an essential first step in determining broad patterns of Lyme disease risk under climate change, but ongoing surveillance efforts and mechanistic studies linking changes in vector ecology under climate change to human disease incidence should be conducted to refine these risk assessments.

Acknowledgements:

All data used in this study are free, publicly available, and can be accessed here: https://github.com/lcouper/LymeDiseaseClimateChange. We are grateful to the CDC Division of Vector-Borne Diseases for supplying Lyme disease case data, Mohammad Alhamdan from NASA for supplying climate data. and to Iain Caldwell, Jamie Caldwell, Marissa Childs, Johannah Farner, Elizabeth Hadly, Morgan Kain, Devin Kirk, Giulio de Leo, Nicole Nova, and Marta Shocket for providing helpful feedback on the manuscript. LIC was funded by the Stanford Graduate Fellowship. EAM was funded by an NSF Ecology and Evolution of Infectious Diseases grant (DEB-1518681), the Terman Award, and the NIH NIGMS Maximizing Investigators' Research Award (1R35GM133439-01). AJM was funded by a UC Santa Barbara Faculty Research Grant.

References:

Allen PG, Fildes R. 2001. Econometric Forecasting. In: **Principles of Forecasting** (J.S. Armstrong, ed). Vol. 30 of. Springer US:Boston, MA. 303–362.

Anwar H, Fischbacher CM, Leese GP, Lindsay RS, McKnight JA, Wild SH. 2011. Assessment of the under-reporting of diabetes in hospital admission data: a study from the Scottish Diabetes Research Network Epidemiology Group. **Diabet Med** 28:1514–1519; doi:10.1111/j.1464-5491.2011.03432.x.

Armstrong PM, Brunet LR, Spielman A, Telford III SR. 2001. Risk of Lyme disease: perceptions of residents of a Lone Star tick-infested community. **Bull World Health Organ** 79:916–925; doi:10.1590/S0042-96862001001000004.

Bascle G. 2008. Controlling for endogeneity with instrumental variables in strategic management research. **Strateg Organ** 6:285–327; doi:10.1177/1476127008094339.

Berger KA, Ginsberg HS, Dugas KD, Hamel LH, Mather TN. 2014a. Adverse moisture events predict seasonal abundance of Lyme disease vector ticks (Ixodes scapularis). **Parasit Vectors** 7:181; doi:10.1186/1756-3305-7-181.

Berger KA, Ginsberg HS, Gonzalez L, Mather TN. 2014b. Relative humidity and activity patterns of Ixodes scapularis (Acari: Ixodidae). **J Med Entomol** 51:769–776; doi:10.1603/ME13186.

Berry K, Bayham J, Meyer SR, Fenichel EP. 2018. The allocation of time and risk of Lyme: a case of ecosystem service income and substitution effects. **Environ Resour Econ** 70:631–650; doi:10.1007/s10640-017-0142-7.

Bertrand MR, Wilson ML. 1996. Microclimate-dependent survival of unfed adult Ixodes scapularis (Acari: Ixodidae) in nature: life cycle and study design Implications. **J Med Entomol** 33:619–627; doi:10.1093/jmedent/33.4.619.

Bourne PA. 2009. Impact of poverty, not seeking medical care, unemployment, inflation, self-reported illness, and health insurance on mortality in Jamaica. **North Am J Med Sci** 1: 99–109.

Brinkerhoff RJ, Folsom-O'Keefe CM, Tsao K, Diuk-Wasser MA. 2011. Do birds affect Lyme disease risk? Range expansion of the vector-borne pathogen Borrelia burgdorferi. **Front Ecol Environ** 9:103–110; doi:10.1890/090062.

Brownstein JS, Holford TR, Fish D. 2003. A climate-based model predicts the spatial distribution of the Lyme disease vector Ixodes scapularis in the United States. **Environ Health Perspect** 111:1152–1157; doi:10.1289/ehp.6052.

Brownstein JS, Holford TR, Fish D. 2005a. Effect of climate change on Lyme disease risk in North America. **EcoHealth** 2:38–46; doi:10.1007/s10393-004-0139-x.

Brownstein JS, Skelly DK, Holford TR, Fish D. 2005b. Forest fragmentation predicts local scale heterogeneity of Lyme disease risk. **Oecologia** 146:469–475; doi:10.1007/s00442-005-0251-9.

Burtis JC, Sullivan P, Levi T, Oggenfuss K, Fahey TJ, Ostfeld RS. 2016. The impact of temperature and precipitation on blacklegged tick activity and Lyme disease incidence in endemic and emerging regions. **Parasit Vectors** 9; doi:10.1186/s13071-016-1894-6.

Caldwell J, Heron S, Eakin C, Donahue M. 2016. Satellite SST-based coral disease outbreak predictions for the Hawaiian archipelago. **Remote Sens** 8:93; doi:10.3390/rs8020093.

Cameron AC, Miller DL. 2015. A practitioner's guide to cluster-robust inference. **J Hum Resour** 50:317–372; doi:10.3368/jhr.50.2.317.

Carroll JF, Kramer M. 2003. Winter activity of Ixodes scapularis (Acari: Ixodidae) and the operation of deer-targeted tick control devices in Maryland. **J Med Entomol** 40:238–244; doi:10.1603/0022-2585-40.2.238.

Ciesielski CA, Markowitz LE, Horsley R, Hightower AW, Russell H, Broome CV. 1988. The geographic distribution of Lyme disease in the United States. **Ann N Y Acad Sci** 539:283–288; doi:10.1111/j.1749-6632.1988.tb31862.x.

Clark DD. 1995. Lower temperature limits for activity of several Ixodid ticks (Acari: Ixodidae): effects of body size and rate of temperature change. **J Med Entomol** 32:449–452; doi:10.1093/jmedent/32.4.449.

Clark JS, Carpenter SR, Barber M, Collins S, Dobson A, Foley JA, et al. 2001. Ecological forecasts: an emerging imperative. **Science** 293:657–660; doi:10.1126/science.293.5530.657.

Clow KM, Leighton PA, Ogden NH, Lindsay LR, Michel P, Pearl DL, et al. 2017a. Northward range expansion of Ixodes scapularis evident over a short timescale in Ontario, Canada. **PLoS ONE** 12:e0189393; doi:10.1371/journal.pone.0189393.

Clow KM, Ogden NH, Lindsay LR, Michel P, Pearl DL, Jardine CM. 2017b. The influence of abiotic and biotic factors on the invasion of Ixodes scapularis in Ontario, Canada. **Ticks Tick-Borne Dis** 8:554–563; doi:10.1016/j.ttbdis.2017.03.003.

Connally NP, Durante AJ, Yousey-Hindes KM, Meek JI, Nelson RS, Heimer R. 2009. Peridomestic Lyme disease prevention: results of a population-based case–control study. **Am J Prev Med** 37:201–206; doi:10.1016/j.amepre.2009.04.026.

Dennis DT, Nekomoto TS, Victor JC, Paul WS, Piesman J. 1998. Reported distribution of Ixodes scapularis and Ixodes pacificus (Acari: Ixodidae) in the United States. **J Med Entomol** 35:629–638; doi:10.1093/jmedent/35.5.629.

Dister SW, Fish D. 1997. Landscape characterization of peridomestic risk for Lyme disease using satellite imagery. **Am J Trop Med Hyg** 6.

Doshi AM, Van Den Eeden SK, Morrill MY, Schembri M, Thom DH, Brown JS. 2010. Women with diabetes: understanding urinary incontinence and help seeking behavior. **J Urol** 184:1402–1407; doi:10.1016/j.juro.2010.06.014.

Duffy DC, Campbell SR. 1994. Ambient air temperature as a predictor of activity of adult Ixodes scapularis (Acari: Ixodidae). **J Med Entomol** 31:178–180; doi:10.1093/jmedent/31.1.178.

Dumic I, Severnini E. 2018. "Ticking bomb": the impact of climate change on the incidence of Lyme disease. **Can J Infect Dis Med Microbiol;** doi:10.1155/2018/5719081.

Eisen RJ, Eisen L, Ogden NH, Beard CB. 2016a. Linkages of weather and climate with *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae), enzootic transmission of *Borrelia burgdorferi* , and Lyme disease in North America. **J Med Entomol** 53:250–261; doi:10.1093/jme/tjv199.

Eldin C, Parola P. 2018. Update on tick-borne bacterial diseases in travelers. **Curr Infect Dis Rep** 20:17; doi:10.1007/s11908-018-0624-y.

Estrada-Peña A. 2002. Increasing habitat suitability in the United States for the tick that transmits Lyme disease: a remote sensing approach. **Environ Health Perspect** 110:635–640; doi:10.1289/ehp.110-1240908.

Falco RC, Fish D. 1988. Prevalence of Ixodes dammini near the homes of Lyme disease patients in Westchester county, New York. **Am J Epidemiol** 127:826–830; doi:10.1093/oxfordjournals.aje.a114865.

Frank DH, Fish D, Moy FH. 1998. Landscape features associated with Lyme disease risk in a suburban residential environment. **Landsc Ecol** 13:27–36; doi:10.1023/A:1007965600166.

Githeko AK, Lindsay SW, Confalonieri UE, Patz JA. 2000. Climate change and vector-borne diseases: a regional analysis. **Bull World Health Organ** 12.

Glass GE, Schwartz BS, Morgan JM, Johnson DT, Noy PM, Israel E. 1995. Environmental risk factors for Lyme disease identified with geographic information systems. **Am J Public Health** 85:944–948; doi:10.2105/AJPH.85.7.944.

González C, Wang O, Strutz SE, González-Salazar C, Sánchez-Cordero V, Sarkar S. 2010. Climate change and risk of Leishmaniasis in North America: predictions from ecological niche models of vector and reservoir species. A.P. Galvani, ed **PLoS Negl Trop Dis** 4:e585; doi:10.1371/journal.pntd.0000585.

Gray JS, Dautel H, Estrada-Peña A, Kahl O, Lindgren E. 2009. Effects of climate change on ticks and tick-borne diseases in Europe. **Interdiscip Perspect Infect Dis** 2009:1–12; doi:10.1155/2009/593232.

Hair JF, Black WC, Babin B, Anderson R, eds. 2014. **Multivariate data analysis.** 7th ed. Pearson.

Harris MI, Eastman RC. 2000. Early detection of undiagnosed diabetes mellitus: a US perspective. **Diabetes Metab Res Rev** 16:230–236; doi:10.1002/1520-7560(2000)9999:9999<::AID-DMRR122>3.0.CO;2-W.

Hayhoe K, Edmonds J, Kopp RE, LeGrande AN, Sanderson BM, Wehner MF, et al. 2017. Climate models, scenarios, and projections. In: **Climate Science Special Report: Fourth National Climate Assessment, Volume I** (D.J. Wuebbles, D.W. Fahey, K.A. Hibbard, D.J. Dokken, B.C. Stewart, and T.K. Maycock, eds). U.S. Global Change Research Program Washington, DC, USA. 133–160.

Hii YL, Rocklöv J, Ng N, Tang CS, Pang FY, Sauerborn R. 2009. Climate variability and increase in intensity and magnitude of dengue incidence in Singapore. **Glob Health Action** 2:2036; doi:10.3402/gha.v2i0.2036.

Hijmans RJ. 2012. Cross-validation of species distribution models: removing spatial sorting bias and calibration with a null model. **Ecology** 93:679–688; doi:10.1890/11-0826.1.

Humphrey PT, Caporale DA, Brisson D. 2010. Uncoordinated phylogeography of Borrelia burgdorferi and its tick vector, Ixodes scapularis. **Evolution** 64:2653–2663; doi:10.1111/j.1558-5646.2010.01001.x.

Jackson LE, Hilborn ED, Thomas JC. 2006. Towards landscape design guidelines for reducing Lyme disease risk. **Int J Epidemiol** 35:315–322; doi:10.1093/ije/dyi284.

Jaenson TGT, Lindgren E. 2011. The range of Ixodes ricinus and the risk of contracting Lyme borreliosis will increase northwards when the vegetation period becomes longer. **Ticks Tick-Borne Dis** 2:44–49; doi:10.1016/j.ttbdis.2010.10.006.

Jones CJ, Kitron UD. 2000. Populations of Ixodes scapularis (Acari: Ixodidae) are modulated by drought at a Lyme disease focus in Illinois. J **Med Entomol** 37:408–415; doi:10.1093/jmedent/37.3.408.

Judge G, Griffiths W, Carter R, Lutkepohl H, Lee T. 1985. **The Theory and Practice of Econometrics.** Wiley:New York.

Kain DE, Sperling FAH, Daly HV, Lane RS. 1999. Mitochondrial DNA sequence variation in Ixodes pacificus (Acari: Ixodidae). **Heredity** 83:378–386; doi:10.1046/j.1365-2540.1999.00611.x.

Kain DE, Sperling FAH, Lane RS. 1997. Population genetic structure of Ixodes pacificus (Acari: Ixodidae) using allozymes. **J Med Entomol** 34:441–450; doi:10.1093/jmedent/34.4.441.

Killilea ME, Swei A, Lane RS, Briggs CJ, Ostfeld RS. 2008. Spatial dynamics of Lyme disease: a review. **EcoHealth** 5:167–195; doi:10.1007/s10393-008-0171-3.

Kilpatrick AM, Dobson ADM, Levi T, Salkeld DJ, Swei A, Ginsberg HS, et al. 2017. Lyme disease ecology in a changing world: consensus, uncertainty and critical gaps for improving control. **Philos Trans R Soc B Biol Sci** 372:20160117; doi:10.1098/rstb.2016.0117.

Kilpatrick AM, Randolph SE. 2012. Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. **The Lancet** 380:1946–1955; doi:10.1016/S0140-6736(12)61151-9.

Kirby JB, Kaneda T. 2005. Neighborhood socioeconomic disadvantage and access to health care. **J Health Soc Behav** 46:15–31; doi:10.1177/002214650504600103.

Knülle W, Rudolph D. 1982. Humidity relationships and water balance of ticks. In: **Physiology of Ticks**. Elsevier. 43–70.

Kurtenbach K, Hanincová K, Tsao JI, Margos G, Fish D, Ogden NH. 2006. Fundamental processes in the evolutionary ecology of Lyme borreliosis. **Nat Rev Microbiol** 4:660–669; doi:10.1038/nrmicro1475.

Lafferty KD, Mordecai EA. 2016. The rise and fall of infectious disease in a warmer world. **F1000Research** 5; doi:10.12688/f1000research.8766.1.

Lane RS, Kleinjan JE, Schoeler GB. 1995. Diel activity of nymphal Dermacentor occidentalis and Ixodes pacificus (Acari: Ixodidae) in relation to meteorological factors and host activity periods. **J Med Entomol** 32:290–299; doi:10.1093/jmedent/32.3.290.

Larsen AE, MacDonald AJ, Plantinga AJ. 2014. Lyme disease risk influences human settlement in the wildland–urban interface: evidence from a longitudinal analysis of counties in the northeastern United States. **Am J Trop Med Hyg** 91:747–755; doi:10.4269/ajtmh.14-0181.

Larsen AE, Meng K, Kendall BE. 2019. Causal analysis in control-impact ecological studies with observational data. **Methods Ecol Evol;** doi:10.1111/2041-210X.13190.

Leighton PA, Koffi JK, Pelcat Y, Lindsay LR, Ogden NH. 2012. Predicting the speed of tick invasion: an empirical model of range expansion for the Lyme disease vector Ixodes scapularis in Canada. **J Appl Ecol** 49:457–464; doi:10.1111/j.1365-2664.2012.02112.x.

Lindgren E, Tälleklint L, Polfeldt T. 2000. Impact of climatic change on the northern latitude limit and population density of the disease-transmitting European tick Ixodes ricinus. **Environ Health Perspect** 108:119–123; doi:10.1289/ehp.00108119.

Lindsay LR, Barker IK, Surgeoner GA, McEwen SA, Gillespie TJ, Robinson JT. 1995. Survival and development of Ixodes scapularis (Acari: Ixodidae) under various climatic conditions in Ontario, Canada. **J Med Entomol** 32:143–152; doi:10.1093/jmedent/32.2.143.

Loevinsohn ME. 1994. Climatic warming and increased malaria incidence in Rwanda. **The Lancet** 343:714–718; doi:10.1016/S0140-6736(94)91586-5.

MacDonald AJ, Larsen AE, Plantinga AJ. 2019a. Missing the people for the trees: identifying coupled natural–human system feedbacks driving the ecology of Lyme disease. **J Appl Ecol** 56:354–364; doi:10.1111/1365-2664.13289.

MacDonald AJ, O'Neill C, Yoshimizu MH, Padgett KA, Larsen AE. 2019b. Tracking seasonal activity of the western blacklegged tick across California. **J Appl Ecol** 56:2562–2573; doi:10.1111/1365-2664.13490.

Martens W, Jetten T, Rotmans J, Niessen L. 1995. Climate change and vector-borne diseases: a global modelling perspective. **Glob Environ Change** 5:195–209; doi:10.1016/0959-3780(95)00051-O.

Mattingly PF. 1969. **The biology of mosquito-borne disease.** London: George Allen and Unwin Ltd.

Maupin GO, Fish D, Zultowsky J, Campos EG, Piesman J. 1991. Landscape ecology of Lyme disease in a residential area of Westchester county, New York. **Am J Epidemiol** 133:1105–1113; doi:10.1093/oxfordjournals.aje.a115823.

McCabe GJ, Bunnell JE. 2004. Precipitation and the occurrence of Lyme disease in the northeastern United States. **Vector-Borne Zoonotic Dis** 4:143–148; doi:10.1089/1530366041210765.

McEnroe WD. 1977. The restriction of the species range of Ixodes scapularis, Say, in Massachusetts by fall and winter temperature. **Acarologia.**

McPherson M, García-García A, Cuesta-Valero FJ, Beltrami H, Hansen-Ketchum P, MacDougall D, et al. 2017. Expansion of the Lyme disease vector *Ixodes scapularis* in Canada inferred from CMIP5 climate projections. **Environ Health Perspect** 125:057008; doi:10.1289/EHP57.

Mills JN, Gage KL, Khan AS. 2010. Potential influence of climate change on vector-borne and zoonotic diseases: a review and proposed research plan. **Environ Health Perspect** 118:1507–1514; doi:10.1289/ehp.0901389.

Mordecai EA, Caldwell JM, Grossman MK, Lippi CA, Johnson LR, Neira M, et al. 2019. Thermal biology of mosquito-borne disease. **Ecol Lett** 22:1690–1708; doi:10.1111/ele.13335.

Morshed MG, Scott JD, Fernando K, Geddes G, Mcnabb A, Mak S, et al. 2006. Distribution and characterization of Borrelia burgdorferi isolates from Ixodes scapularis and presence in mammalian hosts in Ontario, Canada. **J Med Entomol** 43:762–773; doi:10.1093/jmedent/43.4.762.

Nakicenovic N, Alcamo J, Grubler A, Riahi K, Roehrl RA, Rogner H-H, et al. 2000. **Special Report on Emissions Scenarios (SRES), A Special Report of Working Group III of the Intergovernmental Panel on Climate Change.** Cambridge University Press:Cambridge.

Needham GR, Teel PD. 1991. Off-host physiological ecology of Ixodid ticks. **Annu Rev Entomol** 36:659–681; doi:10.1146/annurev.en.36.010191.003303.

Nieto NC, Holmes EA, Foley JE. 2010. Survival rates of immature Ixodes pacificus (Acari: Ixodidae) ticks estimated using field-placed enclosures. **J Vector Ecol** 35:43–49; doi:10.1111/j.1948-7134.2010.00056.x.

Ogden N, Koffi J, Pelcat Y, Lindsay L. 2014a. Environmental risk from Lyme disease in central and eastern Canada: a summary of recent surveillance information. **Can Commun Dis** Rep 40: 74–82.

Ogden NH. 2017. Climate change and vector-borne diseases of public health significance. **FEMS Microbiol Lett** 364; doi:10.1093/femsle/fnx186.

Ogden NH, Bigras-Poulin M, O'Callaghan CJ, Barker IK, Lindsay LR, Maarouf A, et al. 2005. A dynamic population model to investigate effects of climate on geographic range and seasonality of the tick Ixodes scapularis. **Int J Parasitol** 35:375–389; doi:10.1016/j.ijpara.2004.12.013.

Ogden NH, Lindsay LR. 2016. Effects of climate and climate change on vectors and vector-borne diseases: ticks are different. **Trends Parasitol** 32:646–656; doi:10.1016/j.pt.2016.04.015.

Ogden NH, Lindsay LR, Beauchamp G, Charron D, Maarouf A, O'Callaghan CJ, et al. 2004. Investigation of relationships between temperature and developmental rates of tick *Ixodes scapularis* (Acari: Ixodidae) in the laboratory and field. **J Med Entomol** 41:622–633; doi:10.1603/0022-2585-41.4.622.

Ogden NH, Radojevic´ M, Wu X, Duvvuri VR, Leighton PA, Wu J. 2014b. Estimated effects of projected climate change on the basic reproductive number of the Lyme disease vector Ixodes scapularis. **Environ Health Perspect** 122:631–638; doi:10.1289/ehp.1307799.

Ogden NH, St-Onge L, Barker IK, Brazeau S, Bigras-Poulin M, Charron DF, et al. 2008. Risk maps for range expansion of the Lyme disease vector, Ixodes scapularis, in Canada now and with climate change. **Int J Health Geogr** 7:24; doi:10.1186/1476-072X-7-24.

Ostfeld R, Brunner J. 2015. Climate change and Ixodes tick-borne diseases of humans. **Philos Trans R Soc B Biol Sci** 370:20140051; doi:10.1098/rstb.2014.0051.

Ostfeld RS. 1997. The ecology of Lyme-disease risk: complex interactions between seemingly unconnected phenomena determine risk of exposure to this expanding disease. **Am Sci** 85: 338–346.

Parola P, Paddock CD. 2018. Travel and tick-borne diseases: Lyme disease and beyond. **Travel Med Infect Dis** 26:1–2; doi:10.1016/j.tmaid.2018.09.010.

Porretta D, Mastrantonio V, Amendolia S, Gaiarsa S, Epis S, Genchi C, et al. 2013. Effects of global changes on the climatic niche of the tick Ixodes ricinus inferred by species distribution modelling. **Parasit Vectors** 6:271; doi:10.1186/1756-3305-6-271.

Purse BV, Mellor PS, Rogers DJ, Samuel AR, Mertens PPC, Baylis M. 2005. Climate change and the recent emergence of bluetongue in Europe. **Nat Rev Microbiol** 3:171–181; doi:10.1038/nrmicro1090.

Raghavan RK, Almes K, Goodin DG, Harrington JA, Stackhouse PW. 2014. Spatially heterogeneous land cover/land use and climatic risk factors of tick-borne feline cytauxzoonosis. **Vector-Borne Zoonotic Dis** 14:486–495; doi:10.1089/vbz.2013.1496.

Rand PW, Holman MS, Lubelczyk C, Lacombe EH, DeGaetano AT, Smith RP. 2004. Thermal accumulation and the early development of Ixodes scapularis. **J Vector Ecol** 13.

Randolph SE. 2004. Tick ecology: processes and patterns behind the epidemiological risk posed by ixodid ticks as vectors. **Parasitology** 129:S37–S65; doi:10.1017/S0031182004004925.

Randolph SE. 2010. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? **Vet Parasitol** 167:92–94; doi:10.1016/j.vetpar.2009.09.011.

Randolph SE, Green RM, Hoodless AN, Peacey MF. 2002. An empirical quantitative framework for the seasonal population dynamics of the tick Ixodes ricinus. **Int J Parasitol** 32:979–989; doi:10.1016/S0020-7519(02)00030-9.

Randolph SE, Storey K. 1999. Impact of microclimate on immature tick-rodent host interactions (Acari: Ixodidae): implications for parasite transmission. **J Med Entomol** 36:741–748; doi:10.1093/jmedent/36.6.741.

Ricketts TH, Dinerstein E, Olson DM, Eichbaum W, Loucks CJ, Kavanaugh K, et al. 1999. **Terrestrial Ecoregions of North America: A Conservation Assessment.** Island Press.

Rizzoli A, Hauffe H, Carpi G, Vourc'h G, Neteler M, Rosa R. 2011. Lyme borreliosis in Europe. **Euro Surveill** 16.

Robinson SJ, Neitzel DF, Moen RA, Craft ME, Hamilton KE, Johnson LB, et al. 2015. Disease risk in a dynamic environment: the spread of tick-borne pathogens in Minnesota, USA. **EcoHealth** 12:152–163; doi:10.1007/s10393-014-0979-y.

Rodgers SE, Zolnik CP, Mather TN. 2007. Duration of exposure to suboptimal atmospheric moisture affects nymphal blacklegged tick survival. **J Med Entomol** 44:372–375; doi:10.1093/jmedent/44.2.372.

Rogelj J, Meinshausen M, Knutti R. 2012. Global warming under old and new scenarios using IPCC climate sensitivity range estimates. **Nat Clim Change** 2:248–253; doi:10.1038/nclimate1385.

Rogers DJ, Randolph SE. 2006. Climate change and vector-borne diseases. In: **Advances in Parasitology.** Vol. 62 of. Elsevier. 345–381.

Roiz D, Neteler M, Castellani C, Arnoldi D, Rizzoli A. 2011. Climatic factors driving invasion of the tiger mosquito (Aedes albopictus) into new areas of Trentino, northern Italy. M. Baylis, ed **PLoS ONE** 6:e14800; doi:10.1371/journal.pone.0014800.

Rosenberg R, Lindsey NP, Fischer M, Gregory CJ, Hinckley AF, Mead PS, et al. 2018. Vital signs: trends in reported vectorborne disease cases — United States and territories, 2004–2016. **Morb Mortal Wkly Rep** 67:496–501; doi:10.15585/mmwr.mm6717e1.

Salkeld DJ, Lane RS. 2010. Community ecology and disease risk: lizards, squirrels, and the Lyme disease spirochete in California, USA. **Ecology** 91:293–298; doi:10.1890/08-2106.1.

Schauber EM, Ostfeld RS, Jr ASE. 2005. What is the best predictor of annual Lyme disease incidence: weather, mice, or acorns? **Ecol Appl** 15:575–586; doi:10.1890/03-5370.

Schmidt GA, Kelley M, Nazarenko L, Ruedy R, Russell GL, Aleinov I, et al. 2014. Configuration and assessment of the GISS ModelE2 contributions to the CMIP5 archive. **J Adv Model Earth Syst** 6:141–184; doi:10.1002/2013MS000265.

Schulze TL, Jordan RA, Hung RW. 2001. Effects of selected meteorological factors on diurnal questing of Ixodes scapularis and Amblyomma americanum (Acari: Ixodidae). **J Med Entomol** 38:318–324; doi:10.1603/0022-2585-38.2.318.

Scott J, Scott C. 2018. Lyme disease propelled by Borrelia burgdorferi-infected blacklegged ticks, wild birds and public awareness ─ not climate change. **J Vet Sci Med** 6:01–08; doi:10.13188/2325-4645.1000035.

Smith JR, Letten AD, Ke P-J, Anderson CB, Hendershot JN, Dhami MK, et al. 2018. A global test of ecoregions. **Nat Ecol Evol** 2:1889–1896; doi:10.1038/s41559-018-0709-x.

Sohl TL, Sayler KL, Bouchard MA, Reker RR, Friesz AM, Bennett SL, et al. 2014. Spatially explicit modeling of 1992–2100 land cover and forest stand age for the conterminous United States. **Ecol Appl** 24:1015–1036; doi:10.1890/13-1245.1.

Sonenshine DE, Roe RM. 2013. **Biology of Ticks.** Oxford University Press, New York.

Stafford KC. 1994. Survival of immature Ixodes scapularis (Acari: Ixodidae) at different relative humidities. **J Med Entomol** 31:310–314; doi:10.1093/jmedent/31.2.310.

Subak S. 2003. Effects of climate on variability in Lyme disease incidence in the northeastern United States. **Am J Epidemiol** 157:531–538; doi:10.1093/aje/kwg014.

Tabachnick WJ. 2010. Challenges in predicting climate and environmental effects on vector-borne disease episystems in a changing world. **J Exp Biol** 213:946–954; doi:10.1242/jeb.037564.

Taylor KE, Stouffer RJ, Meehl GA. 2012. An overview of CMIP5 and the experiment design. **Bull Am Meteorol Soc** 93:485–498; doi:10.1175/BAMS-D-11-00094.1.

Tuite AR, Greer AL, Fisman DN. 2013. Effect of latitude on the rate of change in incidence of Lyme disease in the United States. **CMAJ Open** 1:E43–E47; doi:10.9778/cmajo.20120002.

U.S. Census Bureau. 2000. Annual projections of the total resident population as of July 1: middle, lowest, highest, and zero international migration series, 1999 to 2100. **US Census Bur**.

Vail SG, Smith G. 1998. Air temperature and relative humidity effects on behavioral activity of blacklegged tick (Acari: Ixodidae) nymphs in New Jersey. **J Med Entomol** 35:1025–1028; doi:10.1093/jmedent/35.6.1025.

van Vuuren DP, Edmonds J, Kainuma M, Riahi K, Thomson A, Hibbard K, et al. 2011. The representative concentration pathways: an overview. **Clim Change** 109:5–31; doi:10.1007/s10584-011-0148-z.

Vandyk JK, Bartholomew DM, Rowley WA, Platt KB. 1996. Survival of Ixodes scapularis (Acari: Ixodidae) exposed to cold. **J Med Entomol** 33:6–10; doi:10.1093/jmedent/33.1.6.

Wenger SJ, Isaak DJ, Dunham JB, Fausch KD, Luce CH, Neville HM, et al. 2011. Role of climate and invasive species in structuring trout distributions in the interior Columbia River Basin, USA. **Can J Fish Aquat Sci** 68:988–1008; doi:10.1139/f2011-034.

Wenger SJ, Olden JD. 2012. Assessing transferability of ecological models: an underappreciated aspect of statistical validation. **Methods Ecol Evol** 3:260–267; doi:10.1111/j.2041-210X.2011.00170.x.

Wilking H, Stark K. 2014. Trends in surveillance data of human Lyme borreliosis from six federal states in eastern Germany, 2009–2012. **Ticks Tick-Borne Dis** 5:219–224; doi:10.1016/j.ttbdis.2013.10.010.

Wimberly MC, Yabsley MJ, Baer AD, Dugan VG, Davidson WR. 2008. Spatial heterogeneity of climate and land-cover constraints on distributions of tick-borne pathogens. **Glob Ecol Biogeogr** 17:189–202; doi:10.1111/j.1466-8238.2007.00353.x.

Wolff JO. 1996. Coexistence of white-footed mice and deer mice may be mediated by fluctuating environmental conditions. **Oecologia** 108:529–533; doi:10.1007/BF00333730.

World Health Organization. 2014. A global brief on vector-borne diseases. **World Health Organ Tech Rep.**

Yamashita T, Yamashita K, Kamimura R. 2007. A stepwise AIC method for variable selection in Linear Regression. **Commun Stat - Theory Methods** 36:2395–2403; doi:10.1080/03610920701215639.

Yang L, Jin S, Danielson P, Homer C, Gass L, Bender SM, et al. 2018. A new generation of the United States National Land Cover Database: requirements, research priorities, design, and implementation strategies. **ISPRS J Photogramm Remote Sens** 146:108–123; doi:10.1016/j.isprsjprs.2018.09.006.

Zhang Z. 2016. Variable selection with stepwise and best subset approaches. **Ann Transl Med** 4:136–136; doi:10.21037/atm.2016.03.35.

Tables

Table 1. Climate variables tested for models of disease incidence by region, along with descriptions and justification of their relevance to disease transmission.

Climate Variable	Description	Biological Relevance
Lagged winter temperature	Average monthly temperatures for Dec - Feb 1.5 years prior. Identified by Subak, 2003 as significantly positively correlated with Lyme disease incidence in highly endemic areas.	Colder winter temperatures are associated with reduced host-seeking abilities of the adult tick (Duffy and Campbell 1994; Clark 1995; Carroll and Kramer 2003) and reduced abundance of the white-footed mouse, a highly competent reservoir host (Wolff 1996).
Spring precipitation	Average precipitation in May and June. Identified by McCabe and Bunnell, 2004 as significantly positively correlated with Lyme disease incidence in highly endemic areas.	Greater precipitation during the late spring and early summer increases the moisture of the leaf litter, providing conditions which promote the survival and questing activity of the nymphal life stage (Knülle and Rudolph 1982; Berger et al. 2014).
Hot, dry days	The number of days with temperature > 25°C and precipitation = 0 during May – July (or May – June for counties with *Ixodes pacificus*). Identified by Burtis et al. 2016 as significantly negatively correlated with Lyme disease incidence in highly endemic areas.	Hot, dry conditions are associated with decreased questing activity and questing height of ticks (Randolph and Storey 1999; Schulze *et al.* 2001), reducing the likelihood of attachment to humans (Arsnoe et al. 2015). The May through July, and May through June, time periods capture the peak nymphal questing periods for *I. scapularis* and *I. pacificus*, respectively (Eisen et al. 2016).
Cumulative average temperature	The sum of average daily temperatures (°F) over the entire year	Cumulative temperature appears to control most developmental stages of *I. scapularis* (Lindsay et al. 1995; Rand et al. 2004). Lower cumulative temperature is associated with longer development periods and/or higher tick mortality (McEnroe 1977; Estrada-Peña 2002; Brownstein et al. 2003; Ogden et al. 2004; Leighton et al. 2012).
Cumulative daily precipitation	The sum of total daily precipitation (mm) over the entire year	Greater precipitation increases the moisture of the leaf litter, providing conditions which promote tick survival and questing activity (Knülle and Rudolph 1982; Jones and Kitron 2000; Berger et al. 2014a).
Temperature variance	The variance in average daily temperatures (°F) over the entire year	Frequent temperature variation can decrease tick survival, even beyond that of constant cold exposure, due to energetic costs associated with adapting to changing temperatures (Gigon 1985; Herrmann and Gern 2010); however, effects will vary based on the average temperature of the region.

Precipitation variance	The variance in total daily precipitation (mm) over the entire year	Both drought and heavy rainfall are associated with deceased tick questing activity and survival (Randolph 1997; Jones and Kitron 2000; Perret et al. 2004). Variation in precipitation, as opposed to consistent rainfall supplying favorable high relative humidity conditions, may thus be detrimental for tick survival, but will depend on the average precipitation of the region and the magnitude of variation.

Table 2. Effect of climate and non-climate variables on Lyme disease incidence by region. Only variables included in the best model, as determined by variable selection, are shown. The scaled coefficient estimates (Coef.) shown here reflect the standard deviation change in Lyme disease incidence for a one standard deviation change in the climate variable. The coefficients are scaled so that the effects of different variables are directly comparable. The standard errors (SE) shown are clustered by the agricultural statistics district (see Methods: Statistical approach). Statistically significant ($p < 0.05$) coefficients are denoted with *.

	Northeast		Midwest		Pacific		Pacific Southwest		Southwest		Southeast	
Variable	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE
Climate variables												
Avg. Winter Temp.	0.117	0.145	0.398*	0.168			0.872	0.653				
Avg. Spring Precip.	-0.095	0.053	-0.045	0.042	-0.319	0.178			-0.915	0.644		
Hot, Dry Days	-0.141*	0.071	-0.213*	0.079					0.259	0.181		
Cumulative Temp	0.503	0.364										
Cumulative Precip.			-0.070	0.076					2.634	1.734	-0.054*	0.024
Temp. Variance	0.271	0.202	-0.134	0.153								
Precip. Variance									-0.750	0.469		
Non-climate variables												
Lag 'Ticks' Search	0.211*	0.053	0.008	0.019	0.026	0.025	0.028	0.083	0.11	0.092	-0.01	0.017
Poverty												
Percent Insured												
Diabetes	-0.025	0.065	-0.026	0.032	0.052	0.132	0.022	0.094	0.062	0.064	-0.041	0.026
Forest Cover			-3.323	6.121	-0.769	1.706					0.416	0.404
Mixed Dev. Cover	-1.608	0.989					4.57	4.516	2.736	3.439		
R^2	0.796		0.824		0.417		0.375		0.443		0.356	
Model with only county dummy variable												
R^2	0.606		0.331		0.156		0.114		0.090		0.149	
Model with only year dummy variable												
R^2	0.045		0.018		0.028		0.139		0.007		0.010	

Table 3. Observed and estimated total Lyme disease incidence for 2008 – 2017 (i.e. sum of all cases within a region across this time period). Hindcasted values were generated using the climate and land cover variables included in the best model for each region as well as county and year dummy variables. 95% prediction intervals are listed below each estimate. Correlation coefficients indicate the similarity between the estimated and observed Lyme disease incidence for a given county and year.

		Upper climate change scenario (RCP 8.5)		**Moderate climate change scenario (RCP 4.5)**	
	Observed	**Hindcasted**	**Correlation coefficient**	**Hindcasted**	**Correlation coefficient**
Northeast	205664	205664 [99607, 311721]	0.862	205664 [98451, 312877]	0.859
Midwest	107110	107110 [17494, 196726]	0.898	107110 [17201, 197019]	0.897
Pacific	898	818 [-404, 2039]	0.512	847 [-438, 2133]	0.513
Pacific Southwest	678	678 [-1612, 2968]	0.343	678 [-1611, 2967]	0.344
Southwest	1598	1680 [-5129, 8489]	0.335	1602 [-5229, 8433]	0.346
Southeast	4677	4265 [-5795, 14505]	0.494	4348 [-6428, 15125]	0.493

Table 4. Predicted change in the number of Lyme disease cases, relative to hindcasted 2010 – 2020 levels, for each region under upper and moderate climate change scenarios. Point estimates and 95% prediction intervals are shown.

	Upper climate change scenario (RCP 8.5)		**Moderate climate change scenario (RCP 4.5)**	
	2040 - 2050	2090 - 2100	2040 – 2050	2090 - 2100
Northeast	19625 [-209, 39460]	29813 [8311, 51315]	12915 [-7053, 32884]	25565 [4697, 46434]
Midwest	-2566 [-10597, 5465]	-3432 [-12688, 5823]	2554 [-5254, 10362]	8872 [-66, 17810]
Pacific	27 [-134, 189]	59 [-150, 268]	-8 [-162, 146]	-18 [-193, 156]
Pacific Southwest	-13 [-1343, 1317]	-25 [-1406, 1357]	-42 [-1345, 1260]	-164 [-1539, 1211]
Southwest	-16 [-764, 731]	-34 [-787, 718]	-27 [-778, 723]	-56 [-814, 702]
Southeast	614 [-275, 1504]	1248 [252, 2244]	4 [-900, 909]	-15 [-960, 930]
US Total	17672 [-13322 48666]	27630 [-6468, 61727]	15395 [-15493, 46284]	34183 [1124, 67243]

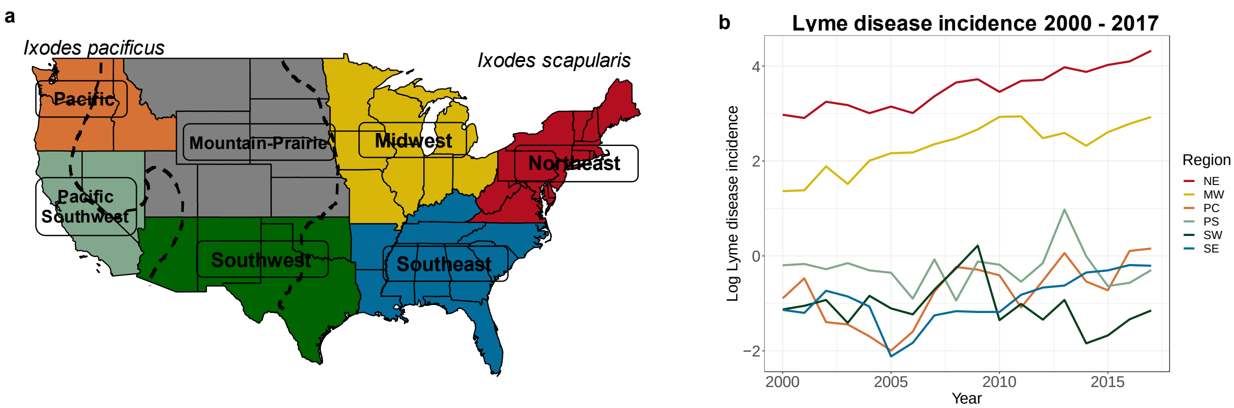

Figure 1. a) Regional boundaries designated by US Fish & Wildlife Service. These regions were used to analyze spatial variation in the effects of climate conditions on disease outcomes. Map recreated from: https://www.fws.gov/endangered/regions/index.html. Dashed black lines denote the approximate eastern boundary of *Ixodes pacificus* and western boundary of *Ixodes scapularis,* respectively, based on distribution maps created by the CDC. **b)** Regional time series of log Lyme disease incidence (the number of cases per 100,000 people in the population) from 2000 – 2017. The Mountain Prairie region is not shown here as it was removed from the analysis due to low vector presence.

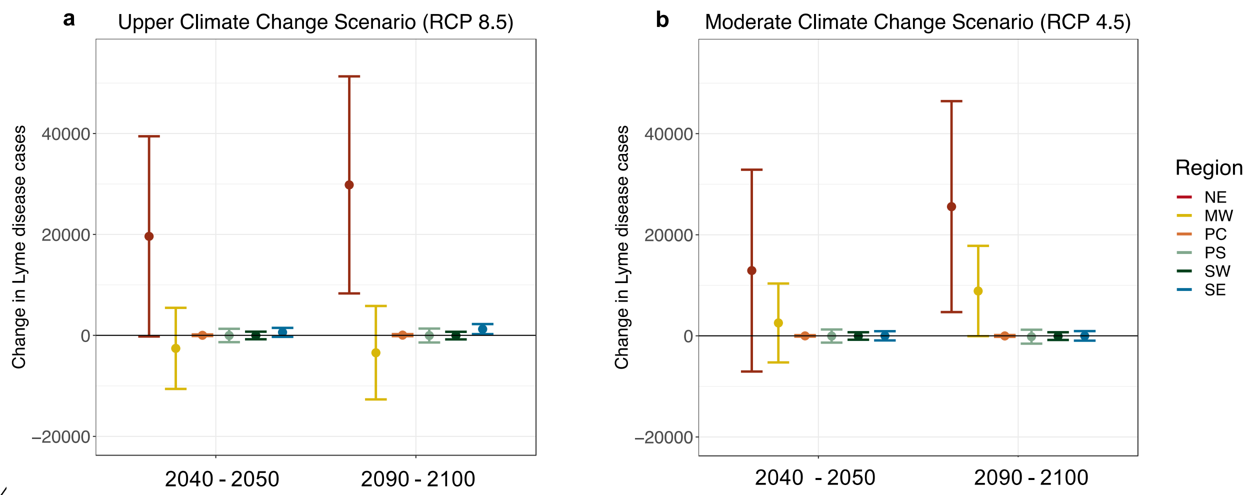

Figure 2. Predicted change in Lyme disease cases by region for 2040 – 2050 and 2090 – 2100 under the **a)** upper and **b)** moderate climate change scenarios. Case changes refer to raw case counts rather than incidence and indicate the average change in cases for a particular decade relative to hindcasted values for 2010 – 2020. Bars represent 95% prediction intervals. Regions are defined in Fig. 1.

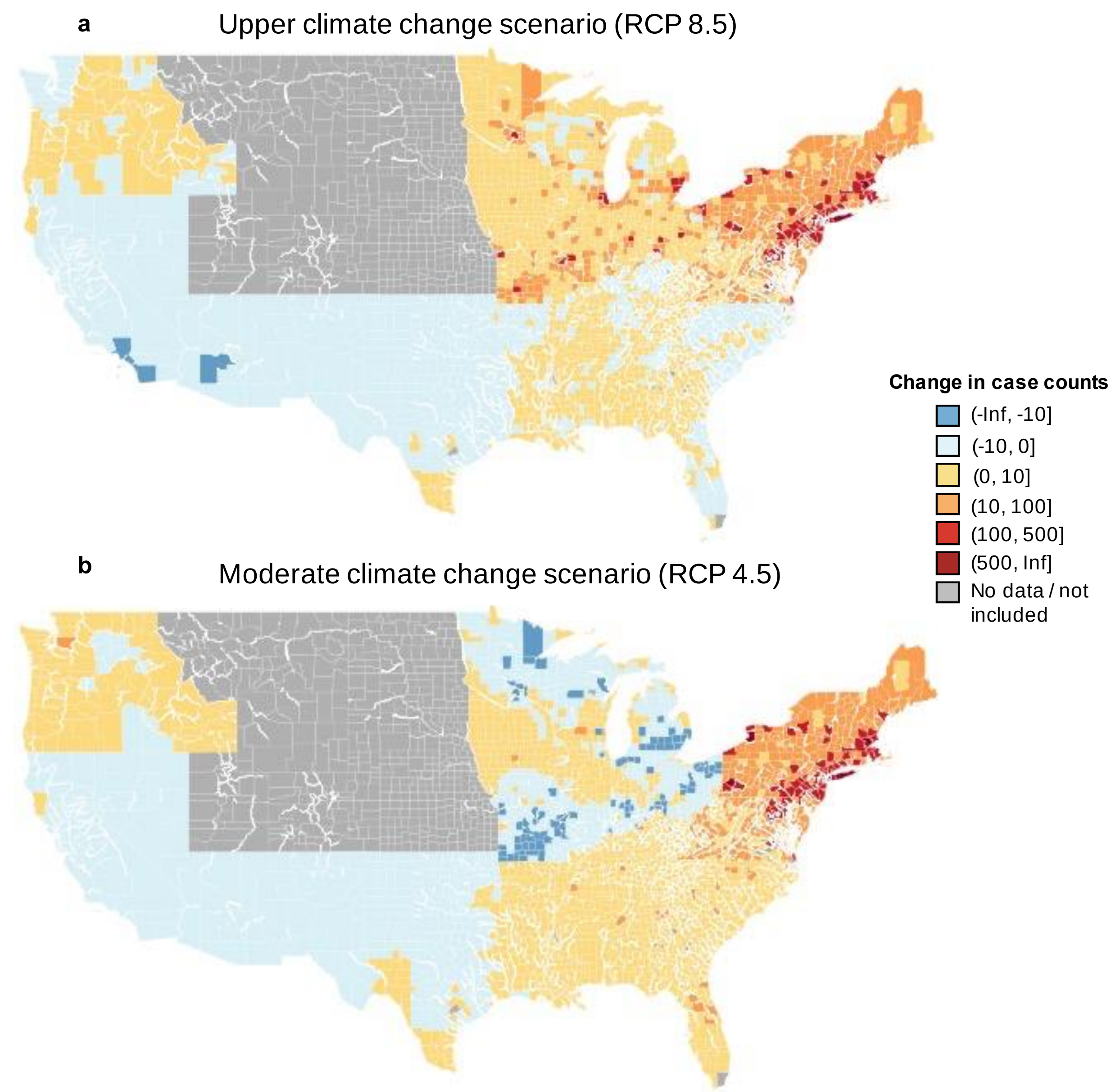

Figure 3. Predicted change in Lyme disease cases for 2100 shown at the county level under the **a)** upper and **b)** moderate climate change scenarios. Case changes refer to raw case counts rather than incidence and are relative to hindcasted values for 2010 – 2020. All counties within the Mountain Prairie are shown in gray as this region was not included in the analysis. Other counties shown in gray (n = 49) containing missing disease, land cover or climate data.