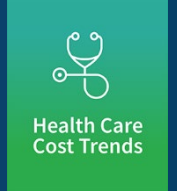


Climate Impact on Tick-Borne Illnesses: An Illustration of Lyme Disease: Modelling Drivers, Health Care Costs and Trends

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Climate Impact on Tick-Borne Illnesses

An Illustration of Lyme Disease: Modelling Drivers, Health Care Costs, and Trends

AUTHORS Yubo Wang, PhD, Columbia University
Sara Goldberg, FSA, Gen Re
Sarah Hoge Kamp, DAV, Gen Re
Yaryna Kolomytseva, MA, Gen Re
R. Dale Hall, FSA, Society of Actuaries Research Institute

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Climate Impact on Tick-Borne Illnesses

An Illustration of Lyme Disease: Modelling Drivers, Health Care Costs, and Trends

Executive Summary

Climate change is at the forefront of changes in ecosystems, biodiversity, and implicitly researchers are only just beginning to understand climate change's effect on human health.

In previous generations, the spread of rodents and other animals paved the way for infectious disease and pandemic such as the infamous Black Death. This arguably came about in part due to climate, with the "so-called medieval climatic optimum."¹ Is the world entering an era of pandemics and infectious disease? With this as a backdrop, this report researches the complex relationship between climate variables and the spread of one infectious disease, Lyme Disease (LD), in the United States.

LD is a well-known disease particularly in the eastern U.S., and also endemic in other geographies explored in Section 5. While by no means a major contributor to causes of death, it is a debilitating and long-term disease particularly if left untreated. Its costs can range from small amounts, such as a course of antibiotics, to expensive and lengthy complications from neurological and musculoskeletal impairments to paralysis, according to a sample dataset explored.

This report explores the shifting geography of LD in the U.S. and beyond and some of the potential determinants of its spread. The host (ticks) and intermediate host activity, range, and survival ultimately determine potential for exposure to LD; the other factor is human activity in high-exposure areas. As humans and nature come closer together, the prognosis here may not be positive; on the other hand, models do suggest some extreme weather events to have both a mitigating effect on tick survival as well as, in layman's terms, the supposition that no one enjoys hiking in high-tick areas on high-precipitation weeks. For example, with extreme weather events, drought appears to be negatively correlated with LD incidence – so while in Germany, recent drought years have brought devastation to mature forests and invite disease from beetles, this does not provide ideal climate for tick activity. Climate and other influential determinants of incidence going forward are found to be minimum average temperature and ranges, land use, and to a less extent precipitation, drought or frost, and certain socioeconomic factors which we explored as proxy for LD awareness and reporting.

In addition to the finding that climate has a material if complex relationship in LD increase in the U.S., the authors add to existing literature on the topic by

- Linking disease to health care costs and complications
- Offering an international scan
- Using a modelling approach which accounts for geographic dependence through novel use of spatial autoregressive model with autoregressive disturbances (SARAR)
- Extended feature engineering over the period of a tick's life span, accounting for time lags effects of precipitation and temperature

¹ Henson R, The Rough Guide to Weather, p383. ISBN 1-85828-827-4

- Offering the regression model as a framework for other infectious diseases and their link to climate
In particular, the modelling techniques described in Section 5.1 and the Appendix A.2 leverages largely unexplored spatial models in the actuarial profession and insurance industry. There exist applications of spatial models to non-life insurance pricing (see, for example, (Rivas-Lopez, et al. 2021)), but there are implications of this modelling approach elsewhere in the industry as well.



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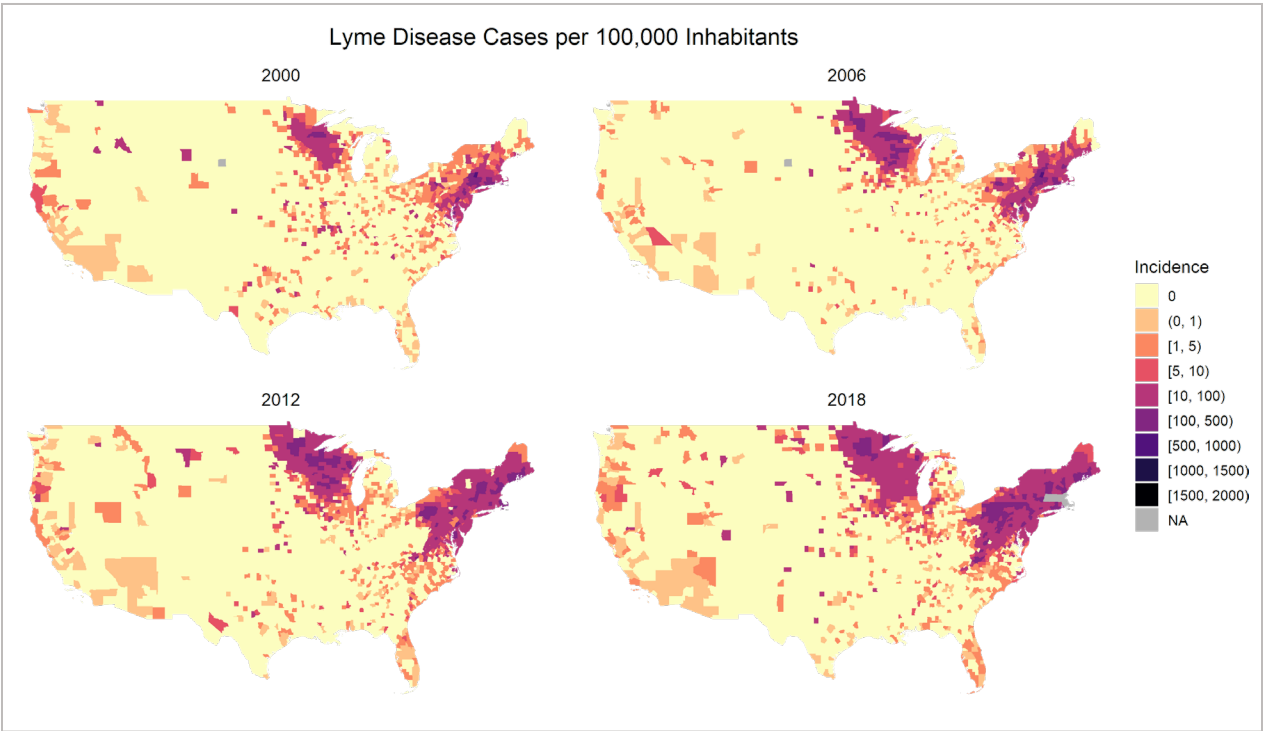
Section 1: Introduction

Lyme disease (LD) is a tick-borne infectious disease, transmitted through the Spirochetes tick species named *Borrelia burgdorferi*. LD is also sometimes referred to simply as borreliosis. *Borrelia* is named after biologist Amédée Borrel, and is perhaps false friends with the term boreal, since transmission to humans usually occurs in forests or forest-adjacent areas. Hiking and outdoor exposure without protection is associated with transmission.

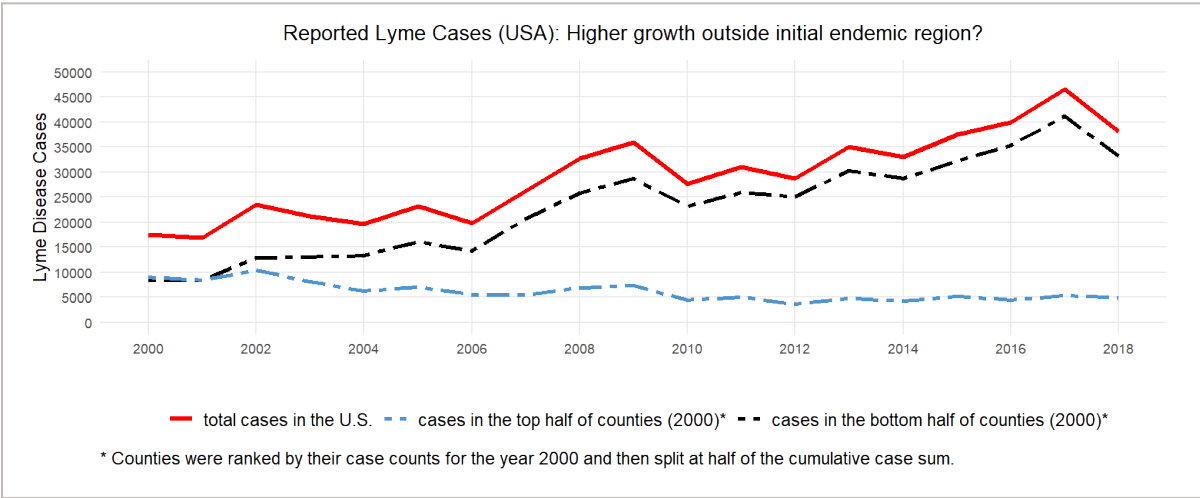
The disease, prevalent in most of central and increasingly northern Europe, is also endemic in the U.S. The disease was first recognized in the U.S. in the 1970s due to a large number of juvenile representations of rheumatoid arthritis and emerged at that time according to some due to modified land use and reforested farmland. LD can be a helpful example of how regional health care claims costs might be impacted by changes in climate trends, and potentially the movement of known diseases to new geographic regions that may not have experienced them as prominently in the past. Changes in temperature or precipitation trends have the potential to bring higher incidence of some infectious diseases to new geographies. Similarly, severe weather events may impact where certain diseases may quickly arise in new areas. For example, a type of fungus which causes coccidioidomycosis, thrives in the soil of dry areas of the Southwest United States and Mexico, where summers are warm but with short, moist winters. Humans become infected when they inhale the fungus from the soil. Extreme windstorms have been cited that lift soil and deposit it further north in California, outside the normal endemic region of the disease (Flynn, et al. 1979).

Section 2: Patterns of Lyme disease in the U.S.

2.1 GEOGRAPHIC SHIFTS OVER TIME



Residents of the northeast and surrounding areas of the disease’s namesake Lyme, Connecticut, are acutely aware of LD and its dangers. This is less true elsewhere in the U.S. and internationally, though regions with long histories of LD exhibit exceptions (see Section 5.2 and 5.3). Awareness may be picking up as incidence spreads, and we note the driver of increased reported cases is from outside the earlier epicenter of the states of New York, Connecticut and New Jersey.



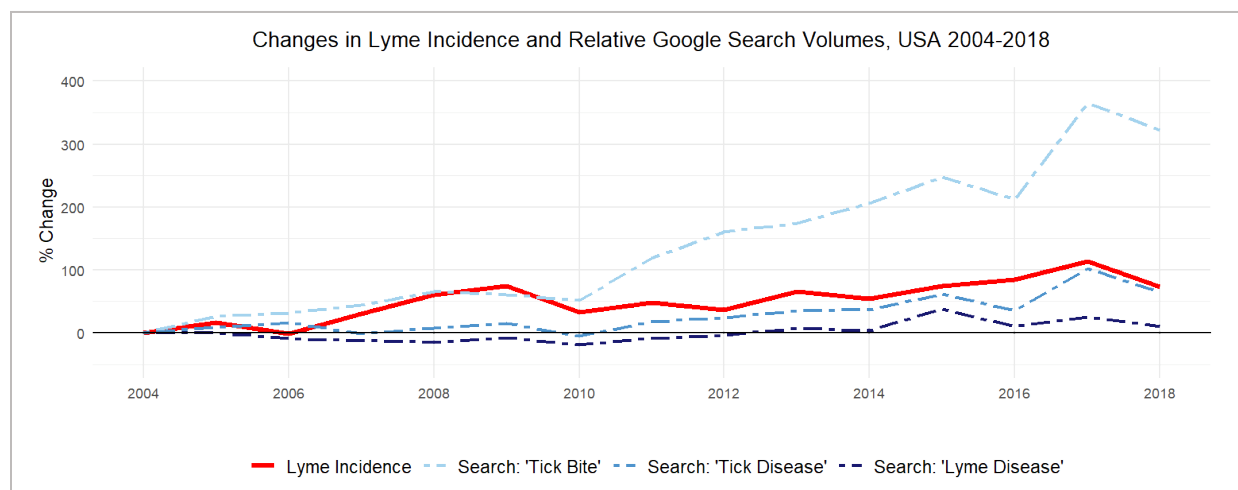
Note on data preparation and case count quality: The Centers for Disease Control and Prevention (CDC) reports cases in two ways: weekly and annual by state (Centers for Disease Control and Prevention (CDC) 2021) and annual by county (Centers for Disease Control and Prevention (CDC) 2022). The weekly statistics are published immediately

as provisional information and therefore are subject to change. New or updated information will not be corrected in already published tables, but only used for future publications. Consequently, cumulative counts can increase or decrease depending on the type of the new information. Only finalized and quality reviewed data will be published as annual report. We assessed both publications and decided to proceed with the annual dataset by county, which provided us with better data quality and geographic granularity.

We kept CDC LD cases for 48 states, except for Hawaii and Alaska, and all counties within these states except for Nantucket County, MA, and San Juan County, WA, since these do not have any neighbors in the context of spatial modeling. We then imputed the LD cases for a handful of counties with either missing values or stark changes in reporting over the observation period (Massachusetts for 2016–2018 and county code 46102 for 2000–2009). The case of Massachusetts highlights that surveillance of infectious disease relies on accurate reporting, which has been contested in Massachusetts in recent years.² Our approach to correcting this via imputation was through extrapolating a simple moving average (rolling 5 years). Alternate approaches via random sampling, spline interpolation, and interpolation using linear weighted moving averages all proved similar.

2.2 REPORTING AND AWARENESS

The trouble with reported cases through the CDC or other governments' disease surveillance is similar to what we have come to understand with COVID-19: unreported cases, and skew in reported cases based on access to testing and socioeconomic bracket. Increasing awareness for Lyme disease can be observed in Google trends. Since 2010 there has been a rapid increase in Google searches for Lyme-related search terms.



The Google search volumes were obtained from Google Trends. For a given search term, Google assigns a value between 0 and 100 as an indicator of the number of searches relative to all other searches, thus controlling for increasing search engine usage. The highest search volume of an observed period (here: 2004–2018) is set to 100, and, for each search term, the rest of the observations are relative to this. Data is available monthly from 2004 onwards. Here, due to the strong seasonality component, we chose to calculate yearly values by averaging over months. To visualize changes over time, Lyme incidence (nationwide, per 100,000 inhabitants) and search volumes are expressed in percentage point changes relative to the observations in 2004.

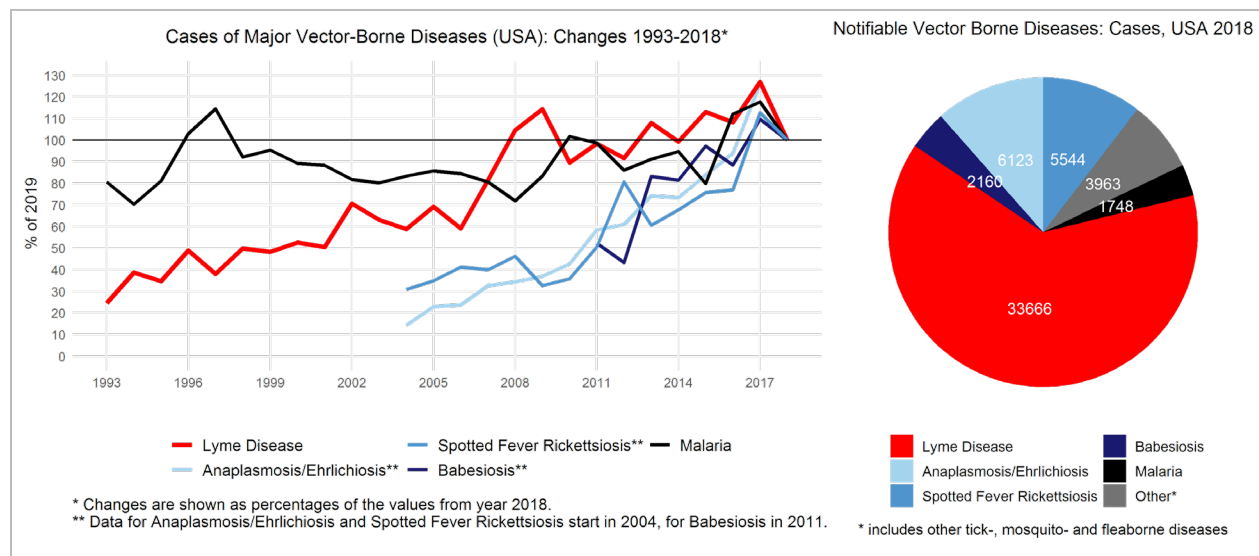
² <https://www.lymedisease.org/massachusetts-disputes-cdcs-claim-drop-lyme-cases/>

One alternate measure of LD incidence could be through tracking health care intervention, such as hospitalization rates. This data was not nationally available, but the regional estimates help us to quantify the impact of underreporting, for example a study suggests underreporting of cases meeting surveillance criteria of 29% (Schiffman, et al. 2018). A recent study on national health claims data suggests that in states with low Lyme incidence only 2% of claims get reported to the CDC whereas in high incidence states approximately 14% of the cases get reported (Schwartz, et al. 2021). The reality of underreporting is likely lower because health claims include suspected cases of LD and therefore are prone to overestimating the actual incidence. Still, this clearly shows that awareness plays a role in CDC's case counts.

An analogy to Germany (Section 5.2) shows that reported cases are on the rise whereas hospitalizations have decreased over time – perhaps not incongruous due precisely to awareness enabling early treatment by primary doctor and hence usually no hospitalization required.

2.3 LYME VERSUS BROADER VECTOR-BORNE ILLNESSES

The role of climate change in the general setting of vector-borne diseases is not clean cut: other factors are at play. There are various concerning vector-borne illnesses in the U.S. and elsewhere, many of which have been observed with increasing frequency across the U.S. Anaplasmosis/ehrlichiosis exhibits a stark trend. Malaria is a major killer globally outside of North America but has also seen increased trends in the United States. While surveillance data to infer the true incidence rate may be flawed – subject to reporting completion and definition changes – the CDC reporting does give indication to increases in vector-borne illness over the past few decades.



We have selected a deeper dive on LD given its increases in reported incidence, expanded geography and being the most common reported tick-borne disease in the U.S. and Europe (Marques, Strle und Wormser 2021). Importantly, it is also endemic in the U.S. and most of Europe. There are also travel-based diseases, or mixed travel/endemic, which make the county of reporting or diagnosis under CDC surveillance less relevant.

Section 3: Existing literature on climate's role

3.1 CLIMATE CHANGE AND LIFE CYCLE OF TICK-BORNE DISEASES

Hosts play a key role in the tick life cycle, which means that the tick population is not only affected directly by their reaction to environmental factors but also indirectly by the impact environmental changes have on their hosts. The following table describes the four stages of the life cycle of *Ixodes scapularis*³.

Stage	Season	Host	Description
Eggs	Spring (-1) - Summer (-1)		The adult females, made larger and sustained by their adult stage ingestion of mammalian host blood, lay eggs on the ground. The egg laying typically begins in late spring, and usually occurs near the site where they detach from their mammalian hosts.
Larva	Summer (-1) - Spring (0)	Small mammals and birds	In summer, eggs that were deposited in late spring begin to hatch into larvae. The larvae begin to feed on a variety of small mammals or birds. After dropping from the host to the ground they begin to pass through and wait out the winter season and molt. After hatching, larvae do not carry tick-borne pathogens but they may have the tendency to pick up pathogens during their sourcing of nutrients from a diseased host. Animals such as the white-footed mouse are often the principal source of the disease pathogens causing LD, babesiosis and a type of ehrlichiosis.
Nymph	Spring (0) - Fall (0)	Wild and domestic mammals, humans	In the spring of the following year, larvae emerge as nymphs. Nymphal-stage ticks will begin to feed and peak activity is often from the months of May through July. Depending on the climate, however, the process may start earlier. Nymphs may transmit disease-causing organisms to hosts, including humans. Due to its small size the tick is more likely to transmit pathogens to humans in their nymphal stage (less than 2 mm) when detection and removal is less likely.
Adult	Fall (0) - Spring (+1)	Medium to large wild and domestic mammals, humans	During the fall nymphs molt into adult ticks. They seek to find mammalian hosts, particularly white-tailed deer during the fall, warm days of winter and the spring. The females feed, mate, lay eggs, and die. If they don't feed in the fall, they try to find a large mammal host the following spring. Frost conditions do not kill blacklegged ticks and they can become active as soon as it is warm and above cold or freezing temperatures. Males attach to a host to wait for females but are not thought to take a blood meal and therefore are not known to transmit tick-borne pathogens. White-tailed deer are the principal host for the adult ticks, an important means of transport and tick abundance is closely linked to the abundance of these animals.

Geographical distribution and magnitude of LD incidence depend on a variety of factors including the availability of (infected) hosts, transportation via hosts such as white-tailed deer, temperature and humidity. In all stages, host-seeking requires temperatures above 7° Celsius (Süss, et al. 2008) and high humidity (European Centre for Disease Prevention and Control 2014) increases the activity. White-tailed deer density in high-LD areas of the U.S. may change over time with hunting practices and land management. Of temperature, precipitation, and extreme weather, increasing temperature is thought to be the key determinant of disease spread and longer seasonal tick activity. There may be mitigating factors with climate change bringing increasingly extreme weather events; while

³ <https://wisconsin-ticks.russell.wisc.edu/ixodes-scapularis-life-cycle/>

these extreme events are inversely correlated with tick survival, they are thought to be more mitigating for mosquitoes than for ticks who can seek cover in forest (Bouchard, et al. 2019).

Apart from temperature and precipitation we do incorporate land use in Section 5's modelling, which may affect both the interaction between humans and ticks as well as the availability of a variety of hosts. Land use (subsequently referred to as a variable group "land class") is indirectly symbiotic with climate, with modified use of Amazonian rainforests being perhaps a visceral example. Also, with climate change and increasing extreme events, forests can become weakened in periods of drought; old forests can be very resilient, yet quickly destroyed by wildfires and preyed on by insects such as the bark beetle in Germany currently. Hence land use is an important variable in the report's modelling and is not unrelated to climate change.

3.2 IPCC FRAMEWORK

The IPCC (Intergovernmental Panel on Climate Change) published its sixth assessment report in August 2021 (Delmotte, et al. 2021). They find that North America will see an increase in temperatures and in extreme high temperatures amongst all evaluated climate projections with a high probability. The increase is likely to exceed the global average increase. The expectations for precipitation changes are somewhat more mixed. In the high northern regions (Canada, Alaska) precipitation is expected to increase with high confidence. In most of the U.S. it is highly likely that extreme precipitation increases and at medium confidence the scenarios also show increases in mean precipitation, which is in some regions restricted to winter season.

Like the US, there is a high confidence that Europe will see above-historical-average increases in temperature in all scenarios. However, precipitation projections for Europe show a more diverse picture but most areas can expect an increase in both flooding events and droughts.

This prognosis for the climate appears according to both existing literature and our modelling to have mixed signals on the direction of LD and possibly other tick-borne illnesses. The increasing temperature and higher precipitation could mean increased potential for tick activity and survival, but with droughts and extreme events counterbalancing this. The next section provides a scan of existing literature on these relationships.

3.3 OTHER NOTABLE LITERATURE

Study	Objective	Modeling	Results
Burtis, et al. (2016)	To investigate the impact of extreme weather factors (the number of hot and dry days) on the LD incidence in the long-term versus recently endemic regions in the United States (p. 2).	Mixed effects generalized additive models were used, with the log-transformed LD incidence as a target variable (p. 5). The models also included county random effects and CDC's reporting type and accounted for spatial correlation in the LD incidence (p. 5).	In the long-term endemic regions, the LD incidence was found to be negatively associated with dry summer weather during the questing period of nymphs in a given year (p. 5). In the recently emerging regions, the time trend was detected, indicating that the LD was increasing over the period 2000–2011 (p. 5).
Couper, MacDonal, & Mordecai (2020)	To investigate the impact of temperature, precipitation, and dry summer weather on the LD incidence in six U.S. regions as well as to predict LD incidence under the RCP 4.5 and RCP 8.5 climate scenarios (p. 4).	A nonspatial fixed effects model with county and time effects was used for each U.S. region and included also tick and LD awareness, health-seeking behavior, and land cover factors as potential LD drivers (pp. 4–6). AIC-based procedure was applied for variable selection and cluster-robust standard errors were computed to account for spatial correlation (p. 6).	The LD incidence was found to be positively associated with average winter temperature (Northeast, Midwest, and Pacific Southwest) and cumulative temperature (Northeast) and negatively associated with average spring precipitation (Northeast, Midwest, Pacific, and Southwest) and precipitation variance (Southwest) (p. 27). The effects of other climatic variables differed in sign across regions (p. 27).
Dong, Huang, Zhang, Wang, & La (2020)	To investigate the impact of climatic and land cover factors on the number of LD cases in the Northeast and Upper Midwest regions of the United States (p. 2).	Negative binomial regression was used to account for the overdispersion in LD cases (p. 4).	Based on the model-averaging results, in the Upper Midwest, LD case counts were found to be positively associated with the edge length and density of developed-open space as well as with the percentage of deciduous forest (p. 6). In the Northeast, LD case counts were found to be positively associated with the edge density of deciduous forests, the edge length of developed-low intensity space, as well as the percentage of developed-high intensity space and negatively associated with the evergreen forest (p. 6).
Burtis, et al. (2016)	To investigate the impact of extreme weather factors (the number of hot and dry days) on the LD incidence in the long-term versus recently endemic regions in the United States (p. 2).	Mixed effects generalized additive models were used, with the log-transformed LD incidence as a target variable (p. 5). The models also included county random effects and CDC's reporting type and accounted for spatial correlation in the LD incidence (p. 5).	In the long-term endemic regions, the LD incidence was found to be negatively associated with dry summer weather during the questing period of nymphs in a given year (p. 5). In the recently emerging regions, the time trend was detected, indicating that the LD was increasing over the period 2000–2011 (p. 5).

Section 4: Disease burden – Costs and complications

4.1 EPIDEMIOLOGY AND TREATMENT

In Lithuania, where LD is highly endemic and exhibiting reported incidence between 80–100 annual cases per 100,000, the most common symptom associated with the diagnosis is erythema migrans (an expanding circular rash, shown in 76% of cases), followed by arthralgia, headaches, weakness and fever (Petrulionienė, et al. 2020). The clinical representation can at first be subtle. Incubation period is 3–30 days. If the infection remains untreated and spreads it can cause severe damage to the nervous and cardiovascular system. Sequelae can develop within weeks or progress over several months in the absence of treatment. Serious health consequences can often be prevented if the infection is detected early and treated with antibiotics. If not treated promptly, LD can be difficult to treat and manage.⁴

Lab diagnosis, tick autopsy and an attempt at antibiotics is the more likely initial treatment route and based on the presence of erythema migrans. However, the clinician or patient may not be looking for this, even if the tick bite was identified, due either to lack of patient awareness or sometimes skepticism in the care setting if the locality is not traditionally prevalent with Lyme-carrying ticks.

4.2 ASSOCIATED CONDITIONS, COMPLICATIONS

In-hospital mortality due to LD is rare, and short of mortality, the cases with complications are in the minority. However, this small minority of cases presents with both high costs and significant lifestyle impact. Using patient level data provides U.S. with the opportunity to track future claim costs and identify complications and conditions associated with a particular disease.

Table 4-1 presents annual claim cost distributions associated with Lyme disease patients. This patient group consists of those with a Lyme disease diagnosis, identified by one of the relevant ICD-10 codes, in the Symphony database. The Symphony database is a large private repository of patient-level integrated data and contains prescription and health insurance claims records. The Symphony database has a broad coverage of more than 280 million patients, made available to us from mid-2019 by the COVID-19 Research Database partners.⁵ Please reference Table A2 in appendix for this and other data sources used throughout the report.

Most patients have less than 3 years of history in the database since coverage only began in mid-2019. We therefore report the estimated claim cost distributions for the first year and the second year from the date of the initial Lyme disease diagnosis. Since claim costs for Lyme disease alone are typically moderate, reported claim costs in Table 4-1 are associated with future diagnoses of all diseases and conditions over the reporting period. Conditions that were present as of the initial Lyme disease diagnosis are excluded.

⁴ <https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/lyme-disease>

⁵ <https://covid19researchdatabase.org/>

TABLE 4-1. FUTURE CLAIM COST DISTRIBUTIONS OF LYME DISEASE PATIENTS

Percentile	Year 1 Costs	Year 2 Costs
25th	\$641	\$781
50th	\$3,389	\$3,697
75th	\$17,603	\$18,068
85th	\$43,396	\$44,317
95th	\$192,626	\$201,091
Mean	\$53,719	\$60,888
Standard Deviation	\$415,556	\$509,059

To identify complications and conditions to which Lyme disease patients are more susceptible, we compare the likelihood of a specific diagnosis among Lyme-disease patients to that among a comparison group of non-Lyme-disease patients. The comparison group is a matched random sample, with a matching age-gender-size profile.

For each disease or condition, we use the ratio of cases in the Lyme-disease patient group to those in the comparison group to help identify if it mostly occurs in the Lyme-disease patient group. Table 4-2 presents the top 10 diagnoses as ranked by this ratio.

TABLE 4-2. TOP CANDIDATES FOR POTENTIAL COMPLICATIONS AND CONDITIONS

ICD10	Description	Proportion (%)	Ratio
A44.9	Bartonellosis, unspecified	0.0395	639
B60.0	Bartonellosis	0.0387	417
A68.1	Tick-borne relapsing fever	0.0053	172
A77.40	Ehrlichiosis, unspecified	0.0100	163
A77.0	Spotted fever due to <i>Rickettsia rickettsii</i>	0.0137	147
A44.8	Other form of bartonellosis	0.0042	135
A77.41	Ehrlichiosis chafeensis	0.0037	120
A26.0	Cutaneous erysipeloid	0.0037	119
A69.0	Necrotizing ulcerative stomatitis	0.0027	88
A69.8	Other specified spirochetal infections	0.0023	75

Of the 10 candidates identified in Table 4-2, most have a connection with tick-borne diseases except for erysipeloid and stomatitis. Our statistical approach appears to be effective in this regard. To the extent that LD is an initial misdiagnosis among patients from tick bites, ratios associated with tick-borne diseases may be slightly overstated by subsequent corrections to the LD diagnosis. In general, while medical knowledge is necessary to identify whether diagnoses are true complications and associated conditions of a particular disease, this statistical approach appears to help identify those to which such patients are most susceptible.

Note that the top candidate diseases and conditions identified are not necessarily the most common ones among Lyme disease patients. This is evident from the proportion information in Table 4-2, the top 10 candidates represent only 0.12% of all subsequent diagnoses.

We can use the same approach to identify the more frequent future diagnoses to which Lyme-disease patients are more susceptible, by ranking the ratio associated with the most frequent future diagnoses among Lyme-disease patients. Results are shown in Table 4-3. The purpose of Table 4-3 is not to identify conditions medically associated with Lyme disease per se, but to identify frequent future conditions that are also more likely in Lyme disease patients.

TABLE 4-3. FREQUENT DIAGNOSES THAT ARE ALSO MORE LIKELY IN LYME DISEASE PATIENTS

ICD10	Description	Proportion (%)	Ratio
Z86.19	Personal history of other infectious and parasitic diseases	0.27	5.77
M25.50	Pain in unspecified joint	0.34	4.04
R53.82	Chronic fatigue, unspecified	0.17	3.75
M79.10	Myalgia, unspecified site	0.21	2.35
R20.2	Paresthesia of skin	0.20	1.93
R51.9	Headache, unspecified	0.30	1.73
R53.83	Other fatigue	0.73	1.72
M54.12	Radiculopathy, cervical region	0.16	1.72
E53.8	Deficiency of other specified B group vitamins	0.16	1.72
R21	Rash and other nonspecific skin eruption	0.27	1.70

Information on claim cost distributions and top future diagnoses can be informative, for example, for insurance and financial resource allocation. While Lyme disease is not a major disease, our statistical approach can be adopted for other major diseases of interest.

Section 5: The big picture - Climate impact on Lyme in multiple locations

Tick-borne illnesses exhibit visible changes in frequency and geography in the U.S., Germany, Finland, and Japan. We explore this subset of countries to paint a broader picture of distinct temperate climates experiencing a prevalence of ticks and potential for both hosts and disease spreading around these areas. Our primary focus for modelling climate's link to LD incidence is in the continental U.S.

5.1 UNITED STATES

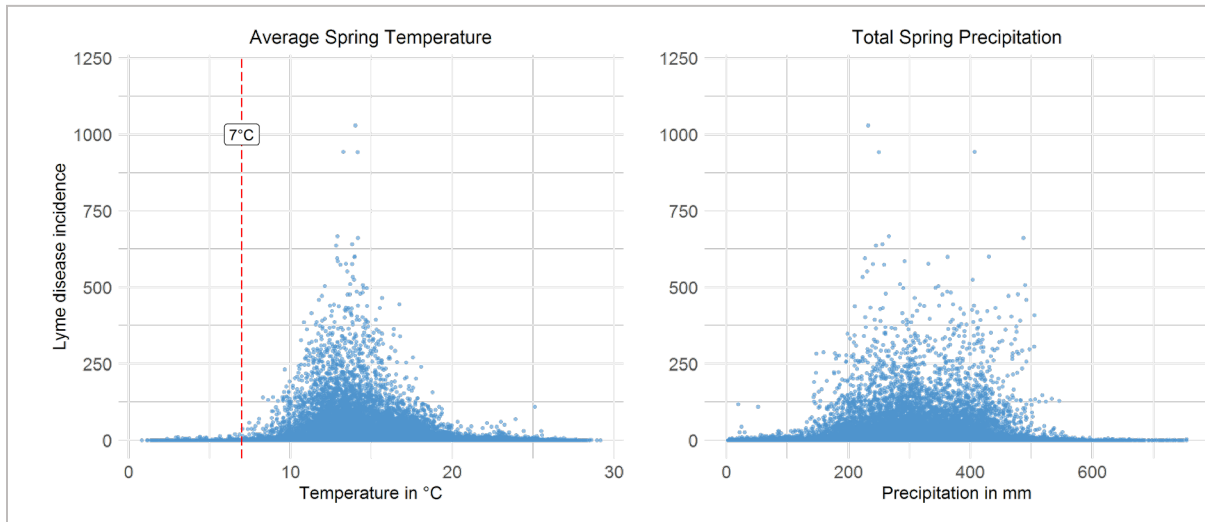
Section 2 illustrated increases and movements in reported LD cases over the past two decades. In this section we explore regression models to account for climate-related and non-climate-linked influences of disease incidence in counties across the US.

5.1.1 CLIMATE-LINKED AND OTHER VARIABLES EXPLORED

From the literature we have identified the following variables as determinants of LD, all of which affect the tick population, the interaction between humans and ticks and/or the likelihood that a case of LD is diagnosed and reported (For a detailed list of variables and the literary foundations for climate linkage to our models, see Table A3 in Appendix A.1 and References respectively):

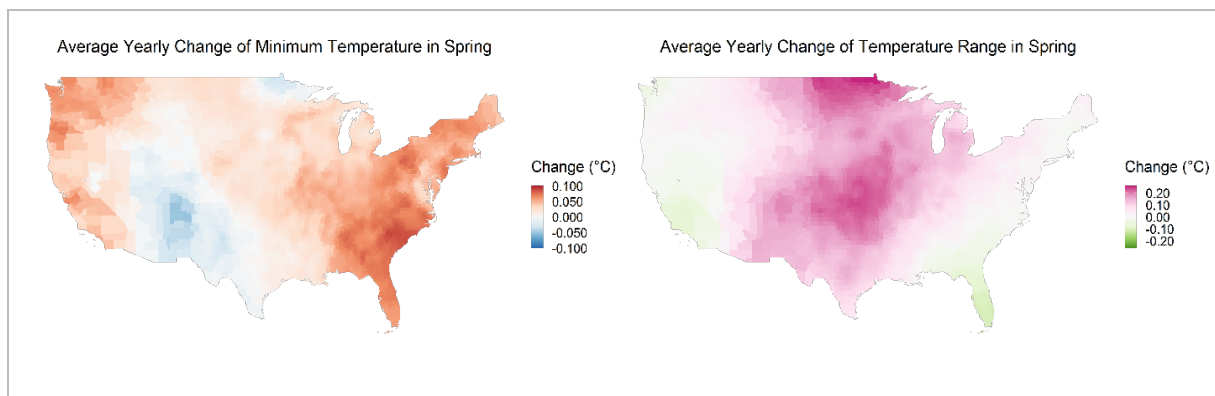
- **Land cover.** Land use affects the tick population, their animal hosts and human exposure to them (Bouchard, et al. 2019, 83). Transmission of LD occurs where humans and ticks interact. This category comprises percentages of the following land cover classes: cropland or pasture/rangeland, forest, as well as unmanaged grass/shrubland. We also include the edge density between urban areas and nature.
- **Temperature.** Literature suggests that the ticks host seeking activity depends on the surrounding temperature (Süss, et al. 2008, Couper, MacDonald und Mordecai 2020, Burtis, et al. 2016). Two groups of temperature variables, average minimum temperature and temperature range in different seasons and years of tick life cycle, were included to capture diverse effects that temperature may have on the incidence.
- **Precipitation.** Humidity affects the tick population differently through the various stages of their lifecycle (Süss, et al. 2008, Couper, MacDonald und Mordecai 2020, Burtis, et al. 2016). Therefore, precipitation is included for the current and proceeding years seasons.
- **Extreme weather.** Tick mortality is associated with frost (low humidity and temperatures below 0°C) and drought (low humidity and high temperature) (Bouchard, et al. 2019, Burtis, et al. 2016).
- **Socioeconomic variables.** To approximate human health-seeking behavior we used unemployment rates. In addition, we include population density as a control variable.

Looking at annual Lyme disease incidence in relation to both temperature and precipitation in spring (defined as April to July) we observe a clear correlation between the climate variables and the nymphs host-seeking behavior. As soon as the average spring temperature exceeds 7°C we see a strong increase in Lyme incidence, indicating high host-seeking activity of ticks. Precipitation is less clear, but we can see that there is preferred range for tick activity – both a “too dry” where hardly any transmission occurs, as well as high precipitation at the extremes not exhibiting high LD transmission either.



The focus of this research is on the impact of climate change. Hence, it is interesting to see the changes in our climate predictor variables over time, many of which overlap with variables utilized in the Actuaries Climate Index.

For example, both spring temperature and spring temperature range have increased over most of the U.S. While temperature increases are most pronounced in the eastern and western coastal regions, temperature variability has increased more in central states. The average yearly change was estimated by fitting an ordinary least squares regression line for each county.



5.1.2 MODELING APPROACH

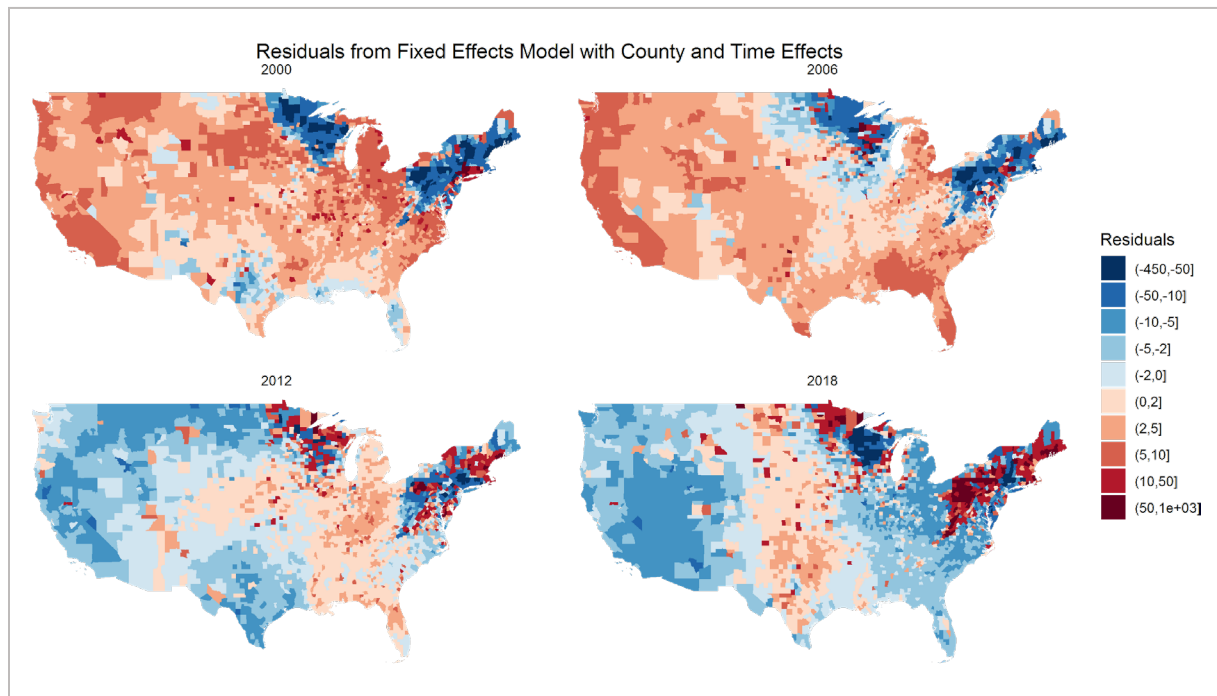
We combined data on the Lyme disease incidence as well as weather, land cover, and socioeconomic variables for 3,104 U.S. counties over the period 2000–2018. Information about cartographic boundary files and data sources used is provided in Table A1 and Table A2 and the definition of predictor variables are provided in Table A3 in Appendix A.1. Nantucket County, MA and San Juan County, WA were excluded from the analysis, since these counties are islands and could not be considered for spatial modeling. The target variable is the Lyme disease incidence, which is the number of reported Lyme disease cases in a county per 100,000 inhabitants.

We considered both nonspatial and spatial fixed effects models to estimate the partial effects of predictor variables. Spatial fixed effects models generalize nonspatial ones, because they relax the assumption of constant direct effects of predictor variables across counties and allow for the existence of spatial spillover effects (see Appendix A.2). In the nonspatial fixed effects model, the effect of a unit change in a specific predictor in a given county on the LD incidence in that county is equal to the beta coefficient associated with that predictor and, hence, is the same for all counties. This effect is referred to as the *direct* effect (LeSage und Pace 2009, 34-37). Furthermore, the effect of a

change in a specific predictor in a county on the LD incidence in any other county is zero by construction. This effect is referred to as the *indirect* or *spillover* effect (LeSage und Pace 2009, 34-37).

In the context of infectious diseases, spillover effects might exist because more welcoming climatic conditions or the expansion of tick habitats in a county might increase tick density and activity during the host-seeking period. Consequently, host migration could potentially lead to increased LD incidence in neighboring counties. Nonspatial models would explain incidence variation that arises from spillover effects by overstating the true direct effects of included predictor variables (LeSage und Pace 2009, 20), which can be also observed in Table A4 in Appendix A.3.

In addition to the presence of spillover effects, there may also exist spatial correlation in unobserved factors captured by the error term. The map of residuals from the nonspatial fixed effects model can be used to visually inspect whether this is the case (LeSage und Pace 2009, 5). In the year of 2000, for example, the observed LD incidence in most counties in the Northeast and a group of counties in the Midwest was lower than the incidence predicted by the model, whereas most counties in the West had incidence above the predicted one. If the nonspatial fixed effects model was correctly specified, then the error term would exhibit no spatial correlation (Greene 2008, 200) and it would not be possible to identify clusters of counties based on the sign of their residuals (LeSage und Pace 2009, 5).

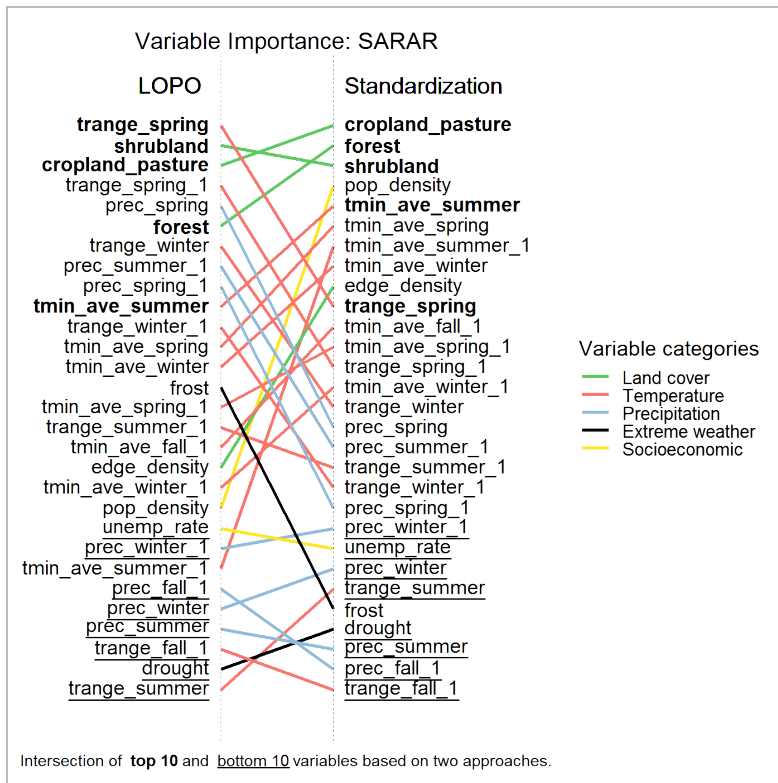


Therefore, our preferred national model specification is the fixed effects spatial autoregressive model with autoregressive disturbances, the SARAR model, with county and time effects (Kelejjan und Prucha 1998, 100, Anselin, Gallo und Jayet 2008, 640, Millo und Piras 2012, 10-11). Since the direct and indirect effects of each predictor variable in the SARAR model vary across counties, their summary measures are provided in Table A4 in Appendix A.3. The summary measure of the direct effects represents the average effect of a unit change in a predictor variable in a county on the incidence in that county (LeSage und Pace 2009, 36-37). The summary measure of the indirect effects can be interpreted in two different ways: either as the total impact on the incidence in one county of a unit change in a predictor in all other counties, or as the total impact on the incidence in all other counties of a unit change in a predictor in one county (LeSage und Pace 2009, 37).

To determine relative importance of predictor variables, we compute variable importance scores using two different approaches. In the leave-one-predictor-out (LOPO) approach, the importance score of a specific predictor variable is computed as the percentage change in the mean squared difference between the observed and fitted values from the model excluding that variable relative to the model including all variables. In the second approach, predictor variables are first standardized, that is, centered and scaled by one standard deviation (Schielzeth 2010). The absolute value of the estimates of the average total effects (the sum of the average direct and indirect effects) in the SARAR model are then taken as the importance scores.

5.1.3 NATIONAL SPATIAL MODELING

The variable importance plot for the SARAR model depicts rankings of predictor variables based on the variable importance scores generated using the LOPO and standardization approaches. In the plot, predictor variables in bold are ranked in the top 10 and underlined variables, in the bottom 10 based on both approaches.



All included land cover classes variables—cropland or pasture/rangeland, forest, and unmanaged grass/shrubland—as well as average minimum summer temperature and spring temperature range appear to have relatively high total impact on the LD incidence. These fields appear relatively important in two complementary approaches to quantify variable importance, so their intersection as illustrated in bold above bolsters our finding of their relative importance. In contrast, preceding-year winter and fall precipitation, given-year winter and summer precipitation, temperature range in fall of a preceding year and in summer of a given year, extreme weather events (drought), as well as the unemployment rate appear to have relatively low total impact on the incidence.

Table A4 in Appendix A.3 contains estimates of the direct effects for the nonspatial fixed effects model as well as of the average direct and indirect effects for the fixed effects SARAR model with county and time effects. The estimate of the spatial autoregressive parameter in the SARAR model is 0.86 ($p < 0.0001$) (see Table A5 in Appendix A.3), which indicates strong positive spatial dependence in the LD incidence on the county level (LeSage und Pace 2009, 17). Based on the SARAR estimation results, the following observations can be made for different categories of

predictor variables. (In parentheses below, “D” stands for the estimate of the average direct effect and “I”, of the average indirect effect).

- Land cover.** The effects of the forest land cover class on the LD incidence were found to be positive ($D = 0.45, p = 0.0003; I = 1.85, p = 0.0003$). A percentage point increase in the forest class in a county was estimated to increase (on average) the LD incidence in that county by 0.45 cases per 100,000 inhabitants. Furthermore, a percentage point increase in the forest class in one county was estimated to increase the LD incidence in all other counties in total by 1.85 cases per 100,000 inhabitants. The effects of the cropland or pasture/rangeland as well as unmanaged grass/shrubland classes were also found to be positive. For a fixed population density, expanding habitats of ticks or their hosts may increase the number of infected ticks that could potentially come into contact with humans (Wood und Lafferty 2013, 246). In addition, we hypothesized that tick-human interactions were most likely to occur at the edges between the urban class and tick or host habitats and that increasing edge density may increase human exposure to Lyme disease. The estimated effects of the edge density are positive ($D = 1.02, p = 0.24; I = 4.19, p = 0.24$) and thus do not contradict our hypothesis.
- Temperature.** The effects of the average minimum temperature in spring and summer of a given and preceding years on the LD incidence were found to be positive, whereas the effects of spring, summer, and winter temperature ranges in both years were found to be negative. Temperature range variables capture the difference between temperature extremes in different seasons. Long-term exposure to temperature extremes may increase tick mortality rates due to overheating and dehydration in summer or freezing in winter (Eisen, et al. 2016, 252). Fieler, et al. (2021) found that the upper and lower lethal temperatures for *Ixodes scapularis* larvae in vitro were -15°C and 41°C , respectively. Hence, higher larval mortality could be one of reasons why the impact of lagged temperature ranges on the LD incidence was found to be negative. In a given year, high temperatures may, in addition, negatively affect host-seeking abilities of nymphs (Eisen, et al. 2016, 253) and lead to the reduction in time spent by humans in tick habitats.
- Precipitation.** The effects of total precipitation in all seasons and in both given and preceding years on the LD incidence were found to be negative. The average precipitation in May and June of a given year was also found to have negative impact on the LD incidence in four U.S. regions in Couper, et al. (2020, 8). Precipitation in a given year may have concurrent effects on the LD incidence. High humidity is generally beneficial for nymphal survival and questing (Eisen, et al. 2016, Rodgers, Zolnik und Mather 2007), but humans tend to stay indoors or use rain protection on rainy days, which protects them from tick bites. The negative estimates of the effects of precipitation in a given year on the LD incidence may indicate that the negative impact of precipitation on humans dominated its positive impact on nymphs. In previous studies, precipitation was also found to have positive impact on larval survival and questing; however, larvae may drown when precipitation is excessive (Leal, et al. 2020, 430). This indicates that precipitation in a preceding year may have nonlinear effects on the LD incidence, and hence the negative estimates of direct and indirect effects should be interpreted with caution.
- Extreme weather.** Extreme weather events are represented by two variables: frost, which captures below zero temperatures in the (near) absence of snow cover, and drought, which captures high temperatures in the (near) absence of precipitation. The effects of drought on the LD incidence were found to be negative ($D = -0.13, p = 0.54; I = -0.53, p = 0.54$), which is consistent with the findings in Burtis, et al. (2016, 5) for the long-term endemic regions. The frost effects were also found to be negative ($D = -0.25, p = 0.24; I = -1.03, p = 0.24$). An additional month in a given or preceding year with maximum temperature below 0°C and total precipitation below 10 mm in a county was estimated to decrease (on average) the LD incidence in that county by 0.25 cases per 100,000 inhabitants. Furthermore, an additional month of frost in one county was estimated to decrease the LD incidence in all other counties in total by 1.03 cases per 100,000 inhabitants.

These results are consistent with previous findings that extreme weather events, especially if they are repeating over time, may reduce tick survival (Stafford 1994, Eisen, et al. 2016) and host-seeking capacities (Schulze, Jordan und Hung 2001).

- **Socioeconomic variables.** The effects of the population density on the LD incidence were found to be negative ($D = -5.38, p = 0.1; I = -22.12, p = 0.1$), which is consistent with the findings in Bayles and Allan (2014, 1918) and Xie, et al. (2018, 25). Included land cover class and edge density variables control for tick habitats and potential human–tick interactions. In this case, Bayles and Allan (2014) suggest that the negative effect of the population density on the incidence can be attributed to human behaviors that arise in the context of low population density and are associated with the increased risk of exposure (1922). The unemployment rate was included as a proxy for socioeconomic status and access to healthcare. Its effects on the LD incidence were found to be positive ($D = 0.05, p = 0.37; I = 0.21, p = 0.37$). The sign of the effects is at odds with a hypothesis stated in Couper, et al. (2020) that reduced ability to seek healthcare may lead to the underreporting of a disease (5).

5.1.4 REGIONAL NONSPATIAL MODELING

In addition to the national analysis, we performed the analysis for each of three U.S. regions—Midwest, Northeast, and Southeast (the Southwest and West were excluded due to low LD case counts). Regional comparisons were also made in Couper, et al. (2020) and Dong, et al. (2020). The definitions of regions are provided in Figure A1 and the estimation results for the nonspatial fixed effects model, in Table A7 in Appendix A.4. The fixed effects SARAR model was not considered for regional modeling due to the potential misspecification of a spatial weight matrix when regions are considered in isolation.

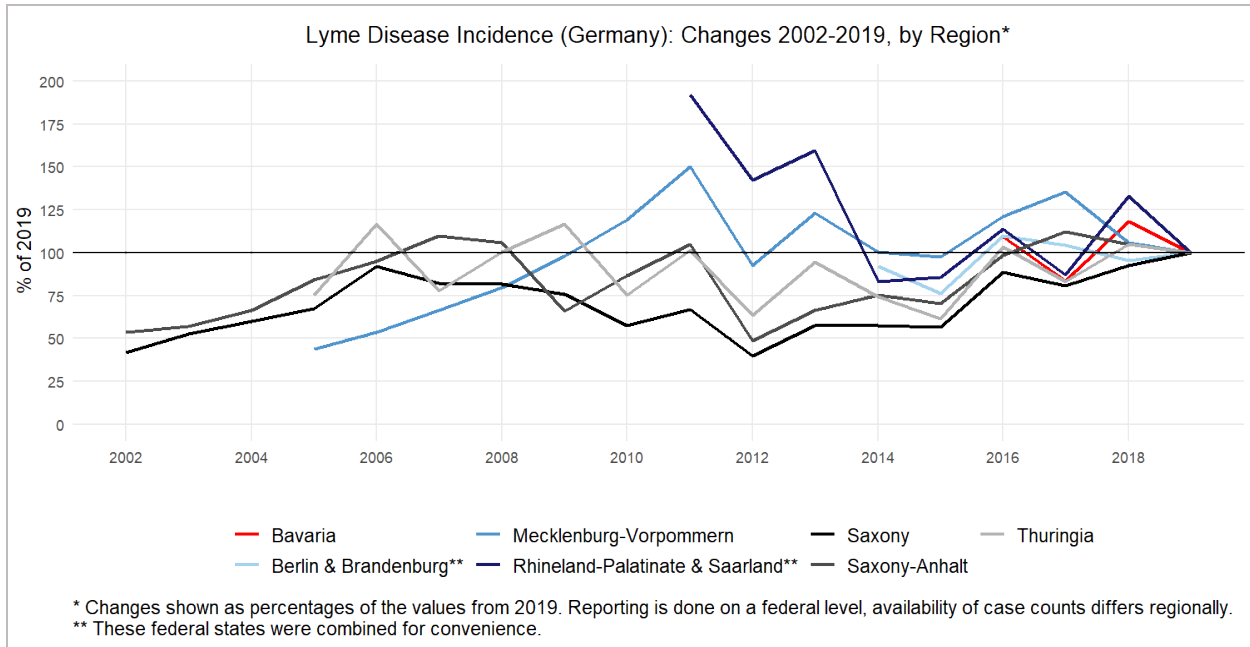
5.2 OTHER DATAPOINTS

The U.S. model has shown that there is a possible connection between climate change and the incidence of LD. To emphasize the global importance of vector borne diseases we further reviewed disease and temperature trends in Europe (Germany and Finland) and Asia (Japan).

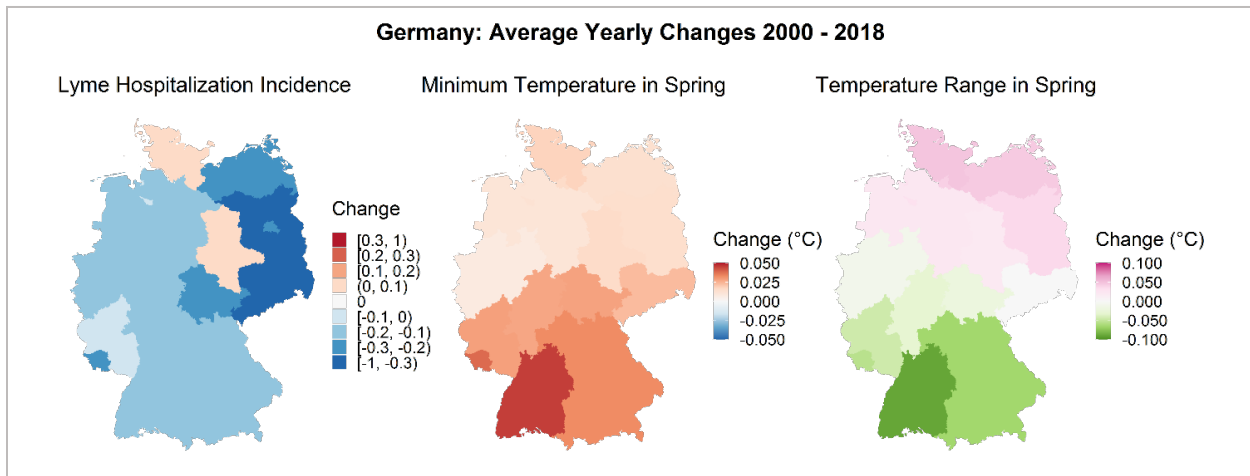
5.2.1 GERMANY

The Robert Koch Institute is Germany’s corresponding disease surveillance organization. Its reported cases have limitations for deriving trends because the regions with material cases only started reporting recently: eastern Germany has 20 years of trend but with few cases. Hence, we look at the hospitalization statistics, which comprise the more severe cases, available through the Federal Statistical Office of Germany (Statistische Ämter des Bundes und der Länder 2022, Statistisches Bundesamt 2021).

Using hospitalization data has two major weaknesses: First, only a small fraction of LD cases reaches a severity that requires hospitalization and second, with improvements in medical treatments and increasing disease awareness people can receive more effective, earlier treatment resulting in an observed decrease in hospitalizations even when LD incidence is increasing.



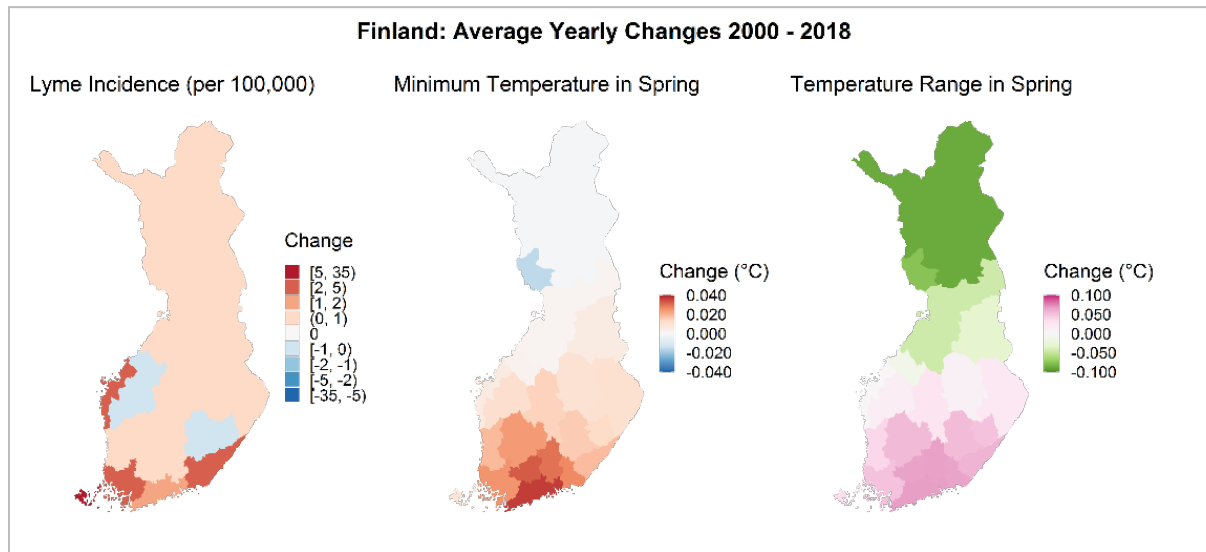
The hospitalization statistics show decreasing incidence of LD in Germany in all but two states. A study on health claims has also shown stagnating LD incidence (Akmatov, et al. 2021). At the same time other vector borne diseases show increasing incidence and regional distribution, where previously unexposed geographies have just been labelled a high-risk area for diseases such as SSME (Spring summer meningoencephalitis) (Robert Koch-Institut 2022). Some vector borne diseases that were previously only detected in Southern Europe are now transmitted within Germany (such as West Nile virus) (Robert Koch-Institut 2022). Though neither the surveillance nor hospitalization data in Germany lent well to a full regression model, we share a few of the key climate-related variables and their shifts over time.



5.2.2 FINLAND

LD has been endemic in Finland for decades, more in the southern regions but with ranges widening northwards presumably as the season of tick activity in above-freezing temperatures expands. Also, of concern and with serious health consequences in Finland is tick-borne encephalitis, which is most prevalent on the West Coast and where it is

common to be vaccinated against this. The University of Turku has a tick research unit which has concluded that climate change is a likely contributor to the increasing public health threat through vector borne diseases.⁶



The plots hint towards increasing incidence of LD, that is in areas where both spring temperature and spring temperature range have increased most drastically between 2000 and 2018.

5.2.3 JAPAN

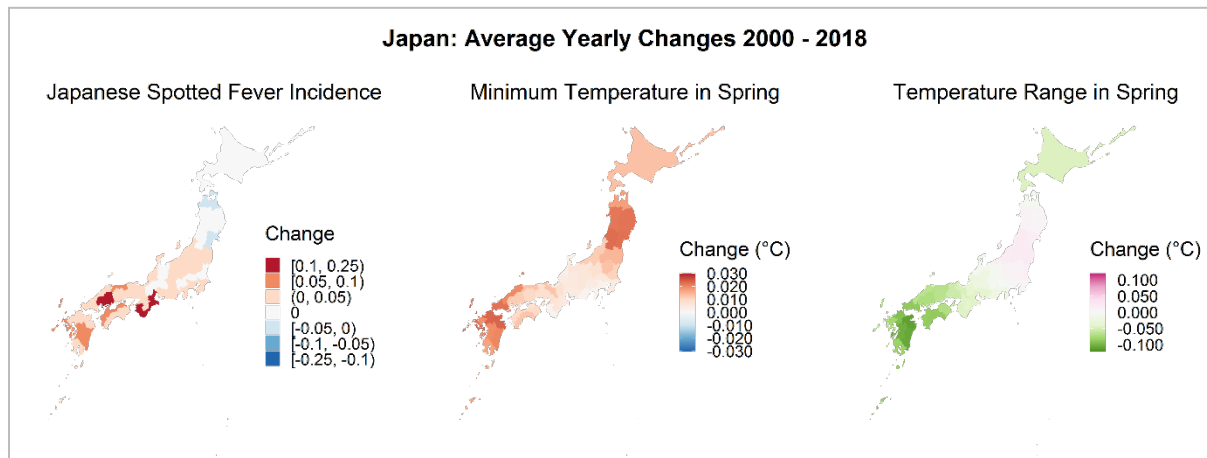
In Japan, LD is a much rarer disease, with 10 reported cases per year.⁷ There are other related diseases, though, transmitted by similar vectors, including Japanese spotted fever, Scrub typhus (tsutsugamushi disease), Severe fever with thrombocytopenia syndrome (SFTS) and tick-borne encephalitis. The latter peaked in the 1960s with more than 1,000 annual reported cases, but thanks to both available vaccine and sanitation improvements, only 55 cases were reported in the last decade.⁸

As Japanese spotted fever is the most frequent tick-borne diseases in Japan nowadays, we look at the incidence development over time compared to changing temperature.

⁶ <https://sites.utu.fi/puutiaisest/en/>

⁷ <https://www.niid.go.jp/niid/ja/diseases/ra/lyme.html>

⁸ <http://idsc.nih.gov/disease/JEncephalitis/QAJE02/fig01.gif>

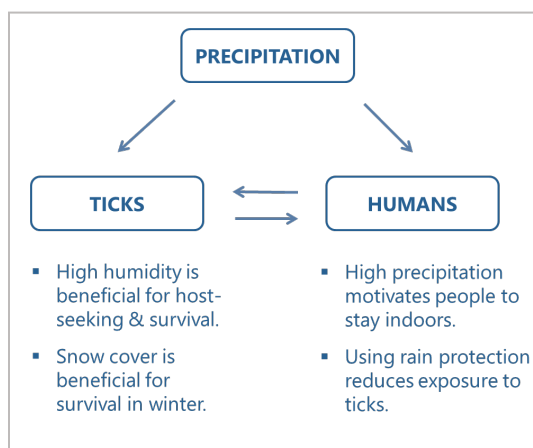


Japanese spotted fever appears to have intensified in western Japan over the years. This partially correlates with areas of increasing spring temperature. However, we also see increasing temperature in the north where incidence has decreased slightly. Another factor that has likely contributed to the changing geographical scope of spotted fever is the host expansion through deer and rodents.⁹

Section 6: The behavioral wild card

We have researched the most relevant factors that affect a tick's lifecycle and incorporated them into our model. Not all effects are what we expected – precipitation has a negative impact even though ticks prefer a humid environment. What we should not forget is that we do not model the size of tick-populations but the incidence of tick-transmitted LD in humans. Hence, it is not only about tick-suitable environmental factors, but also about the interaction frequency between humans and ticks, which comes back to human behavior. We have discussed the implications of awareness and health-seeking behavior in section 2. This section will further look into two aspects of human behavior and LD: rationalizing the unexpected impact of precipitation on LD through behavioral factors and studying how LD was affected by behavioral changes during the Covid-19 pandemic.

6.1 HUMANS, TICKS, AND PRECIPITATION



Contrary to our initial assumptions the models have consistently shown a negative impact of precipitation on Lyme disease. One plausible reason is that we only regarded the impact that precipitation is supposed to have on ticks but not the effect it has on humans or other hosts. While high humidity is beneficial for host-seeking and survival it might decrease the likelihood of human-tick interactions. Leisure activities with high human-tick-interaction such as hiking are especially negatively affected by high precipitation. Even if the occupation requires time to be spent outside the use of rain protection not only protects from rain but also from ticks.

⁹ <http://www.scj.go.jp/ja/info/kohyo/pdf/kohyo-24-t280-1.pdf>

6.2 CASE STUDY—COVID-19 RESTRICTIONS

While there is evidence of changed indoor/outdoor behaviors particularly in the early stages of the pandemic, what will ultimately occur for 2022 and beyond related to tick exposure is unclear. In earlier lockdowns, there was likely mixed behavior dependent on the geography: some people substituted indoor activities with outdoor hikes, and perhaps were not familiar with post-hike tick checks. Others rather avoided any outdoor areas, though we note that another vector-borne disease, dengue, can also transfer indoors, and there are signs of illness and increased death due to Dengue in India. This may be a tale of changed indoor/outdoor behavior but is also a signal of delayed treatment and missed diagnoses. Dengue, like Lyme and other vector-borne illness, is often treatable and without serious side effects if diagnosed and treated promptly. However, over the past two years, globally we have witnessed not only missed cancer screenings but an overall decreased inclination to seek treatment and diagnosis in traditional healthcare settings, due partly to supply disruptions and fear of contracting COVID-19. While the data is not available to prove increased complications with LD over the past 1-2 years, this is a cautionary tale for public awareness of diseases and prompt treatment.

We explored the influence of local features, such as weather and COVID-19 restriction patterns, on tick-borne diseases in a specific geographical area. We used patient-level data from the Symphony database to track tick-borne disease cases for a specific area in Pennsylvania. Records are available from mid-2019, which covers both the period during and before the COVID-19 pandemic.

We relied on the ICD-10 codes recorded for diagnosis to identify tick-borne disease cases, which for this analysis include Lyme disease, Ehrlichiosis, spotted fever rickettsiosis, babesiosis, tularemia, and tick-borne encephalitis.

In the Symphony database, ZIP codes at the patient level are masked with only the first two digits disclosed. For this analysis, we focused on an area in Pennsylvania with 15 as the leading digits in local ZIP codes (PA15). According to the CDC data, Pennsylvania is one of the top U.S. states in terms of Lyme diseases cases and incidence rates.

We obtained climate data from the Global Historical Climatology Network Database (GHCN). We focused on temperature and precipitation, which have been shown to have meaningful connections to the tick population and tick-borne diseases in literature and our long-term regression modelling in Section 5. We aggregated temperature and precipitation measurements from land surface stations in the PA15 area.

Counties in the PA15 area have experienced various degrees of COVID-19 restrictions, sometimes asynchronously. Pennsylvania's COVID-19 restriction phases are coded as Red, Yellow, Green, and Open. We constructed an Openness Index for the PA15 area to reflect the local restriction trend. The Openness Index is a county-population weighted measure of openness with population obtained from the 2020 U.S. census.

Table 6-1 presents a Poisson regression of tick-borne diseases on local temperature, precipitation, and openness. The Poisson regression is fitted with data from May 2019 to the end of July 2021. The offset is derived from the 2020-census population for the PA25 area. The explanatory variables are lagged by a month to accommodate a potential lag between incidents and their recording. Results are similar at various degrees of lag.

TABLE 6-1. TICK-BORNE DISEASES IN PA15

	Constant	Temperature (C)	Precipitation (mm)	Openness Index
Estimate	-13.6327	0.0457	0.0306	0.1904
Standard Error (SE)	0.0645	0.0013	0.0045	0.0597
Estimate/SE	-211.23	35.04	6.79	3.19

In this case, temperature, precipitation and COVID-19 restrictions appear to be statistically significant in connection with tick-borne disease incidence. As one would expect, policies that tend to limit human-tick interactions are associated with reduced tick-borne disease rates, all else being equal.

Of course, cases may not appear in the medical claims, due to modified behavior and unreported / untreated LD, would affect regression coefficients. However, this would result in increased complications downstream.

This analysis also highlights an approach to incorporate socioeconomic factors in these models. If justified by data and theory, one can also substitute our climate trend proxies with a fuller model based on biology, ecology, and epidemiology.

Section 7: Conclusions—from Lyme disease to broader context

This report explores an example of determining climate-related drivers of LD and its related costs. However, although the burden of disease is well documented, the conclusions are not about Lyme per se.

We note that vector-borne diseases are not insignificant and account for over 15% of all infectious diseases. Also, within borreliosis, there are non-LD emerging and re-emerging borreliae from related species (Cutler, Ruzic-Sabljić und Potkonjak 2017). In the end for LD itself, it is possible that an accepted vaccine will emerge; there was in fact a recombinant vaccine (LYMERix) which was pulled from the market due in part to reports of side effects; however, this may yet prove a viable vaccine, and significant mRNA research at the moment may also hold promise for preventing or mitigating LD.¹⁰

The authors hence view the report as both an illustration of a concerning disease globally and a framework for considering other diseases of climate concern.

7.1 BURDEN TO INSURED LOSSES

Generally, there are questions posed from internal functions of insurers and from regulators to understand liabilities faced due to climate risk and increasing needs from the industry to understand trend risk and tail risk due to climate change and extreme weather.

Today, it is fair to say that medical costs and insured health costs see but a blip from payment due to direct and indirect effects from LD. This is true both in the U.S. and internationally. In the U.S., LD also comprises the vast majority of medical claims due tick-borne illness, and the impact is to disability-adjusted life years is not significant compared with other debilitating illnesses.¹¹ Other lines affected also presumably hence see minimal effects – disability claims, life insurance, and critical illness. Expanding to all vector-borne diseases, the effects are much higher when incorporating the heavy burdens of dengue and malaria in certain regions. However, in our key regions of study in this report – the U.S. and Germany and briefly Finland and Japan – tropical diseases are rather from travel and hence not related to the local climate. Hence today, vector-borne disease does not pose a significant burden to life & health business in the U.S. and other temperate climates.

Medical reimbursement business also tends to be a short-term risk; hence one could push any changes due to climate outside an insured risk horizon. However, if we consider longer term business such as disability and critical illness in certain markets, the projections shown in 5.1.4 would be more relevant to insurers. Long-term effects of LD and other debilitating vector-borne disease can result in disability with potentially long recovery periods. One other note of caution to insurers is in the diseases covered for critical illness policies, and that the climate-driven uncertainties for climate-impacted disease be taken into account. First, LD can be a covered definition occasionally,

¹⁰ <https://www.newscientist.com/article/2297648-mrna-vaccine-against-tick-bites-could-help-prevent-lyme-disease/>

¹¹ <https://pubmed.ncbi.nlm.nih.gov/31739768/>

and if not, its complications may well be; second, other vector-borne illness often appear on critical illness policies with lengthier definition lists; thirdly, the typical guarantee period of many critical illness markets cause climate to be a consideration when formulating benefit and product design.

7.2 METHODOLOGICAL FRAMEWORK

Perhaps of broader implication is that this report offers methodological approaches to quantify problems which may continue to emerge in coming decades. The papers provide an example of an approach to consider climate's influence on health and infectious disease in particular, with Section 5.1's advanced regression modelling, which illustrates how the spread of a disease can be modelled under the impact of spatially correlated unobserved covariates and a spatially correlated outcome such as the infectious disease occurrence itself. A spatial model allows investigation of the spillover effects of environmental factors and to explore interactions between different geographical units, e.g., thinking about medical costs and a flood in a neighboring country affecting other areas due to disrupted healthcare, infectious disease and polluted water to name a few. Section 4.2. then provides an illustration of medical expenditures and their complications against a reference cohort. Together, a framework is offered to consider both spreading of infectious disease through spatially correlated outcomes, its relation to climate variables, and ensuing medical costs.


7.3 DANGER IN CHANGING GEOGRAPHICAL PATTERNS

One danger of climate change in human health lies in infectious disease spreading in non-endemic areas. We can see increasing incidence of certain vector-borne diseases in the U.S., which may be facilitated by changing climate. Our model has shown that LD incidence is positively influenced by increasing average minimum spring and summer temperature while being negatively affected by increasing temperature ranges i.e., more extreme weather.

Lack of awareness, for example from checking for presence of ticks after a hike to seeking prompt medical treatment, can have consequences, where an area of suggested further research would be to compare rate of major complications from vector-borne illnesses in long-endemic compared with emerging geographic regions.

Somewhat apart from though not entirely unrelated to climate change are mobility patterns. With travel restrictions loosening, leisure travel is booming this summer and international mobility gives rise to introduction of both invasive species, novel diseases (recall the recent pandemic), and spread of travel diseases.¹² Last month a region plagued by LD, Maine, also saw a resident fatality due to a novel tick-borne illness.¹³ An alarming scenario would be endemic tropic diseases such as dengue becoming endemic in the Mediterranean regions or malaria being re-introduced.¹⁴


Awareness and information from disease monitoring organizations, local health care providers as well as the insurance industry can help to mitigate this.



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¹² <https://nature.com/articles/nature06536>

¹³ <https://www.msn.com/en-us/health/medical/maine-resident-dies-after-catching-rare-virus-spread-by-tick-bites/>

¹⁴ https://www.euro.who.int/__data/assets/pdf_file/0003/307272/Facsheet-malaria-elimination.pdf

Section 8: Acknowledgments

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Project Oversight Group members:

Cindy Bruyere, PhD

Priya Rohatgi, FSA

Betty-Jo Walke, FCAS

Timothy Cheng, FSA

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Appendix A: Spatial and fixed effects models, statistical methods, and regional analysis

A.1 DATA AND DEFINITIONS

TABLE A1. CARTOGRAPHIC BOUNDARY FILES

Regions	Country	Sources & Notes
Counties	The U.S.	Cartographic boundary files with the resolution 1:5,000,000 for the year 2018 were taken from the U.S. Census Bureau (The U.S. Census Bureau 2021). The following legal/statistical area description (LSAD) codes were selected: 06, 15, and 25. The Alaska and Hawaii states were excluded. County FIPS codes were taken from the USDA NRCS (The U.S. Department of Agriculture Natural Resource Conservation Service).
NUTS 1 regions	Germany	The NUTS250 dataset was taken from the Federal Agency for Cartography and Geodesy (Bundesamt für Kartographie und Geodäsie 2019). Geofactor was set to 4 to remove the territories of the North and Baltic Seas as well as Lake Constance.
Hospital districts	Finland	The SHP2019 dataset from the R package mapsFinland (Haukka 2020) was used.
Prefectures	Japan	Japan's subnational administrative boundaries data were taken from the Humanitarian Data Exchange of OCHA's Regional Office for Asia and the Pacific (OCHA Regional Office for Asia and the Pacific 2019). Okinawa Prefecture was excluded from the plots in the report.

TABLE A2. DATA SOURCES

Data	Country	Sources & Notes
Symphony Database	The U.S.	The COVID-19 Research Database partners, https://covid19researchdatabase.org/
Lyme disease case counts	The U.S.	Publicly available surveillance data was taken from the CDC (Centers for Disease Control and Prevention (CDC) 2022).
Lyme disease hospitalizations	Germany	A dataset containing the number of hospitalized patients by 3-digit ICD-10 codes, gender, and NUTS 1 regions for the years 2000–2018 (Statistische Ämter des Bundes und der Länder) and 2019 (Statistisches Bundesamt 2021) was used.
Lyme disease case counts	Finland	A Lyme borreliosis dataset, containing the annual number of Lyme disease cases by hospital district for the period 1995–2022, was taken from the Finnish Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos 2022).
Japanese spotted fever case counts	Japan	Data on notified Japanese spotted fever cases by prefecture over the period 1999–2019 were taken from the National Institute of Infectious Diseases (The National Institute of Infectious Diseases 2020).
Case counts of vector borne diseases	The U.S.	Summary of notifiable infectious diseases for the period 1993 – 2015 was taken from the CDC (Centers for Disease Control and Prevention (CDC) 2022). Data on nationally notifiable infectious diseases and conditions for the period 2016–2018 were taken from the CDC (Centers for Disease Control and Prevention (CDC)).
Population	The U.S.	Annual resident population estimates by county for 2000–2009 (The U.S. Census Bureau 2021) and for 2010–2018 (The U.S. Census Bureau 2021) were taken from the U.S. Census Bureau.
Population	Germany	Population numbers by gender (Statistische Bundesamt 2021) and age group (Statistische Bundesamt 2021) for NUTS 1 regions were taken from the Database of the Federal Statistical Office of Germany, GENESIS-Online. To be consistent with population data for other countries, population on December 31 of a given year was treated as population on January 1 of a subsequent year.
Population	Finland	Population data (December 31) for hospital districts (2022) were taken from the Statistics Finland database 11ra – Key figures on population by region, 1990–2021 (Statistics Finland). To be consistent with population data for other countries, population on December 31 of a given year was treated as population on January 1 of a subsequent year.
Population	Japan	Data on the total population (item A1101) were taken from the Portal Site of Official Statistics of Japan, e-Stat (The Portal Site of Official Statistics of Japan 2021).
Historical monthly weather data	Global	Historical monthly weather data for 1960–2018 (WorldClim), downscaled from CRU-TS-4.03 (Harris, et al. 2014) using WorldClim 2.1 (Fick und Hijmans 2017), were used. WorldClim leverages data from sources such as the Global Historical Climatology Network (GHCN as reference on p21 of report) and others. The R package <i>exactextractr</i> (version 0.7.2) was used to create temperature and precipitation variables.
Historic Land Dynamics Assessment+ (HILDA+)	Global	A dataset on land use/cover change over 1960–2019, HILDA+, was taken from PANGAEA® Data Publisher for Earth & Environmental Science (Winkler, et al. 2020). The R packages <i>exactextractr</i> (version 0.7.2) and <i>landscapemetrics</i> (version 1.5.4) were used to create land cover and edge density variables.
Unemployment rate	The U.S.	A county-level dataset “Unemployment and median household income for the U.S., States, and counties, 2000-20” was taken from the USDA’s Economic Research Service (The U.S. Department of Agriculture Economic Research Service 2022).
Land area	The U.S.	Land area data were taken from the U.S. Census Bureau database for USA Counties: 2011 (The U.S. Census Bureau 2021).
Google search frequencies	Global	Google Trends data for different search terms was taken from the section “Interest over time” (Google Ireland Limited).

TABLE A3. PREDICTOR VARIABLE DEFINITIONS FOR U.S. MODELS

Variable	Category	Definition
tmin_ave_winter	Temperature	The average of minimum temperature values in Jan, Feb, Mar of a given year (in °C).
tmin_ave_spring	Temperature	The average of minimum temperature values in Apr, May, Jun of a given year (in °C).
tmin_ave_summer	Temperature	The average of minimum temperature values in Jul, Aug, Sep of a given year (in °C).
tmin_ave_winter_1	Temperature	The average of minimum temperature values in Jan, Feb, Mar of a preceding year (in °C).
tmin_ave_spring_1	Temperature	The average of minimum temperature values in Apr, May, Jun of a preceding year (in °C).
tmin_ave_summer_1	Temperature	The average of minimum temperature values in Jul, Aug, Sep of a preceding year (in °C).
tmin_ave_fall_1	Temperature	The average of minimum temperature values in Oct, Nov, Dec of a preceding year (in °C).
trange_winter	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in winter of a given year (in °C).
trange_spring	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in spring of a given year (in °C).
trange_summer	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in summer of a given year (in °C).
trange_winter_1	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in winter of a preceding year (in °C).
trange_spring_1	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in spring of a preceding year (in °C).
trange_summer_1	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in summer of a preceding year (in °C).
trange_fall_1	Temperature	The difference between the maximum of maximum monthly temperatures and the minimum of minimum monthly temperature in fall of a preceding year (in °C).
prec_winter	Precipitation	The sum of monthly total precipitation in winter of a given year (in mm).
prec_spring	Precipitation	The sum of monthly total precipitation in spring of a given year (in mm).
prec_summer	Precipitation	The sum of monthly total precipitation in summer of a given year (in mm).
prec_winter_1	Precipitation	The sum of monthly total precipitation in winter of a preceding year (in mm).
prec_spring_1	Precipitation	The sum of monthly total precipitation in spring of a preceding year (in mm).
prec_summer_1	Precipitation	The sum of monthly total precipitation in summer of a preceding year (in mm).
prec_fall_1	Precipitation	The sum of monthly total precipitation in fall of a preceding year (in mm).
frost	Extreme weather	The number of months in a given and in a preceding year with maximum temperature below 0°C and total precipitation below 10 mm.
drought	Extreme weather	The number of months in a given and in a preceding year with maximum temperature above 30°C and total precipitation below 10 mm.
cropland_pasture	Land cover	The percentage of the cropland or pasture/rangeland land cover class in a county.
forest	Land cover	The percentage of the forest land cover class in a county.
shrubland	Land cover	The percentage of the unmanaged grass/shrubland land cover class in a county.
edge_density	Land cover	The length of all edges between the urban class and classes cropland, pasture/rangeland, forest, and unmanaged grass/shrubland, standardized to the total county area (in meters per hectare).
unemp_rate	Socioeconomic	The percentage of the civilian labor force that is unemployed in a county in a given year.
pop_density	Socioeconomic	Population (in thousands) per square kilometer of land area in a county in a given year.

Among all variables, only the unemployment rate and population density contained missing values, and the R package *imputeTS* (version 3.2) was used to impute them. The unemployment rate was missing for 7 counties in Louisiana and the years 2005 and 2006 and was replaced using spline interpolation. For all counties but Oglala Lakota County, SD, the land area data were available for the years 2000 and 2010, and the remaining years were filled with a previous nonmissing value to compute population density. For Oglala Lakota County, SD, population numbers were not available for the years 2000-2009, and land area was not available for all years. To compute population density for this county, the county area was computed using cartographic boundary files and the Eckert IV projection, and missing population density for the years 2000–2009 was replaced by a county-specific mean.

A.2 MODELING APPROACH

To estimate the effects of weather, land cover, and socio-economic variables on the Lyme disease incidence in the U.S., we considered nonspatial and spatial panel data models.

Nonspatial models

Let N denote the total number of counties, indexed by i , and T denote the total number of years, indexed by t . A general nonspatial linear model for panel data can be formulated as follows (Greene 2008, 197):

$$y_{it} = X_{it}\beta + \alpha_i + \delta_t + \varepsilon_{it},$$

where y_{it} denotes the Lyme disease incidence in a county i and year t , and the terms α_i and δ_t represent county and time effects, respectively. The vector X_{it} contains observed values of K county- and time-varying predictor variables, and β is the vector of unknown parameters.

County effects capture the determinants of the Lyme disease incidence that vary over counties but are constant over time (for example, geographic characteristics (Dumic und Severnini 2018, 4)). Time effects capture time-varying determinants that are constant across counties (for example, nation-wide demographic shifts or changes in the CDC case definition of Lyme disease). If county-varying variables captured by α_i are unobserved but correlated with the included variables, then omitting them will lead to the biased and inconsistent OLS estimator of the unknown parameter vector β (Greene 2008, 183). To address this problem, the fixed effects model includes α_i 's as county-specific intercepts (Greene 2008, 183). Similar logic applies also to time effects. If no correlation between observed and unobserved variables exists, the fixed effects model still yields consistent estimators of β (Greene 2008, 208).

In nonspatial linear models, the partial derivative of the (conditional) expected value of the Lyme disease incidence in a county i with respect to the k th predictor variable in a county i , referred to as a direct effect (LeSage und Pace 2009, 34-37), is

$$\frac{\partial E(y_{it})}{\partial x_{itk}} = \beta_k,$$

which is the same for all counties. The partial derivative of the (conditional) expected value of the Lyme disease incidence in a county j with respect to the k th predictor variable in a county i , referred to as an indirect or spillover effect (LeSage und Pace 2009, 34-37), is

$$\frac{\partial E(y_{jt})}{\partial x_{itk}} = 0, j \neq i.$$

Spatial models

Nonspatial linear models rule out spillover effects of predictor variables by construction. That is, a change in precipitation or temperature in one county is assumed to have no effect on the Lyme disease incidence in any other county, including its neighbors. However, in the context of Lyme disease, it might be reasonable to assume that the migration of tick hosts across counties, for example, may enable the spillover effects of climatic factors. Improved microclimate in one county may increase tick density in that county, and more ticks might be able to migrate to neighboring counties via attaching to their hosts. Spatial models allow for such spillover effects and will be outlined next.

Neighbors and Weight Matrix

First, we state several definitions, provided in LeSage and Pace (2009, 8-9). A county j is said to be a *first-order neighbor*, or just a *neighbor*, of a county i if they share a common border. We require two counties to share more

than one point for the contiguity condition to be satisfied. A county is not a neighbor of itself. A county k is said to be a *second-order neighbor* of a county i if it is a neighbor of a neighbor of a county i . Since a county is a neighbor of its neighbors, it is also a second-order neighbor of itself.

The first-order neighbor relations are captured by an $N \times N$ spatial weight matrix W , which is assumed to remain constant over time. If a county j is a neighbor of a county i , the element W_{ij} is nonzero and represents the weight assigned to this neighbor (LeSage und Pace, 9). We define the weight of a neighbor of a county i as the fraction of a county i 's border shared with this neighbor. Since no county is a neighbor of itself, all diagonal elements of W are zero. The second-order neighbor relations are captured by W^2 , and higher-order relations, by higher powers of W (LeSage und Pace, 14).

For a year t , let y_t denote a vector of the LD incidence values observed in N counties. Since not all U.S. counties share 100% of their border with other U.S. counties, weights for a county i may sum to less than 1. We normalize weights, so that row sums of the matrix W are equal to 1. Consider the product $W y_t$ with the i th element

$$\sum_{j=1}^N W_{ij} y_{jt},$$

which is called a spatial lag (LeSage und Pace 2009, 8). Since weights W_{ij} are nonzero only for the neighbors of a county i and sum to 1, the spatial lag represents the weighted average of the LD incidence values observed in the neighbors of a county i .

Fixed Effects SARAR Model

For the set of observations on N counties in a year t , the fixed effects SARAR model is formulated as follows (Kelejian und Prucha 1998, 100, Anselin, Gallo und Jayet 2008, 640, Millo und Piras 2012, 10-11):

$$y_t = \rho W y_t + \alpha_N + \delta_t \iota_N + X_t \beta + u_t,$$

$$u_t = \lambda W u_t + \varepsilon_t.$$

As before, y_t denotes an $N \times 1$ vector of the LD incidence values, $W y_t$ is a vector of spatial lags, X_t is an $N \times K$ matrix of predictor variables, and β is a vector of unknown parameters. An $N \times 1$ vector α_N contains county effects, whereas ι_N denotes the vector of ones and δ_t is a time effect, which is the same for each of N counties. The error terms in ε_t are assumed to be independently and identically distributed with zero mean and constant variance.

The spatial autoregressive parameter ρ captures the strength of spatial dependence (LeSage und Pace 2009, 10), whereas the spatial autocorrelation parameter λ captures spatial autocorrelation in unobserved factors (Elhorst 2014, 8-10) and, in combination with ρ , allows for more flexible error dependence. The parameters ρ and λ are restricted to the interval $(-1, 1)$ (Kelejian und Prucha 1998, 101).

Expressing the target variable y_{it} for a county i in terms of county and time effects, predictor variables in X_t , and error terms in ε_t yields the following observations. For a given year, the LD incidence in a county i depends not only on predictor values observed in a county i but also on weighted averages of predictor values observed in its first- and higher-order neighbors. The impact of the first- and higher order neighbors is governed by the parameter ρ and its higher powers, respectively, and decays geometrically since $|\rho| < 1$ (LeSage und Pace 2009, 15). Furthermore, the LD incidence in a county i is affected not only by unobserved factors captured in an error term associated with a county i but also by weighted averages of error terms of its first- and higher-order neighbors. The impact of the first- and higher-order neighbors in the error part is governed by two parameters, ρ and λ .

Direct and Indirect Effects

In the SARAR model, the direct effect of the k th predictor in a county i on the LD incidence in a county i is given by (see also Elhorst (2014, 20))

$$\frac{\partial E(y_{it})}{\partial x_{itk}} = \beta_k(1 + \rho W_{ii} + \rho^2 W_{ii}^2 + \dots).$$

The direct effects depend on the parameter β_k , associated with the k th predictor, the spatial autoregressive parameter ρ , as well as the diagonal elements of powers of a spatial matrix W (W_{ii}^2 denotes the i th diagonal element of W^2). Hence, the direct effects differ across counties unless $\rho = 0$. Higher-order effects represent feedback effects, which pass through neighboring counties back to the county of origin (LeSage und Pace 2009, 35-36, Elhorst 2014, 23).

The indirect effect of the k th predictor in a county i on the LD incidence in a county j is given by

$$\frac{\partial E(y_{jt})}{\partial x_{itk}} = \beta_k(\rho W_{ji} + \rho^2 W_{ji}^2 + \dots), j \neq i.$$

In the term ρW_{ji} , the matrix element W_{ji} represents the fraction of a county j 's border that it shares with a county i . If a county i is a first-order neighbor of a county j , then higher fraction of a county j 's border shared with this neighbor implies higher indirect impact of changes in the neighbor's temperature, precipitation, and other predictors on a county j 's incidence. Changes in predictor variables in higher-order neighbors also affect the incidence in a county j but to a lesser extent.

Since the direct and indirect effects differ across counties, their summary measures are usually reported. The average direct effect represents the effect of a unit change in the k th predictor in a county on the incidence in that county (LeSage und Pace 2009, 36-37) and is equal to

$$\frac{1}{N} \sum_{i=1}^N \frac{\partial E(y_{it})}{\partial x_{itk}}.$$

The average indirect effect can be interpreted in two different ways (LeSage und Pace 2009, 36-37). The first approach considers the total impact on the incidence in one county of a unit change in the k th predictor in all other counties, which is computed as

$$\frac{1}{N} \sum_{j=1}^N \sum_{i \neq j} \frac{\partial E(y_{jt})}{\partial x_{itk}}.$$

The second approach considers the total impact on the incidence in all other counties of a unit change in the k th predictor in one county, which is computed as

$$\frac{1}{N} \sum_{i=1}^N \sum_{j \neq i} \frac{\partial E(y_{jt})}{\partial x_{itk}}.$$

These two approaches produce the same numerical value.

A.3 U.S. NATIONAL MODEL RESULTS

Table A4 contains the estimates of the direct effects for the nonspatial fixed effects model and of the direct and indirect effects for the fixed effects SARAR model with county and time effects. The estimation of the nonspatial fixed effects model was performed using the R package *fixest* (version 0.10.4); the reported standard errors are clustered by county. The estimation of the fixed effects SARAR model was performed using the R package *splm* (version 1.5.3) and helper functions from *spdep* (version 1.2.2), whereas the *spatialreg* (version 1.2.1) and *coda* (version 0.19.4) packages were used to estimate the direct and indirect effects as well as the corresponding standard errors.

TABLE A4. NATIONAL RESULTS FOR THE NONSPATIAL AND SPATIAL FIXED EFFECTS MODELS

Variable	FE – Direct effects		SARAR – Direct effects		SARAR – Indirect effects	
	Estimate (Std. Error)	P-Value	Estimate (Std. Error)	P-Value	Estimate (Std. Error)	P-Value
tmin_ave_spring	1.2042 (0.2136)	< 0.0001***	0.2687 (0.1184)	0.0233*	1.1051 (0.4887)	0.0238*
tmin_ave_summer	1.3913 (0.2180)	< 0.0001***	0.3605 (0.1227)	0.0033**	1.4829 (0.5056)	0.0034**
tmin_ave_winter	-0.5676 (0.1105)	< 0.0001***	-0.1369 (0.0668)	0.0419*	-0.5630 (0.2744)	0.0419*
tmin_ave_spring_1	0.7698 (0.1651)	< 0.0001***	0.1205 (0.1158)	0.2880	0.4958 (0.4768)	0.2890
tmin_ave_summer_1	0.6969 (0.2507)	0.0055**	0.2447 (0.1374)	0.0815.	1.0064 (0.5660)	0.0821.
tmin_ave_winter_1	-0.3469 (0.0990)	0.0005***	-0.0711 (0.0626)	0.2570	-0.2923 (0.2577)	0.2575
tmin_ave_fall_1	0.6758 (0.1215)	< 0.0001***	0.1207 (0.1156)	0.3071	0.4966 (0.4759)	0.3075
trange_spring	-0.9523 (0.0960)	< 0.0001***	-0.1870 (0.0469)	< 0.0001***	-0.7692 (0.1928)	< 0.0001***
trange_summer	-0.0934 (0.0668)	0.1621	-0.0343 (0.0530)	0.5231	-0.1409 (0.2179)	0.5228
trange_winter	-0.5042 (0.0624)	< 0.0001***	-0.1020 (0.0317)	0.0013**	-0.4194 (0.1312)	0.0014**
trange_spring_1	-0.8028 (0.1188)	< 0.0001***	-0.1624 (0.0479)	0.0008***	-0.6680 (0.1979)	0.0009***
trange_summer_1	-0.3680 (0.0672)	< 0.0001***	-0.0752 (0.0555)	0.1802	-0.3095 (0.2283)	0.1806
trange_winter_1	-0.3375 (0.0590)	< 0.0001***	-0.0649 (0.0327)	0.0448*	-0.2670 (0.1349)	0.0453*
trange_fall_1	0.0898 (0.0423)	0.0337*	0.0139 (0.0342)	0.6878	0.0573 (0.1405)	0.6879
prec_spring	-0.0152 (0.0016)	< 0.0001***	-0.0029 (0.0009)	0.0011**	-0.0118 (0.0036)	0.0012**
prec_summer	-0.0028 (0.0012)	0.0207*	-0.0007 (0.0009)	0.3741	-0.0030 (0.0036)	0.3742
prec_winter	-0.0048 (0.0011)	< 0.0001***	-0.0010 (0.0012)	0.4160	-0.0042 (0.0049)	0.4161
prec_spring_1	-0.0097 (0.0013)	< 0.0001***	-0.0019 (0.0009)	0.0432*	-0.0077 (0.0038)	0.0437*
prec_summer_1	-0.0121 (0.0012)	< 0.0001***	-0.0027 (0.0009)	0.0030**	-0.0109 (0.0037)	0.0032**
prec_winter_1	-0.0056 (0.0012)	< 0.0001***	-0.0014 (0.0011)	0.2046	-0.0058 (0.0046)	0.2052
prec_fall_1	-0.0033 (0.0010)	0.0012**	-0.0006 (0.0009)	0.5470	-0.0023 (0.0038)	0.5463
drought	-0.2393 (0.1419)	0.0918.	-0.1288 (0.2166)	0.5409	-0.5300 (0.8895)	0.5407
frost	-1.4879 (0.4263)	0.0005***	-0.2495 (0.2110)	0.2386	-1.0261 (0.8672)	0.2388
cropland_pasture	1.0541 (0.2015)	< 0.0001***	0.5203 (0.1257)	< 0.0001***	2.1402 (0.5198)	< 0.0001***
forest	0.8664 (0.1834)	< 0.0001***	0.4490 (0.1255)	0.0003***	1.8470 (0.5182)	0.0003***
shrubland	1.3058 (0.2106)	< 0.0001***	0.6082 (0.1364)	< 0.0001***	2.5016 (0.5652)	< 0.0001***
edge_density	1.5157 (1.7333)	0.3819	1.0199 (0.9057)	0.2386	4.1949 (3.7324)	0.2396
unemp_rate	0.1655 (0.0971)	0.0885.	0.0514 (0.0577)	0.3717	0.2115 (0.2374)	0.3721
pop_density	-12.1475 (4.6217)	0.0086**	-5.3768 (3.2520)	0.1000	-22.1153 (13.3840)	0.1003

P-value codes: "****" < 0.001, "***" < 0.01, "**" < 0.05, "." < 0.1.

Table A5 contains the estimates of the spatial autoregressive parameter ρ , capturing the strength of spatial dependence (LeSage und Pace 2009, 10), as well as of the spatial autocorrelation parameter λ , capturing spatial autocorrelation in unobserved factors (Elhorst 2014, 8-10). The estimate of ρ of 0.86 indicates strong positive spatial dependence in the LD incidence.

TABLE A5. ESTIMATES OF ρ AND λ FOR THE FIXED EFFECTS SARAR MODEL

Parameter	Estimate (Std. Error)	P-Value
rho	0.8568 (0.0034)	< 0.0001***
lambda	-0.3661 (0.0089)	< 0.0001***

A.4 U.S. REGIONAL MODEL RESULTS

The U.S. regions are defined according to the map in Figure A1.

FIGURE A1. THE MAP OF THE U.S. REGIONS

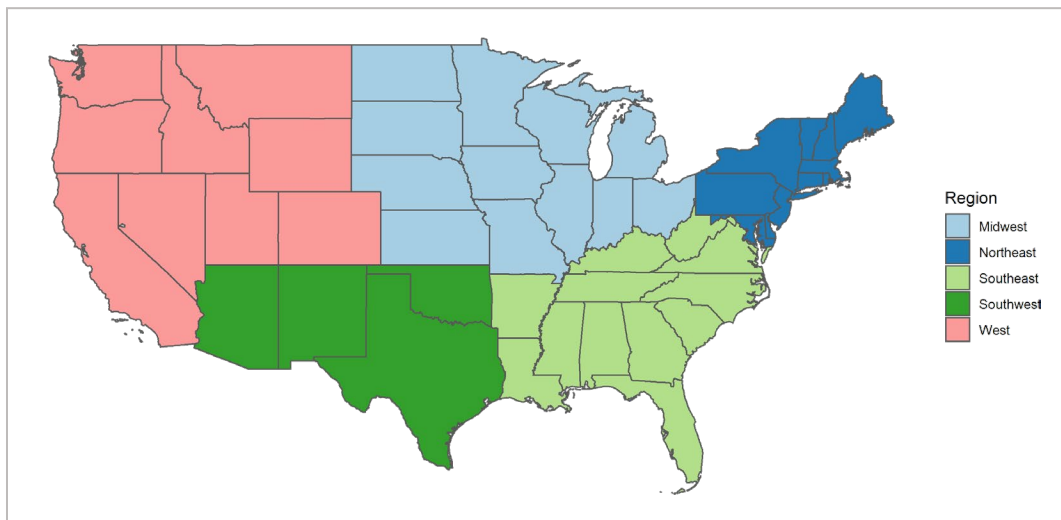


Table A6 provides the mean values of predictors across the five U.S. regions and over the period 2000–2018.

TABLE A6. MEAN VALUES OF PREDICTORS ACROSS THE U.S. REGIONS

Variable	Midwest	Northeast	Southeast	Southwest	West	Total
tmin_ave_spring	9.21	8.00	13.92	14.82	3.96	10.80
tmin_ave_summer	15.00	14.44	18.90	19.75	9.62	16.24
tmin_ave_winter	-7.14	-6.56	1.76	2.40	-5.40	-2.68
tmin_ave_spring_1	9.20	7.98	13.88	14.79	3.84	10.76
tmin_ave_summer_1	14.92	14.33	18.80	19.69	9.56	16.16
tmin_ave_winter_1	-7.06	-6.58	1.73	2.45	-5.34	-2.65
tmin_ave_fall_1	-1.17	0.52	5.46	5.71	-2.64	1.90
trange_spring	24.07	22.62	20.92	22.85	24.45	22.78
trange_summer	18.40	16.37	15.23	18.10	22.81	17.64
trange_winter	20.21	16.92	19.07	21.30	18.09	19.45
trange_spring_1	23.69	22.59	20.63	22.49	24.39	22.49
trange_summer_1	18.67	16.55	15.54	18.21	22.78	17.86
trange_winter_1	20.17	16.88	18.77	21.02	17.99	19.28
trange_fall_1	25.28	21.37	22.19	25.27	24.05	23.77
prec_spring	301.76	321.63	344.81	216.70	128.79	287.39
prec_summer	266.10	315.17	363.84	214.53	77.36	274.98
prec_winter	128.76	231.45	295.50	130.61	177.40	199.83
prec_spring_1	304.54	314.06	339.78	222.51	128.78	286.73
prec_summer_1	260.85	312.54	354.98	208.29	78.75	269.36
prec_winter_1	127.59	232.00	294.02	131.05	179.52	199.27
prec_fall_1	164.09	291.25	286.65	152.95	187.19	217.37
drought	0.01	0.00	0.01	0.43	1.02	0.18
frost	0.26	0.00	0.00	0.00	0.10	0.10
cropland_pasture	69.28	11.07	15.48	59.58	49.19	42.76
forest	23.87	73.42	74.54	19.10	32.47	45.52
Shrubland	1.38	0.54	1.48	13.59	7.32	3.54
edge_density	0.58	0.84	0.74	0.27	0.20	0.58
unemp_rate	5.44	5.81	6.92	5.60	6.24	6.09
pop_density	0.05	0.52	0.09	0.03	0.07	0.10


Table A7 contains the estimates of the direct effects for the nonspatial fixed effects model with county and time effects for the Midwest, Northeast, and Southeast. The West and Southwest regions were not considered due to low LD case counts in most of the counties in those regions. The frost and drought variables were excluded from the analysis, since over the considered time period there was no month with frost in the Northeast and Southeast regions and no month with drought in the Northeast region. The estimation of the nonspatial fixed effects model was performed using the R package *fixest* (version 0.10.4); the reported standard errors are clustered by county.

TABLE A7. REGIONAL RESULTS FOR THE NONSPATIAL FIXED EFFECTS MODEL (DIRECT EFFECTS)

Variable	Midwest		Northeast		Southeast	
	Estimate (Std. Error)	P-Value	Estimate (Std. Error)	P-Value	Estimate (Std. Error)	P-Value
tmin_ave_spring	0.0610 (0.3219)	0.8496	14.9951 (5.1957)	0.0043**	0.8421 (0.3303)	0.0109*
tmin_ave_summer	-0.5752 (0.3205)	0.0729.	14.9388 (4.6326)	0.0014**	1.3418 (0.3943)	0.0007***
tmin_ave_winter	0.0891 (0.1505)	0.5540	14.5726 (3.0128)	< 0.0001***	-1.0437 (0.1656)	< 0.0001***
tmin_ave_spring_1	-2.3573 (0.3836)	< 0.0001***	0.3631 (3.9012)	0.9259	-0.4012 (0.2052)	0.0509.
tmin_ave_summer_1	1.2458 (0.3947)	0.0016**	1.4487 (4.9039)	0.7679	1.5847 (0.4677)	0.0007***
tmin_ave_winter_1	-1.1328 (0.1838)	< 0.0001***	5.3902 (2.1789)	0.0141*	-0.4606 (0.1369)	0.0008***
tmin_ave_fall_1	0.5054 (0.2710)	0.0625.	4.4942 (2.6169)	0.0872.	-0.1571 (0.2245)	0.4842
trange_spring	-0.8952 (0.1543)	< 0.0001***	4.1703 (2.0885)	0.0470*	0.0151 (0.0989)	0.8783
trange_summer	0.2104 (0.1382)	0.1284	-11.4489 (3.1832)	0.0004***	-0.1086 (0.0849)	0.2012
trange_winter	-0.3411 (0.0957)	0.0004***	2.0400 (1.1508)	0.0775.	0.1345 (0.0847)	0.1126
trange_spring_1	-1.8920 (0.2555)	< 0.0001***	4.3483 (2.6128)	0.0974.	-0.2569 (0.1104)	0.0202*
trange_summer_1	0.6824 (0.1543)	< 0.0001***	-12.7598 (2.8003)	< 0.0001***	-0.1920 (0.0942)	0.0418*
trange_winter_1	0.0630 (0.0986)	0.5229	-0.6166 (1.2050)	0.6094	0.3012 (0.0763)	< 0.0001***
trange_fall_1	0.2730 (0.1048)	0.0093**	3.5584 (1.7691)	0.0454*	0.4278 (0.0757)	< 0.0001***
prec_spring	-0.0259 (0.0041)	< 0.0001***	-0.0294 (0.0233)	0.2079	-0.0050 (0.0008)	< 0.0001***
prec_summer	0.0129 (0.0027)	< 0.0001***	0.0079 (0.0158)	0.6175	-0.0042 (0.0008)	< 0.0001***
prec_winter	-0.0357 (0.0061)	< 0.0001***	-0.0701 (0.0220)	0.0016**	0.0006 (0.0008)	0.4561
prec_spring_1	-0.0280 (0.0042)	< 0.0001***	-0.0081 (0.0269)	0.7645	-0.0045 (0.0008)	< 0.0001***
prec_summer_1	-0.0129 (0.0021)	< 0.0001***	0.0151 (0.0226)	0.5052	-0.0068 (0.0013)	< 0.0001***
prec_winter_1	-0.0058 (0.0037)	0.1205	-0.0848 (0.0238)	0.0004***	-0.0053 (0.0010)	< 0.0001***
prec_fall_1	0.0178 (0.0026)	< 0.0001***	0.1003 (0.0303)	0.0011**	-0.0009 (0.0005)	0.0461*
cropland_pasture	1.5337 (0.5237)	0.0035**	19.3746 (5.1684)	0.0002***	0.1444 (0.2199)	0.5115
forest	1.8180 (0.5904)	0.0021**	15.8981 (5.0272)	0.0018**	0.0146 (0.2187)	0.9467
shrubland	1.9969 (0.5428)	0.0002***	27.2087 (8.2872)	0.0012**	0.2976 (0.2682)	0.2674
edge_density	-9.8673 (3.4868)	0.0047**	19.4478 (43.6980)	0.6567	0.9437 (1.8648)	0.6129
unemp_rate	1.1223 (0.2638)	< 0.0001***	-6.0665 (2.1194)	0.0046**	-0.0184 (0.0728)	0.8005
pop_density	19.9734 (11.9534)	0.0950.	-62.5422 (21.0543)	0.0033**	1.2505 (4.0664)	0.7585


P-value codes: "****" < 0.001, "***" < 0.01, "**" < 0.05, "." < 0.1.

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Society of Actuaries Research Institute
475 N. Martingale Road, Suite 600
Schaumburg, Illinois 60173
www.SOA.org