

Impact of Land Use Changes and Habitat Fragmentation on the Eco-epidemiology of Tick-Borne Diseases

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Abstract

The incidence of tick-borne diseases has increased in recent decades and accounts for the majority of vector-borne disease cases in temperate areas of Europe, North America, and Asia. This emergence has been attributed to multiple and interactive drivers including changes in climate, land use, abundance of key hosts, and people's behaviors affecting the probability of human exposure to infected ticks. In this forum paper, we focus on how land use changes have shaped the eco-epidemiology of *Ixodes scapularis*-borne pathogens, in particular the Lyme disease spirochete *Borrelia burgdorferi* sensu stricto in the eastern United States. We use this as a model system, addressing other tick-borne disease systems as needed to illustrate patterns or processes. We first examine how land use interacts with abiotic conditions (microclimate) and biotic factors (e.g., host community composition) to influence the enzootic hazard, measured as the density of host-seeking *I. scapularis* nymphs infected with *B. burgdorferi* s.s. We then review the evidence of how specific landscape configuration, in particular forest fragmentation, influences the enzootic hazard and disease risk across spatial scales and urbanization levels. We emphasize the need for a dynamic understanding of landscapes based on tick and pathogen host movement and habitat use in relation to human resource provisioning. We propose a coupled natural-human systems framework for tick-borne diseases that accounts for the multiple interactions, nonlinearities and feedbacks in the system and conclude with a call for standardization of methodology and terminology to help integrate studies conducted at multiple scales.

Key words: land cover, Lyme disease, urbanization, dilution effect, biodiversity

The human health burden of tick-borne diseases has increasingly been recognized in the last ~50 yr in temperate areas in North America, Europe, and Asia, where they constitute the most commonly occurring vector-borne diseases. In the United States, the number of annual reports of tickborne bacterial and protozoan diseases more than doubled between 2004 and 2016 (Rosenberg et al. 2018). This increase is mostly driven by the increased abundance and geographical expansion of human-biting ixodid tick species (Acari: Ixodidae)—*Ixodes scapularis* Say, *Ixodes pacificus* Cooley and Kohls, *Amblyomma americanum* (L.), *Dermacentor variabilis* (Say), among others—collectively serving as vectors for more than 15 human pathogens (Sonenshine 2018, Stafford III et al. 2018, Eisen and Paddock 2020). In this forum paper, we focus on the impact of land use and landscape configuration on the eco-epidemiology and emergence of *I. scapularis*-borne *Borrelia burgdorferi* sensu stricto (Barbour and Fish 1993, Steere et al. 2004) which, together with *Borrelia mayonii* (Pritt et al. 2016), causes Lyme disease in North America. The high incidence of Lyme disease (300,000 cases

estimated per year), its large geographical range and extensive research resources enable a productive conceptual synthesis; we draw on other tick-borne diseases in the United States and Europe as needed to illustrate patterns or concepts.

Increases in incidence and geographical distribution patterns of ticks, hosts, pathogens, and human disease have been attributed to multiple anthropogenic impacts such as climate change, land use modification, expansion of key hosts, and human behavioral changes leading to increased human contact with ticks (reviewed by Sonenshine et al. 2018, Wikle et al. 2018, among others), with some studies formally considering multiple drivers (e.g., Medlock et al. 2013, Simon et al. 2014). In particular, the geographical expansion and emergence of Lyme disease in North America has followed the range expansion of *Ixodes scapularis* (Ogden et al. 2013, Diuk-Wasser et al. 2016, Hahn et al. 2016, Nelder et al. 2016, Walter et al. 2016, Sonenshine 2018, Gilliam et al. 2020). The expansion of this tick species and the spread and persistence of Ixodes-borne pathogens are, in turn, dependent on the abundance and distribution of hosts able to maintain

tick populations such as white tailed deer (*Odocoileus virginianus*) (Zimmerman; Artiodactyla: Cervidae) and other hosts serving as pathogen reservoirs through complex demographic processes and movement dynamics (Matuschka and Spielman 1986, Barbour and Fish 1993, Spielman 1994, Eisen et al. 2016a, Sonenshine 2018). We focus on historical and current land use and land cover (hereafter 'land use') changes as key drivers of tick-borne disease emergence and explore other causative factors as they interact with land use and landscape configuration, e.g., abiotic conditions linked to specific land use types, host abundance and behavior in relation to landscape structure, and people's interaction with the landscape leading to tick encounters.

In the eastern United States, historical land use trends have been dominated by a decline in agriculture and subsequent reforestation since cropland, pasture, and other cleared lands were abandoned in the 19th and early 20th centuries (Drummond and Loveland 2010). Because of the close association of *I. scapularis* with deciduous forests (Glass et al. 1995, Kitron and Kazmierczak 1997, Guerra et al. 2002, Ferrell and Brinkerhoff 2018, Ginsberg et al. 2020), some researchers postulate that the expansion of forests into previous agricultural areas and more recently urban areas (as urban forests or other greenspaces) was, and continues to be, an important driver in the emergence of tick-borne diseases (Barbour and Fish 1993, Pfäffle et al. 2013, Wood and Lafferty 2013, VanAcker et al. 2019). In contrast, other researchers have implicated forest fragmentation and the decline in biodiversity as the most important drivers of Lyme disease emergence (originally proposed by Ostfeld and Keesing 2000, Allan et al. 2003). In an attempt to accommodate these views, two recent reviews have proposed that the association between Lyme disease risk (the likelihood of human Lyme disease infection given exposure to ticks) and biodiversity (assumed to be linked to forest percent cover or forest intactness) is

scale-dependent and varies across an urban-to-rural gradient (Wood and Lafferty 2013, Kilpatrick et al. 2017). Furthermore, Halliday et al. (2020) emphasized how this association is dependent on the specific driver of biodiversity, in particular biodiversity loss.

In this forum paper, we disentangle the multiple ways land use and habitat fragmentation impact human risk of tick-borne disease, focusing on Lyme disease (Fig. 1). We frame ongoing debates in the field within conceptual frameworks from the fields of landscape ecology, eco-epidemiology, animal behavior, and complex systems. We first address the local abiotic and biotic factors associated with the enzootic hazard, measured as the density of host-seeking *I. scapularis* nymphs infected with *B. burgdorferi* s.s. (DIN) (see next section for terminology). We then explore how landscape configuration, in particular forest fragmentation, influences the enzootic hazard and disease risk. Finally, we propose a coupled natural-human systems framework for tick-borne diseases that accounts for the multiple interactions, nonlinearities, and feedbacks in these systems and conclude with a call for standardization of methodology and terminology to help integrate studies conducted at multiple scales.

Environmental Risk Assessment Framework for Tick-Borne Diseases

A conceptual barrier to disentangling the natural and human components of the Lyme disease system has been the pervading use of the density of infected *I. scapularis* nymphs, referred to as the density of infected nymphs (DIN), the entomological risk index (ERI) (Mather et al. 1996), or the probability of tick exposure (Ginsberg 1993) as a direct predictor of Lyme disease, either infection (e.g., as indicated by serosurveys), or reported cases of disease (conditioned by diagnosis and reporting biases). This metric captures only the component of risk associated with the

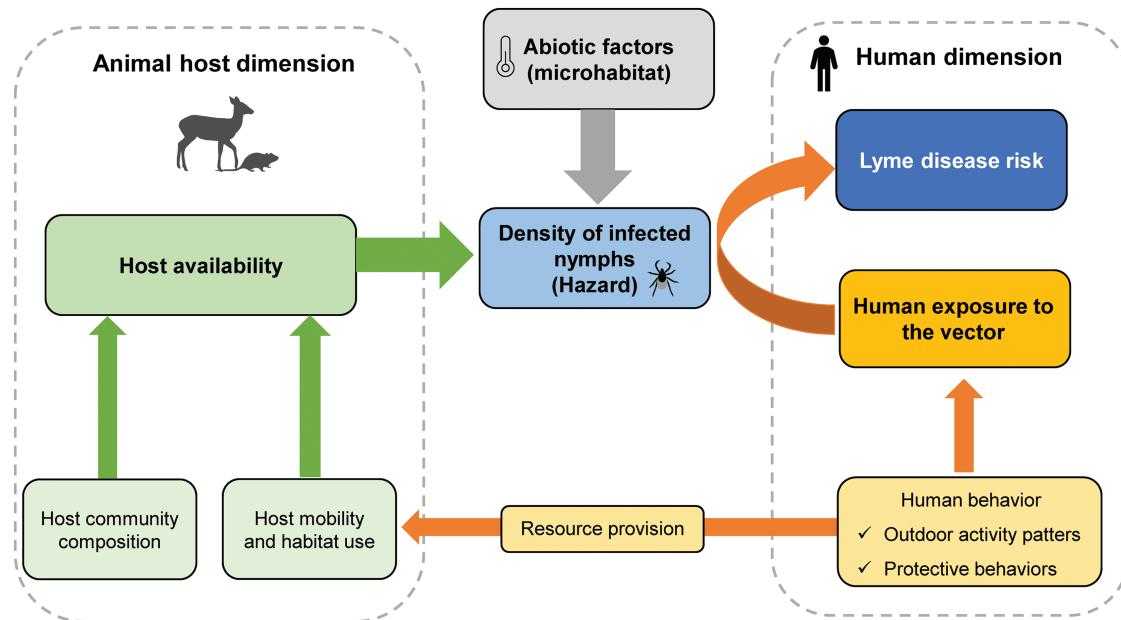


Fig. 1. Components of tick-borne disease risk. Tick-borne pathogen enzootic hazard (the density of infected nymphs, DIN) is determined by abiotic factors (microhabitat) suitable for off-host survival and host availability for ticks and the pathogen's enzootic cycle (the wildlife host dimension). The human dimension includes individual human behaviors affecting human-tick encounters that can occur both peridomestically or within natural areas. Human exposure depends both on the density of infected ticks (enzootic hazard) as well as people's outdoor activities, mobility patterns, and protective behaviors. Prior exposure to ticks can trigger multiple types of responses, including: avoidance of tick habitat, use of personal protection measures to reduce exposure, or no behavioral changes. Humans can influence the natural cycle through resource provisioning to wildlife hosts. The wildlife host dimension includes the host community composition, host movement and behavior which influences the availability of hosts for feeding ticks. Varying reservoir competence levels and the spatio-temporal dynamics of habitat use by hosts dictate whether feeding ticks become infected to produce the enzootic hazard—or DIN.

dynamics of the enzootic transmission, or the ‘source of potential harm’ to humans; the epidemic risk or spillover transmission to humans is mediated by human factors that are generally unmeasured. We postulate that the conceptual framework and terminology used in environmental risk assessment is more appropriate to measure the outcomes of interest to zoonotic diseases (Schneiderbauer and Ehrlich 2006, Priestly 2012, Hosseini et al. 2017). Using this framework, we denote:

- ‘Enzootic hazard’: the potential source of harm (the probability of an infected *I. scapularis* bite), measured as DIN.
- ‘Lyme disease risk’: the likelihood of an adverse effect (Lyme disease infection or disease) *given exposure* to the enzootic hazard by entry into tick habitat.
- ‘Exposure’: the likelihood of a person engaging in activities resulting in contact with an infected nymph and the likelihood that the infected nymph bites the person and remains attached long enough to transmit *B. burgdorferi* (Eisen and Eisen 2016a).

The conversion of the enzootic hazard to Lyme disease risk also depends on the person’s:

- ‘Vulnerability’: the possibility *given exposure* that the microbial hazard can cause harm (e.g., age, immune status)
- ‘Coping capacity’: the ability of individuals/groups to overcome negative outcomes, either by mitigating the hazard (reducing DIN by using tick- or host-targeted control methods), reducing exposure (adaptive behaviors such as applying repellents), accessing prophylaxis or treatment.

Impact of Local Abiotic and Biotic Conditions on the Enzootic Hazard

Tick-borne diseases such as Lyme disease are acquired in environments where the presence of vectors, the etiological agents and reservoir hosts overlap (Barbour and Fish 1993). Human exposure to tick-borne pathogens, in turn, can only occur within these geographical areas, either peridomestically or within natural habitats (Kitron and Kazmierczak 1997, Killilea et al. 2008, Connally et al. 2009, Reisen 2010, Diuk-Wasser et al. 2012, Finch et al. 2014, Berry et al. 2018, Mead et al. 2018). In this section, we discuss how the enzootic hazard is determined by abiotic factors (microhabitat) suitable for off-host tick survival, development, and activity and by the presence and abundance of hosts that support tick populations and pathogen maintenance. We discuss how tick species vary in the range of habitats and the hosts they utilize (habitat and host niche breadth, respectively), which influences their distribution, abundance, and potentially their local coexistence.

Direct Impacts of Land Use and Microhabitat on Off-host Tick Survival, Development, and Activity

Most hard tick species, and all non-nidicolous tick species, spend only a small fraction of their lives associated with vertebrate hosts, with the remainder (~99%) spent in or on soils and other substrates (Sonenshine and Mather 1994). During the off-host period, ticks undergo developmental transitions, diapause, and ‘quest’ for their next bloodmeal (Burtis et al. 2019). Temperature and humidity significantly impact the survival and developmental rates of ticks, with increasing temperatures shortening the tick’s life cycle and humidity being critical for ticks to maintain a positive water balance (Ogden et al. 2004, Gray et al. 2016, Ogden et al. 2018). During the questing period, ticks experience a ‘tradeoff’ between questing for hosts in relatively exposed environments where they deplete limited lipid reserves and increase desiccation risk or remaining in soil/leaf litter refugia to rehydrate (Needham and Teel 1991, McClure and Diuk-Wasser 2019).

The tolerance of ticks to temperature extremes and desiccation determines which habitats are favorable for each species and their habitat niche breadth (Needham and Teel 1991). *Ixodes scapularis* have low tolerance for desiccation and local studies have found greater presence or density of *I. scapularis* in forested rather than grass/shrub habitats (Ginsberg and Ewing 1989, Siegel et al. 1991, Ostfeld et al. 1995, Ginsberg and Zhioua 1996, Ginsberg et al. 2020). Similar association with woody areas has been documented for *Ixodes ricinus* (L.) in Europe (Pfäffle et al. 2013). Canopies of woody plants modify the microclimate beneath and around them by intercepting precipitation and by shading, which influences soil moisture. The permanent leaf litter layer also provides a more constant microclimate beneficial for the development of ticks and the establishment of tick populations (Sonenshine and Mather 1994). Dense woodlands with a ground cover dominated by leaf or fir-needle litter also increase the risk for human encountering *I. pacificus* nymphs in western United States (Eisen et al. 2003, Lane et al. 2004), although *I. pacificus* adults are commonly collected in open or wooded grasslands or chaparral (Lane and Stubbs 1990). In contrast, other tick vector species such as *A. americanum* and *D. variabilis* have wider tolerances for microhabitat conditions and can occupy grassland habitats in addition to forested sites, as well as ecotonal habitats subject to human disturbance (Sonenshine and Stout 1968, Sonenshine and Mather 1994, Childs and Paddock 2003, Stein et al. 2008, Fryxell et al. 2015, Sonenshine 2018, Stafford III et al. 2018, Simpson et al. 2019).

The specificity of the tick species-habitat associations determines the extent to which land use containing these habitats can predict the geographic distribution of ticks and the enzootic hazard, after accounting for the tick and pathogens’ climatic envelope and historical contingencies (Johnson et al. 2019). Because of *I. scapularis* close association with woody vegetation, maps of the distribution of the vector or enzootic hazard often identify forest land cover as a significant predictor of this tick species’ presence or abundance (Glass et al. 1994, Kitron and Kazmierczak 1997, Estrada-Peña 2002, Brownstein et al. 2005a, Diuk-Wasser et al. 2010, Hahn et al. 2016, McClure and Diuk-Wasser 2018). Forest cover is also a strong predictor of habitat suitability for *I. pacificus* (Eisen et al. 2006, 2016b; Hahn et al. 2016). In contrast, the geographical distribution of habitat generalists *A. americanum* and *D. variabilis* is less strongly associated with land use and mostly determined by spatial variability in temperature and humidity-related factors (Atkinson et al. 2012, Fryxell et al. 2015, Springer et al. 2015, Raghavan et al. 2019, Lippi et al. 2020). However, Simpson et al. (2019) reports an exception to *A. americanum* habitat generalism with the finding of greater tick survivorship and *E. chaffeensis* infection prevalence in small but contiguous patches of deciduous forest.

Indirect Impacts of Land Use on the Enzootic Hazard via the Host Community Composition

Although the majority of a tick’s lifespan is spent off-host, on-host periods are key for feeding and movement as well as horizontal pathogen transmission. Tick vector species and life stages vary in the range of hosts with which they are associated (host niche breadth). For example, the immature stages of *I. scapularis* feed on a wide range of mammalian and bird hosts (wide host niche breadth), whereas adult *I. scapularis* depend on white-tailed deer or other large hosts to mate and for females to obtain a bloodmeal (narrow host niche breadth). In contrast, *A. americanum* has a narrower host range, with white-tailed deer serving as the keystone (although not the only) host for all stages of this species (Paddock and Yabsley 2007, Allan et al. 2010).

Vertebrate hosts vary in the quality of the bloodmeal for the ticks as well as their levels of reservoir competence (i.e., host ability to become infected, maintain the pathogen and transmit it to feeding ticks). For example, the white-footed mouse (*Peromyscus leucopus*) (Rafinesque; Rodentia: Cricetidae) has the highest level of reservoir competence for *I. scapularis*-borne *B. burgdorferi* in the northeast United States (Donahue et al. 1987, LoGiudice et al. 2003), whereas other hosts exhibit various levels of reservoir host competence, including eastern chipmunks (*Tamias striatus*) (L.; Rodentia: Sciuridae), northern short tailed shrews (*Blarina brevicauda*) (Say; Soricomorpha: Soricidae), raccoons (*Procyon lotor*) (L.; Carnivora: Procyonidae), Virginia opossums (*Didelphis virginiana*) (Kerr; Didelphimorphia: Didelphidae), eastern gray squirrels (*Sciurus carolinensis*) (Gmelin; Rodentia: Sciuridae), and some ground-foraging birds, among others (LoGiudice et al. 2003, Brinkerhoff et al. 2010, Vuong et al. 2014). White-tailed deer cannot sustain *B. burgdorferi* infections (TelfordIII et al. 1988), although they are the dominant reservoir host for *A. americanum*-borne pathogens such as *Ehrlichia chaffeensis* and *Ehrlichia ewingii* (Paddock and Yabsley 2007, Allan et al. 2010). Ticks of all developmental stages are dispersed while feeding or mating on hosts, with the dispersal distance and potential successful colonization depending on the ticks' feeding duration and the movement speed, dispersal dynamics, and habitat use of the infested host.

A large share of the research linking land use and enzootic hazard or Lyme disease risk has concentrated on the 'dilution effect' hypothesis, which postulates an inverse relationship between host diversity and enzootic hazard or disease risk (Ostfeld and Keesing 2000). This hypothesis predicts that most competent hosts would increase in abundance in smaller habitat patches through predator or competitor release or would benefit from increased edge habitat (Ostfeld and Keesing 2000). A key assumption is that host communities assemble and disassemble in a particular order consistent with nested subsets of species observed in forest fragments in mid-western North America forests (Nupp and Swihart 1996, 1998, 2000; Rosenblatt et al. 1999). An additional assumption is that the relative order in which species are added (or removed) in a community are expected to be in order of their level of reservoir competence (in this case, for *B. burgdorferi* s.s.), with ubiquitous presence of the most reservoir competent hosts (Johnson et al. 2013). Although these assumptions generally apply to the white-footed mice, which are ubiquitous in forest fragments and can feed and infect a large number of immature ticks compared with other vertebrate hosts (Nupp and Swihart 1996, Logiudice et al. 2008), host assembly patterns of mesomammals and white-tailed deer are poorly understood. Particularly complex is the role of white-tailed deer as both a keystone host for adult ticks and a dilution host for *B. burgdorferi* infection, making its net effect on the enzootic hazard difficult to predict (Ogden and Tsao 2009, Huang et al. 2019).

Debate has ensued after the application of the dilution effect hypothesis to tick-borne diseases, both in support (Ostfeld and Keesing 2000, 2013; Logiudice et al. 2008; Keesing et al. 2010; Civitello et al. 2015) and questioning its theoretical basis, assumptions, empirical evidence, or generality (Randolph and Dobson 2012, Randolph 2013, Salkeld et al. 2013, Wood and Lafferty 2013, Linske et al. 2017). We address herein some of the aspects being debated and inconsistencies in the research as they relate to land use and habitat fragmentation, including the use of divergent metrics to assess the impact to human health, the shape of the relationship between these metrics and biodiversity per se (sensu Fahrig 2017) and the use of forest fragmentation as a proxy for the (unmeasurable) biodiversity per se (Kilpatrick et al. 2017, Rohr et al. 2020) (Fig. 2).

Because of the difficulty in directly measuring all relevant hosts at an ecologically relevant spatial scale, no studies have assessed

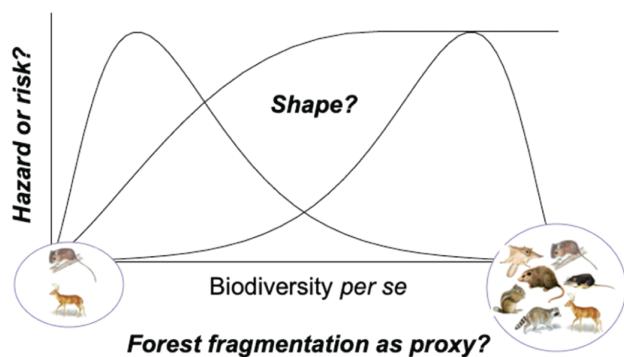


Fig. 2. The 'dilution' effect debates. Three debated aspects of the dilution effect include the use of the enzootic hazard or disease risk as the outcome, the shape of the relationship between either of these and biodiversity *per se* and the use of forest fragmentation as a proxy for biodiversity *per se*. Adapted from Rohr et al. (2020).

the role of biodiversity *per se*, i.e., as measured by species richness (number of species) and more appropriately the relative abundance (e.g., the Shannon diversity index) of all relevant hosts across a range of host community diversities. As examples of studies measuring limited components of the host community diversity, one field study trapped small mammals and used camera trapping for larger mammals (Logiudice et al. 2008), a second measured host densities and relative abundances on a species-poor island site and compared the enzootic hazard to similar sites in the mainland with a diverse host community (States et al. 2014, Huang et al. 2019), and a third assessed presence/absence of all nonrodent hosts in predefined host 'motifs' using camera traps (Ostfeld et al. 2018). The former two studies did not observe an inverse relationship between host diversity and the enzootic hazard, whereas the last one found lower nymphal infection prevalence with *B. burgdorferi* in host community motifs with the presence of rodent predator hosts and 'dilution' hosts, consistent with the dilution effect. Nymphal infection prevalence utilized in Logiudice et al. (2008) and Ostfeld et al. (2018) is, however, an incomplete metric for enzootic hazard since it does not consider the density of nymphs (Eisen and Eisen 2016). We next focus on how land use and habitat fragmentation have been used as proxies for biodiversity and its potential effect on the enzootic hazard and disease risk.

Impact of Land Use and Habitat Fragmentation on the Enzootic Hazard

The discussion about whether 'forestation' or forest fragmentation were the key historical drivers of Lyme disease emergence (Allan et al. 2003, Ostfeld and Keesing 2010, Wood and Lafferty 2013) can be framed in a broader landscape ecology debate about whether habitat fragmentation should be considered as a 'by-product' of habitat loss or as an independent process (fragmentation *per se*). The former school of thought considered habitat fragmentation as an umbrella term that refers to the process by which habitat loss results in the division of large, continuous habitats into a greater number of smaller patches with increasing degree of isolation from each other in a matrix of dissimilar habitat (Didham 2010). The spatial distribution of species assemblages in fragmented landscapes can then be described by the patch-matrix-corridor model where the matrix is considered to be the largest and often most highly modified patch type (Forman 1986, 1995; Forman and Godron 1981). This analysis of modified landscapes as 'island-like' patchy systems represents the

historical origin and traditional stronghold of the ‘fragmentation’ literature (Haila 2002). Such island-like behavior of modified terrestrial ecosystems can be observed in modified landscapes such as in forest fragments in an agricultural matrix in east-central Illinois. In this setting, small mammal species richness increased with forest patch size (Rosenblatt et al. 1999, Lindenmayer 2006).

An alternative school of thought in landscape ecology proposes that, while habitat loss has been shown to have a strong negative effect on biodiversity, the effect of habitat fragmentation per se is weak or even positive (Fahrig 2017). However, results of empirical studies of habitat fragmentation are often difficult to interpret because fragmentation is often measured at the patch rather than the landscape scale and because most studies do not distinguish the effect of habitat loss and habitat fragmentation per se (Fahrig 2003, 2013, 2017; Haila 2002). Fahrig (2013) posits that accounting for habitat amount in the study design is essential because species richness in a sample site is independent of the size of the particular patch in which the sample is located (i.e., the local patch) and instead it depends on the amount of habitat in the area around the sample site (i.e., the local landscape; the ‘habitat amount’ hypothesis). Thus, this hypothesis predicts that increased habitat amount in a given landscape would result in greater biodiversity, irrespective of the individual patch sizes or the amount of edge habitat (Fig. 3).

Because of the lack of distinction between habitat amount and fragmentation in previous study designs (discussed below), we suggest that the debate about whether ‘forestation’ or forest fragmentation were the key historical drivers of Lyme disease emergence (Ostfeld and Keesing 2010; Wood and Lafferty 2013) remains unresolved. In fact, both processes could actually be operating simultaneously, with ‘forestation’ increasing the habitat amount and heterogeneity of habitat available to ticks and their hosts, and fragmentation of forested areas influencing host composition and diversity, as well as human exposure to tick bites because of an increase in edge habitat.

To capture the roles of habitat amount and fragmentation on specific biological phenomena, it is thus essential to identify the appropriate landscape metrics and study design (Cushman et al. 2008,

McGarigal et al. 2009). In this section, we discuss the strengths and limitations of different landscape metrics to quantify ecological patterns and the underlying processes relevant to the enzootic hazard across an urbanization (i.e., rural/natural to urban) gradient. We examine the roles of patch-focused metrics; matrix connectivity; ecotones; host movement and habitat use patterns, and anthropogenic resource subsidies (Fig. 4).

A Focus on Patch Metrics: A Patch as the Landscape or a Landscape of Patches

Most studies of landscape fragmentation proxies for biodiversity and the enzootic hazard have focused on patch-level metrics, either by studying individual patches or patches within a predefined landscape. One of the most cited studies supporting the dilution effect hypothesis was based on a patch level study (Allan et al. 2003). This study identified greater enzootic hazard (measured as DIN) in very small patches (<2 ha) compared with patches between 2 and 8 ha. In contrast, the LoGiudice et al. (2008) study, also performed at the patch-level scale, failed to detect a relationship between *I. scapularis* nymphal infection prevalence (a partial indicator for enzootic hazard) and forest fragment size. Landscape-level studies using patch-level metrics (number of patches, size, and isolation) also have been conducted with mixed results; e.g., the Brownstein et al. (2005b) study identified an inverse link between forest fragmentation and enzootic hazard; Zolnik et al. (2015) and Diuk-Wasser et al. (2012) found no association.

Comparing findings from across studies is challenging because of the variability in the range of patch sizes, the method used for patch delineation and the extent of the study area. Patch sizes in the abovementioned studies ranged from 1 to 8 ha (Allan et al. 2003); 3.2 to 76.1 ha (Brownstein et al. 2005b); 0.3 to 19 ha (LoGiudice et al. 2008), 36 to 7,610 ha (Zolnik et al. 2015); and 100 to 900 ha (Diuk-Wasser et al. 2012). Some studies established a minimum distance from other forested areas to define an isolated patch (1.6 km in Allan et al. 2003, 80 m in LoGiudice et al. 2008, and 200 m in Zolnik et al. 2015), whereas other studies did not. In addition, studies varied in the study area extent; the Allan et al. (2003) study was within a county in NY state; the Brownstein et al. (2005b) study focused on 12 towns in southern CT; the LoGiudice et al. (2008) study encompassed 3 states; the Zolnik et al. (2015) study covered a 115 km transect across southern NY; and the Diuk-Wasser et al. (2012) study covered the eastern half of the United States. For all studies, large differences in sampling effort in each of the patches also limit their comparability.

Despite differences in methodology, the study comparison indicates that the dilution effect may occur at smaller patch sizes and study extents (Allan et al. 2003, Brownstein et al. 2005b) compared with studies at larger scales and extents (LoGiudice et al. 2008, Diuk-Wasser et al. 2012, Zolnik et al. 2015). This is consistent with previous work indicating that the effects of land use and biodiversity are local, whereas the effects of climate occur at a wider geographical scale (Halliday et al. 2020, Rohr et al. 2020). However, the patches in the Allan et al. (2003) study were too small to house resident populations of hosts larger than rodents, requiring larger hosts (in particular white-tailed deer) passing among them and depositing engorged adult ticks (Randolph and Dobson 2012). From the study description, it was unclear what the connectivity between those patches was for larger mammalian hosts. We pose it is important to consider processes occurring beyond the patch level to fully understand ticks and tick-borne pathogen dynamics in the landscape.

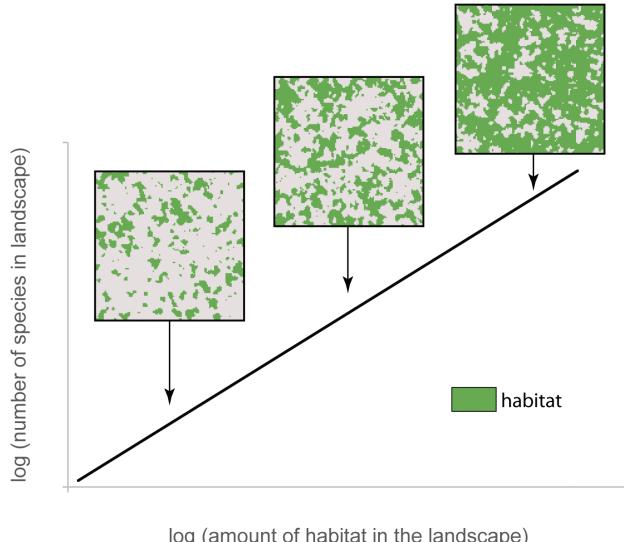


Fig. 3. Increases in biodiversity with increased habitat amount in a fixed-sized landscape. Because of the sample area effect, the total number of species in a given habitat type within the landscape increases alongside the total amount of that habitat in the landscape, irrespective of the sizes of the individual habitat patches in the landscape.

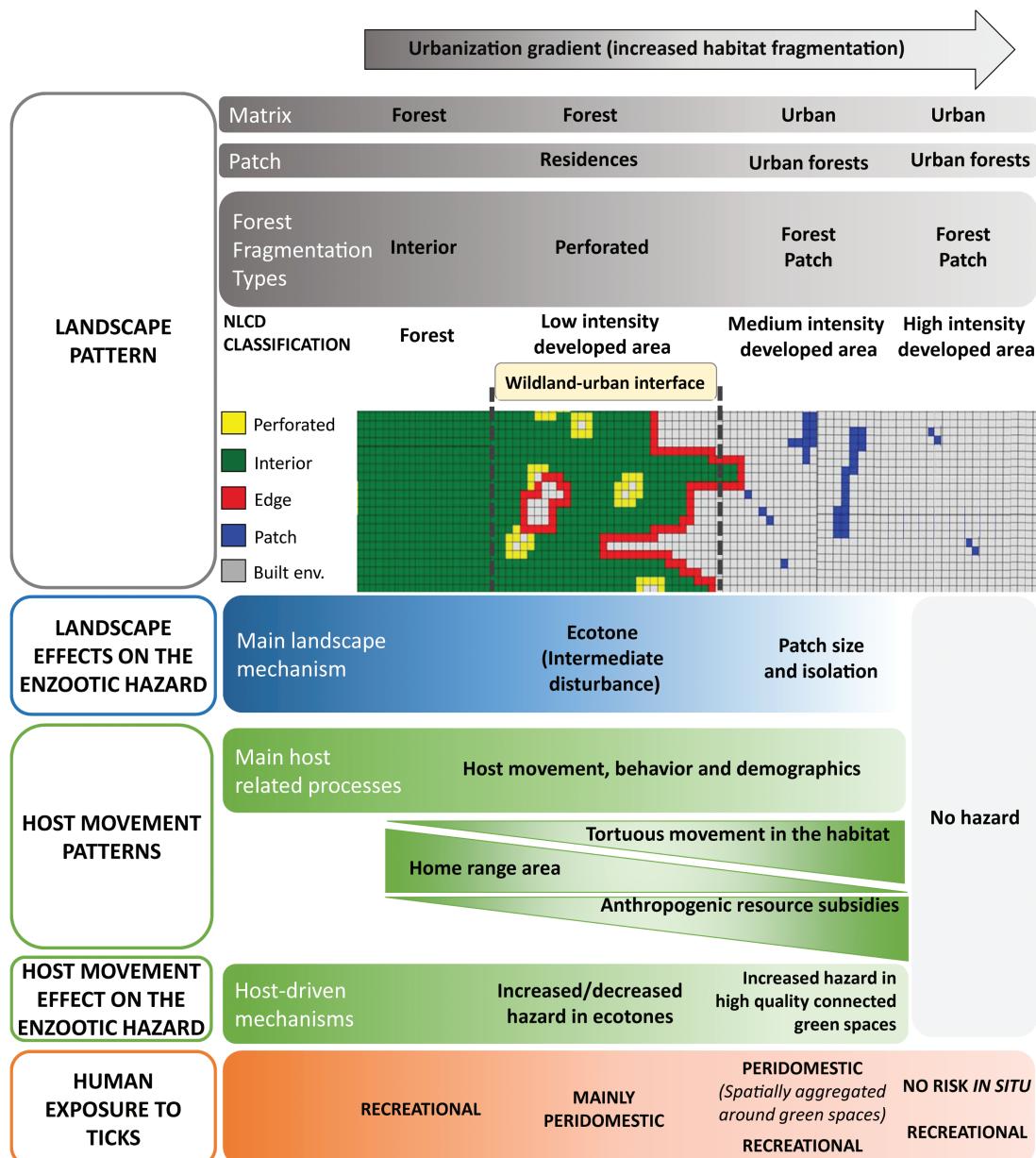


Fig. 4. Shifting landscape patterns and processes influencing tick-borne pathogen hazard and tick-borne disease risk across an urbanization gradient. From left to right, landscape patterns shift from a forest-dominated matrix, through a forest matrix with residences as patches, to an urban matrix with forests as patches, to an urban matrix with very limited urban forests. Existing classification schemes are displayed, namely the forest fragmentation types (Vogt et al. 2006, also in Fig. 5) and the national land cover database (NLCD) developed by the United States Geological Survey (USGS) multi-resolution land characteristics consortium (MRLC) (Jin et al. 2019). The landscape effects on the enzootic hazard transition from the intermediate disturbance in the ecotone zone (or the wildland urban interface, WUI) to the role of patch size and isolation in metapopulation dynamics. With increased habitat fragmentation hosts' home range size decreases due to movement barriers and reduced host movement from increased anthropogenic resource supplementation. Increased tortuosity in habitat patches with urbanization is attributed to both fragmentation and supplemental resources. Hosts will be attracted to the ecotone due to the intermediate disturbance and there can be an increase or decrease of the enzootic hazard depending on the hosts' tick burden and pathogen load. High quality urban forest patches that are well connected will have greater enzootic hazard than lower quality more isolated forest patches due to host habitat selection and patch functional connectivity. Human exposure to ticks transition from recreational in interior forests, to peridomestic in the ecotone, to no local risk with only travel-associated risk.

The Ecological Role of the Matrix: Connectivity Is Key

Although some studies described in *A Focus on Patch Metrics: A Patch as the Landscape or a Landscape of Patches* Section were performed at the landscape scale (Brownstein et al. 2005b and Zolnik et al. 2015), they still focused on patch-specific metrics and did not address the role of the intervening matrix. In particular, the metric 'patch isolation' in Brownstein et al. (2005b) measured

the average minimum distance between patch edges. This metric is expected to increase with reductions in forest cover but does not account for the connectivity of the matrix. The landscape matrix determines how connected the patches are to each other for focal species, with connectivity being either structural (the physical relationship between landscape elements) or functional (the degree to which landscapes facilitate or impede the movement of organism between areas of habitat). For tick-borne pathogens in a fragmented

landscape, we can describe populations of ticks or pathogens as occupying a metapopulation, i.e., a cluster of populations, that can suffer individual stochastic extinction and be recolonized from the other populations in the cluster depending on matrix connectivity (Levins 1969, 1970; Watts et al. 2018; Fig. 4). Therefore, at extreme levels of fragmentation in an unsuitable habitat matrix (low connectivity), populations of *I. scapularis* or *B. burgdorferi* may undergo frequent stochastic extinctions, resulting in very few or no ticks sampled or infected (or too few collected to accurately measure infection prevalence) in the most isolated (and sometimes the smallest) patches (Logiudice et al. 2008; VanAcker et al. 2019). Thus, even if smaller, more isolated patches were expected to have higher enzootic hazard according to the dilution effect; stochastic extinctions would pose a limit to the levels of isolation compatible with sustaining a tick or pathogen local population. Across an urbanization gradient with increasing forest cover, the enzootic hazard would have a zero intercept (i.e., very small or unconnected forest patches in urban or agricultural areas implies no ticks or tick-borne pathogens) and be either asymptotic or unimodal (if a dilution effect operates at the largest patch sizes) (Wood and Lafferty 2013; Kilpatrick et al. 2017; Rohr et al. 2020; Figs. 2 and 4).

The importance of patch connectivity for tick-borne pathogens was quantified for rural areas in Spain (Estrada-Peña 2003, 2005) as well as two urban areas in the United States and Belgium (Heylen et al. 2019; VanAcker et al. 2019). These studies found that patch connectivity, in addition to other patch characteristics, was critical for the persistence of ticks and pathogens in a metapopulation. Matrix properties can affect the dispersal and movement of individuals between patches (Gascon et al. 1999), and the degree of structural contrast between patch and matrix determines the permeability of habitat edges to propagule movement (Collinge and Palmer 2002), which, taken together, can be the prime determinants of colonization—extinction dynamics (Kupfer et al. 2006) and species loss.

As the amount of habitat (in this case forest) increases in an urban-to-rural gradient, the patch-corridor-matrix model becomes less useful. While forest patches and the intervening matrix can sometimes be delineated in high-contrast agricultural (e.g., Rosenblatt et al. 1999) or urban (e.g., VanAcker et al. 2019) landscapes, this

distinction becomes less clear as the amount of forest cover increases, resulting in a landscape of almost continuous forest matrix ‘perforated’ by nonforest, as found in the northeast United States (Fig. 4). To characterize the transition between forest cover as the patches (urban areas) to human-occupied areas as the ‘patches’ (suburban/exurban areas), Vogt et al. (2006) characterized the landscape into four classes of forest patterns described in Figs. 4 and 5 using morphological image classification processing on binary land-cover maps (Vogt et al. 2006, 2009; Vogt and Riitters 2017; described in Fig. 5). This classification system captures contrasting landscape patterns between the Midwest (dominated by patch forests) and the Northeast (dominated by interior and perforated forests) endemic Lyme disease areas (Fig. 5), indicating different landscape ecological processes may operate in these two regions.

At a local scale, the effect of the ‘perforated’ type of forest fragmentation in the northeast United States was assessed for tick-borne pathogens by Linske et al.’s (2017) study design (even though the authors did not explicitly utilize this metric for site selection). This study compared clusters of fragmented residential woodland habitats (perforated forests) to heavily forested sites with closed canopy (interior forests). This study identified greater biodiversity in the perforated (fragmented) than in the interior forests, contradicting the hypothesis that landscape fragmentation reduces biodiversity. The study did, however, find support for an inverse link between biodiversity and enzootic hazard, with lower enzootic hazard in highly biodiverse (and fragmented) residential sites. Future studies of tick-borne pathogens in fragmented landscapes should carefully consider the definition of patch and matrix in the study design and incorporate matrix connectivity and metapopulation/metacommunity dynamics. Patch connectivity is expected to increase in importance as the landscape becomes more fragmented and patch isolation increases along an urbanization gradient (Fig. 4).

Ecotones: The Wildland–Urban Interface

An alternative to sometimes ambiguous definitions of patches and matrices is to focus on the ecotone, defined as ‘a zone of transition between adjacent ecological systems, having a set of characteristics

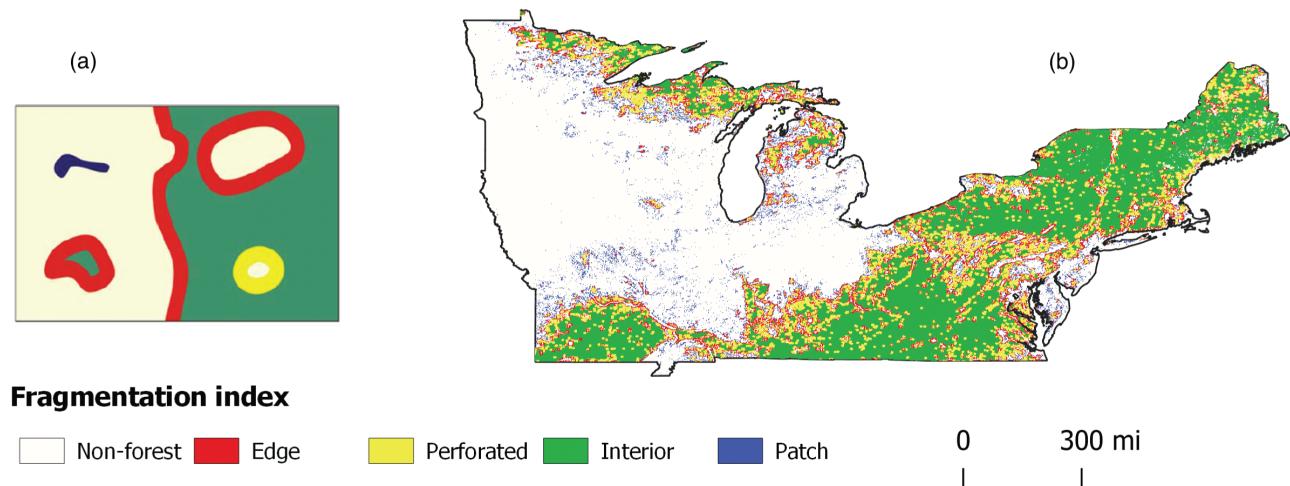


Fig. 5. Forest fragmentation classification using morphological image processing for classifying spatial patterns at the pixel level on binary land-cover maps (Vogt et al. 2006). (a) Four classes of forest pattern, namely ‘interior forest’ (pixels far from forest–nonforest boundary), ‘patch forest’ (coherent forest regions too small to contain interior forest), ‘perforated forest’ (the boundary between interior forest and relatively small perforations), and ‘edge forest’ (interior forest boundaries with relatively large perforations as well as the exterior boundaries of interior forest regions). (b) Contrasting landscape patterns between the Midwest (dominated by patch forests) and the Northeast (dominated by interior and perforated forests) endemic Lyme disease areas. Adapted from Riitters et al. (2000) and Vogt et al. (2006).

uniquely defined by space and time scales and by strength of the interactions between adjacent ecological systems' (Holland et al. 1991; Fig. 4). Ecotones are frequently considered in the zoonotic and vector-borne disease literature as an important interface for vector-host-pathogen contact and a specialized habitat for hosts or vectors (Despommier et al. 2006). Studies in Europe and North America have shown tick vectors of a number of significant zoonotic pathogens are most abundant in ecotones (Goddard 1997, Estrada-Peña 2001, Lindstrom and Jaenson 2003, Pietzsch et al. 2005). A challenge in understanding the role of ecotones is that most studies of the enzootic hazard have examined the distribution of ticks or pathogens within forest fragments of differing sizes, ignoring the intervening matrix (a 'one-sided' approach sensu, Fonseca and Joner 2007) rather than considering the whole gradient from the forest interior through the ecotone to the matrix habitat (a 'two-sided' approach).

The effect of ecotones on the enzootic hazard is difficult to predict because hosts and ticks may respond differently to conditions within the forest patch than in the patch-matrix ecotone. *Ixodes scapularis* abundance was found to be greater in interior forest habitats than in ecotones between forest and open habitats (Maupin et al. 1991, Stafford and Magnarelli 1993, Dister et al. 1997, Horobik et al. 2006, Finch et al. 2014). However, there is no general consensus about how members of the genus *Peromyscus* respond to edge habitats. Some studies reported that the densities of *P. leucopus* at the edge are greater than the densities in the interior, whereas other studies have reported no difference or seasonal differences (Cummings and Vessey 1994, Sekgororoane and Dilworth 1995, Manson et al. 1999, Wolf and Batzli 2002, Anderson et al. 2003). The use of ecotones is also complex in the case of white-tailed deer, a key host in the Lyme disease system. While deer will concentrate foraging along habitat edges (Williamson and Hirth 1985, Johnson et al. 1995, Gaughan and DeStefano 2005, Rohm et al. 2007), they will use interior forest for bed sites where dense understory and canopy cover provide thermal refugia and reduced predation risks (Lang and Gates 1985, Piccolo et al. 2010, DeYoung and Miller 2011); habitat suitability for ticks will vary depending on where they drop off deer. Incorporating this duality of host and tick habitat suitability in a modeling study, Li et al. (2012) found that the presence of grasslands adjacent to woodlands acted as sinks for ticks, since hosts readily used grass land cover types, but ticks were more likely to desiccate there.

A unique type of ecotone critical for tick-borne pathogen transmission is the transitional zone between the forest and residential lawns (Maupin et al. 1991, Stafford III and Magnarelli 1993, Finch et al. 2014). At a large geographical scale, the ecotone can be considered the area where residential properties meet or intermingle with undeveloped private land, termed the 'wildland–urban interface' (WUI; Radeloff et al. 2005). Although WUI indices were developed to measure risk for wildfire, researchers have started using WUI to quantify Lyme disease risk (McClure and Diuk-Wasser 2018) or Lyme disease incidence (Larsen et al. 2014, Bisanzio et al. 2020). The WUI index has also been used as a proxy for land use changes linked to the expansion of suburban development (Larsen et al. 2014). The northeastern forests underwent a dramatic 'forest transition' (Mather 1992), a concept that characterizes forest cover in countries or regions where deforestation dominates in early stages of economic development and forest gain occurs when agriculture and other intensive land use types decline (Mather and Needle 1998). Over a 200-yr span, regional deforestation reduced the Northeast forest area by over half, which led to a forest area minimum in 1920 (Houghton and Hackler 2000, Smith et al. 2005, Drummond and

Loveland 2010). This trend was reversed due to agricultural abandonment and forest recovery leading to the Northeast's forest area maximum around 1973 (Houghton and Hackler 2000, Smith et al. 2005, Drummond and Loveland 2010). Forest gains occurred alongside a fivefold increase in exurban residential land use in the United States from 1950 through the 2000s (Brown et al. 2005), also described as low-intensity developed areas (Jin et al. 2019) or suburbs (Harris 2010). From 1980 through 2000, the rate of land conversion to residential use in exurban areas outpaced human population growth by roughly 25% (Theobald 2005). In turn, the WUI has expanded by 52% since 1970 and continues to expand (Theobald and Romme 2007). The WUI is disproportionately found in the eastern United States—encompassing 83% of the nation's WUI area—providing the physical space for the conversion of the enzootic hazard into risk when humans interface with hosts and vectors that occupy the WUI.

Adding Dynamics: Functional Connectivity in the Matrix Through Host Movement

The distribution of areas with high and low enzootic hazard is often displayed through static risk maps (Glass et al. 1994, Guerra et al. 2002, Diuk-Wasser et al. 2012, Hahn et al. 2016, Vourc'h et al. 2016). However, the distribution of the enzootic hazard is intrinsically dynamic (Fig. 4); vectors and pathogens rely on hosts for long distance dispersal, and host movement contributes to heterogeneity in human exposure to the enzootic hazard and transmission risk. Wildlife movement is the outcome of behavioral decisions that are influenced by the animals' internal state, external biological factors (e.g., competition, predation), and the physical environment (Nathan et al. 2008). Therefore, animals are continuously responding to these three factors through movement, where habitat selection and availability determine the animals' movement patterns (Avgar et al. 2013), and navigation and motion capacity affect the animals' habitat use patterns (Rhodes et al. 2005, Avgar et al. 2015). However, a critical element that determines an animal's ability to use a habitat is its ability to get there (Taylor et al. 1993). Although the physical arrangement of landscape elements can determine structural connectivity, functional connectivity is species-specific, and animals may functionally connect patches that are not structurally connected (Vogt et al. 2009). Thus, identifying the functional connectors for host species of interest can help limit the spread of infected ticks by using control measures to target corridors that allow for interpatch host movement. Functional connectors for host species can be determined through classifying and identifying important morphologies of the landscape (e.g., loops, bridges, branches, Vogt et al. 2009) using field-collected movement data, if available, or when not available, simulated movement or landscape resistance surfaces, both parameterized using the species' underlying biology and/or empirical data (Spear et al. 2010, McRae et al. 2013).

Land use affects movement behaviors because land cover types present differing levels of risk and benefit which vary among species (Johnson et al. 2002, Bélisle 2005, Hernández and Laundré 2005) and cascade to impact the enzootic hazard (Lloyd-Smith et al. 2005). When considering the urbanization gradient, the degree of influence that hosts may have on the enzootic hazard through movement can be scaled by body mass (Jetz et al. 2004), physiology, diet (Tucker et al. 2014), and other traits affecting motion—making some hosts more important in long-range vector or pathogen dispersal (e.g., birds, deer) and other hosts more critical for local vector population and pathogen maintenance (small mammals and some mesomammals). The scale of hosts' influence on the enzootic hazard

can be further modified by the landscape of fear—an animal's spatial trade-off between access to food and predator avoidance (Brown et al. 1999, Laundré 2010, Laundré 2014). Animals' perceived risk will shift along the urbanization gradient, where human activities in urban areas may incite fear and avoidance behaviors for hosts, replacing the role of natural predators in rural landscapes.

The impact of host movement on the enzootic hazard also varies by spatial and temporal scale. For example, white-tailed deer, the keystone host for *I. scapularis* ticks, have larger home ranges in intact forested areas when compared with more developed urban and suburban areas (Swihart et al. 1993, Cornicelli et al. 1996, Kilpatrick and Spohr 2000, Grund et al. 2002; Fig. 4); the reduced spatial scale of deer movement may limit the vector and pathogen distribution across an urban landscape. Because habitat area will be reduced in highly fragmented landscapes, pathogen and tick population persistence in the metapopulation may be determined by smaller scale movements, such as searching or foraging, which can be characterized by the level of tortuosity in the animal's movement and the distribution of step lengths (Fig. 4). Although some studies have incorporated population-level information on the role of deer abundance in determining enzootic hazard and disease risk (Rand et al. 2003, Elias et al. 2011, Cagnacci et al. 2012, Kilpatrick et al. 2014), it is important to also consider individual-level effects on risk such as time-dependent attributes of movement. A deer's residence time (the duration of a visit to a particular point), site fidelity (the tendency to return to a previously occupied location), or periodic movements can greatly influence the hazard depending on the individual's tick burden, which also varies in space and time. Urban adapted wildlife show behavioral modifications in response to human disturbance such as becoming more nocturnal and temporally shifting their foraging to avoid periods of elevated human activity (Lowry et al. 2013, Gaynor et al. 2018), potentially creating a mismatch between host and questing tick activity periods. Similar temporal characteristics of movement are important to consider for reservoir hosts of pathogens as these species may dictate transmission events through tick feeding. The effect of matrix heterogeneity on individual movement and behavior can translate to large effects for populations and Lyme disease emergence patterns (Lloyd-Smith et al. 2005). Therefore, a patch-centered approach is unrealistic to examine population and metapopulation processes and responses to habitat fragmentation (Revilla et al. 2004), which are critical to tick-borne diseases as fragmentation increases in anthropogenic landscapes.

Resource Subsidies in Heterogeneous Landscapes: the Intermediate Disturbance Hypothesis

Habitat fragmentation can have both negative and positive effects on host population dynamics and host diversity (Fahrig 2017, Fletcher et al. 2018). A positive effect on host diversity has been called the 'intermediate disturbance hypothesis', which postulates that the initial human impact of suburbanization is sometimes relatively mild and promotes environmental heterogeneity because different habitats occur alongside each other (McKinney 2008). For many tick host species, human-modified land use types such as those existing in the WUI ecotones provide supplementary or complementary resources that may compensate for limited resource availability in natural habitat patches (Ries et al. 2004, Linske et al. 2017) and provide habitat types that animals may use seasonally or for specific behaviors. When environmental heterogeneity from human modification drives wildlife behavior, it becomes clear that the dividing line between what is a 'patch' and what is a 'matrix' is meaningless and

species may perceive the whole landscape as 'habitat' (Haila 2002). This behavioral response to landscape-scale habitat further supports abandoning a patch-centric approach for Lyme disease studies. Instead, we recommend using the concept of landscape as habitat mosaics varying in habitat quality (Forman and Godron 1981, Forman 1995, Erdős et al. 2018).

Environmental heterogeneity found increasingly with anthropogenic disturbance and human-dominated land use is often in the form of supplemental resources made available to wildlife by humans. These resource subsidies can directly affect host population dynamics through altering immune function, increasing local population densities (Robb et al. 2008a, Prevedello et al. 2013, Galbraith et al. 2015), driving movement behaviors and aggregation (Becker et al. 2015, Satterfield et al. 2018), shifting community interactions (Rodewald et al. 2011, Oro et al. 2013) and altering host–vector contact rates (Bradley et al. 2008). Resource subsidies for wildlife span both suburban and urban land use but may increase in intensity in urban areas with higher human population density and more opportunities for supplementation. Anthropogenic resource subsidies can be intentional, such as through supplemental feeding stations, or accidental to include ornamental gardens, fertilized lawns, byproducts from agriculture, fishing, household waste, or landfills (Becker et al. 2015). The relative importance of these sources varies regionally and along an urban-to-rural gradient (Swihart et al. 1993, West and Parkhurst 2002, Williams et al. 2012). Importantly, because resource subsidies may be predictably distributed, hosts may track patterns of resource supplementation, in turn influencing host dispersal patterns, tick and pathogen metapopulation dynamics (Becker and Hall 2016) and the distribution of the enzootic hazard. Because mammal populations are typically food limited, food subsidies can cause mammals to immigrate to subsidized sites (Prevedello et al. 2013) or delay migratory movements (Jones et al. 2014), altering host movement and genetics across a range of rural and urban landscapes in hosts critical for the U.S. enzootic cycle of *B. burgdorferi* s.s. and other tick-borne pathogens.

An example of a ubiquitous intentional food subsidy are birdfeeders, which are prevalent in suburban and urban landscapes. Reed and Bonter (2018) found that, at feeding sites, there were increased detections of squirrels, deer, and raccoons, up to fourfold higher group sizes for gray squirrels and raccoons, and a localized increase in daily mammal richness. The aggregation of mammalian and avian hosts around feeders can aid in horizontal pathogen transmission from feeding ticks and allow for the transmission of novel pathogens between host species. Limited studies have not found an association between birdfeeders and exposure to the enzootic hazard in backyards (Townsend et al. 2003, Fischhoff et al. 2019b), but more studies are warranted that examine the specific effects of resource subsidies in different contexts. This is increasingly relevant in the United States where an estimated 54.3 million households (73%) provide 500,000 ton of food in the form of supplemental resources for wildlife annually (Robb et al. 2008b).

Suburban deer densities, in particular, can rapidly increase with resource provisioning from birdfeeders and ornamental plants in residential areas (Swihart et al. 1993, Kilpatrick and Spohr 2000) as well as from a lack of predators, minimal hunting pressure (Witham and Jones 1990), and high survival rates (Etter et al. 2002). Prior work has shown that deer browsing intensity and diet diversity increases within 50 m from houses (Swihart et al. 1993), because deer will reduce their activity and movement in areas with abundant foraging resources (Massé and Côté 2013), potentially increasing the enzootic hazard in residential areas. Significant debates exist about the efficacy as well as the logistics and feasibility

of deer reduction as an intervention to reduce the enzootic hazard and Lyme disease risk (Kugeler et al. 2016, Telford III 2017). Telford III (2017) proposed that a reduction in deer density may lead to a synergistic reduction in the enzootic hazard if, at lower density, deer aggregate within the core area of their home range where suitable habitat for ticks exist, but the probability of human encounters with ticks at these interior sites is lower. Telford III further argues that at high deer densities, deer will seek additional resources outside of their core home range area, thus expanding the spatial area where humans can encounter the enzootic hazard (Telford III 2017). The spatial expansion and contraction of the home range area that Telford III proposes is contingent on static spatio-temporal patterns of available resources which are, in fact, dynamic in space and time (Wiens 1976). Ungulates in particular show movement responses to the alteration of resource availabilities (Kilpatrick and Stober 2002) through rapidly tracking resource pulses which can result in larger, spatially-shifted home ranges (Ranc et al. 2020). We would expect tracking of both natural and anthropogenic resources to increase in importance in urban areas where the average home range area is smaller. To explicitly examine the impacts of resource subsidies on white-tailed deer habitat use and its cascading effect on the enzootic hazard and Lyme disease risk, future studies should incorporate deer movement, estimate herd densities, and consider the changing dynamics of natural and anthropogenic resources.

Impact of Land Use and Habitat Fragmentation on Lyme Disease Risk: Translating Hazard into Risk

The presence of *I. scapularis* ticks infected with *B. burgdorferi* is a *sine qua non* for the occurrence of locally acquired human cases of Lyme disease, but the functional relationship between Lyme disease incidence and the enzootic hazard is mediated by human behaviors and movement determining human exposure to the enzootic hazard (Figs. 1 and 4). At a U.S. national scale, Lyme disease risk is geographically clustered, with high incidence states located in the Northeast and Midwest (Kugeler et al. 2015, Bisanzio et al. 2020) that partially correlate with increased enzootic hazard, measured as tick presence and DIN (Diuk-Wasser et al. 2006, Eisen et al. 2016a). However, although Lyme disease incidence has been found to increase with DIN at town and county levels (Kitron and Kazmierczak 1997, Stafford III et al. 1998, Falco et al. 1999, Diuk-Wasser et al. 2012, Pepin et al. 2012), the strength of this association varies (Pepin et al. 2012). At the U.S. national scale, the association between enzootic hazard and Lyme disease risk is partially influenced by genetic differences in *B. burgdorferi* genetic makeup (Pepin et al. 2012). However, most of this variability is likely due to spatial differences in people's interaction with fragmented landscapes, risk behaviors, and engagement in risk reduction practices (Finch et al. 2014, Eisen and Eisen 2018, Bron et al. 2020). In this section, we discuss how land use and habitat fragmentation impact the conversion of enzootic hazard into Lyme disease risk at multiple spatial scales and across urbanization gradients. We discuss patterns at the regional scale, subcounty scale, and within urban areas.

Regional Scale: Lyme Disease Risk Is Maximized at Intermediate Levels of Fragmentation

Lyme disease risk is expected to vary nonlinearly along an urbanization gradient (Wood and Lafferty 2013, Kilpatrick et al. 2017). Lyme disease risk should increase from highly urbanized areas with no exposure to tick habitat to low-intensity residential neighborhoods with intermediate levels of forest and anthropic habitats, resulting

in the maximum expected ecotone habitat (Faust et al. 2018). As semiurban fragmented forests transition to intact forests, Lyme disease risk will depend on how humans interact with natural areas (peridomestic or recreational exposure) and on the association between fragmentation and the enzootic hazard (whether or not there is a dilution effect) (Fig. 2).

The role of forest-herbaceous (mostly residential) ecotones in determining human Lyme disease case distribution has been supported by numerous studies at the county level (McClure and Diuk-Wasser 2018, Jackson et al. 2006, Tran and Waller 2013, Seukep et al. 2015). The WUI has been increasingly used as a metric for ecotones at a regional scale (Larsen et al. 2014, Bisanzio et al. 2020; Fig. 6). Because this metric was originally defined to assess risk for wildfire, further developments to better predict Lyme disease risk is warranted. The role of forest cover and the WUI should also be assessed in counties other than the ones where cases are reported to account for potential travel-related exposure. For example, Bisanzio et al. (2020) found a significant effect of percent forest cover and the population living in the WUI in the first-degree (although not second-degree) neighboring counties on Lyme disease reporting in the focal county.

Consistent with theoretical expectations, those studies that examined Lyme disease risk along an urbanization gradient identified a univariate association with Lyme disease risk peaking at some intermediate level of anthropogenic and forest cover. For example, Jackson et al. (2006) identified a quadratic relationship between Lyme disease incidence and the percentage of forest cover, where half-forested landscapes with a large percentage of forest-herbaceous edge were statistically associated with the highest Lyme disease incidence. A unimodal relationship with percent forest cover was also found by McClure and Diuk-Wasser (2018) when assessing Lyme disease risk in simulated landscapes, with the highest Lyme disease risk at 20% forest cover (Fig. 2).

Sub-county Scale: Disentangling Multiple Sources of Exposure

At the local scale, multiple studies have shown that exposure to ticks is mainly peridomestic (Falco and Fish 1988; Maupin et al. 1991; Connally et al. 2006, 2009; Finch et al. 2014; Hinckley et al. 2016; Stafford III et al. 2017; Mead et al. 2018, among others). This finding is consistent with the high predictive power of the WUI on Lyme disease risk at large spatial scales described in *Regional Scale: Lyme Disease Risk Is Maximized at Intermediate Levels of Fragmentation* Section. Local studies, however, have the potential to address remaining questions, such as to what extent exposure occurs in residential yards, neighborhoods, local parks, or farther locations (recreational exposure). In two recent metaanalyses, Fischhoff et al. (2019a, b) identified factors most frequently predictive of tick bites or Lyme disease incidence at different spatial scales, with variables measured at the neighborhood scale (defined as the area extending 500 m from the property boundary) being generally more predictive than those assessed in the residential yard or 'outside the neighborhood'. The dominant variable at the neighborhood scale was the presence of woods adjacent to or within 500 m of the yard (Glass, 1995, Smith 2001, Connally 2009, Aenishaenslin et al. 2017). Moon et al. (2019) also identified landscape metrics such as percent forest cover and forest edge density at the 'neighborhood' scale (defined as a buffer 805 m in radius) as the most predictive of Lyme disease incidence, compared with the community (defined as the township, borough or city) level associations.

Although studies linking land use to Lyme disease risk have focused on the role of ecotones, some studies have also taken a patch-level approach. For example, Brownstein et al. (2005b), used

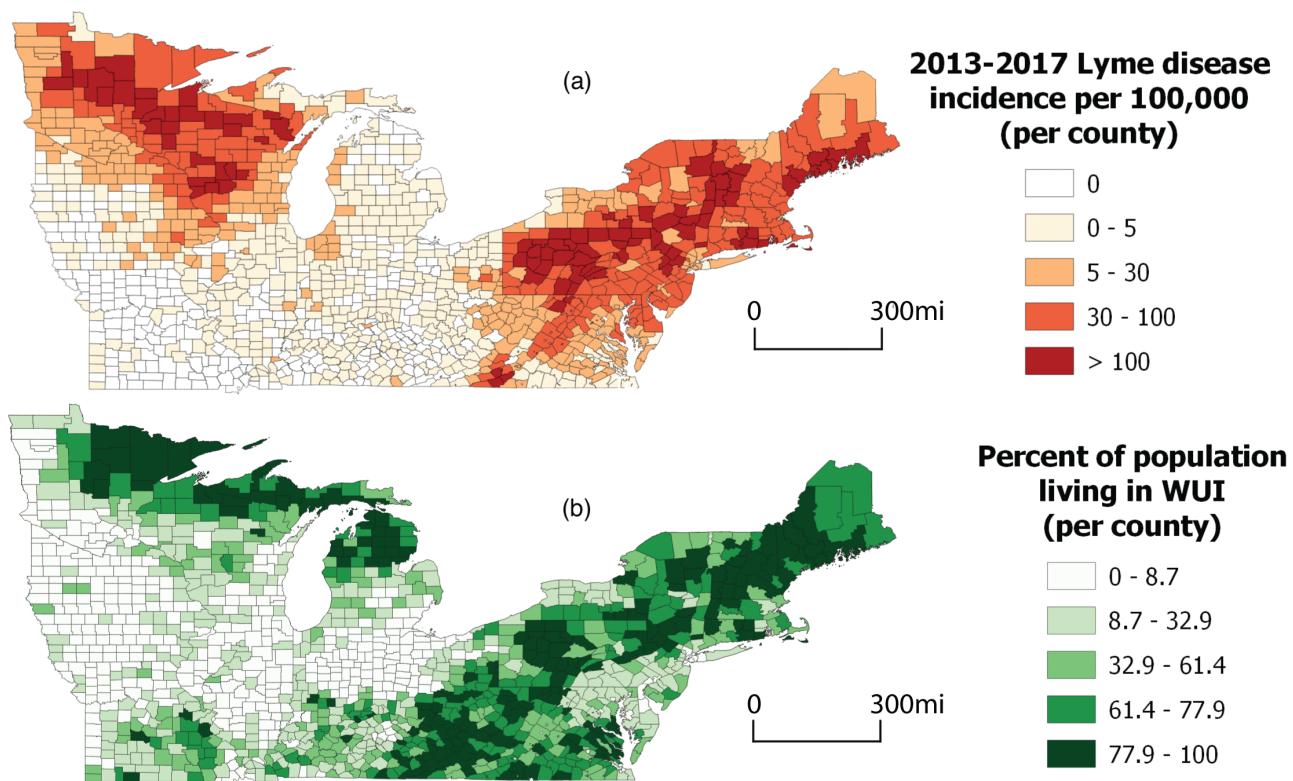


Fig. 6. Comparison between (a) Lyme disease incidence and (b) percent of the county population living in the WUI in the high Lyme disease incidence (Midwest and Northeast) regions in the United States.

patch-level metrics associated with forest fragmentation (i.e., patch size and isolation) to study the association between fragmentation, DIN, and Lyme disease incidence. Although they found the same positive association between enzootic hazard (DIN) and fragmentation patch-level metrics as Allan et al. (2003; *A Focus on Patch Metrics: A Patch as the Landscape or a Landscape of Patches Section*), these authors found Lyme disease incidence had a negative association with fragmentation (Lyme disease incidence was higher with larger patches). Moon et al. (2019) also found that forest patch size was positively associated with Lyme disease incidence in townships in Pennsylvania, but the association was less clear in more densely populated areas (Moon et al. 2019), contributing to the evidence of a nonlinear unimodal relationship between forest patch size and disease risk. Using simulated landscapes, McClure and Diuk-Wasser (2018) partially replicated the positive association between forest patch size and Lyme disease incidence but the association became negative at very large patch sizes (a unimodal association), reflective of reduced risk in more rural settings.

The Rise of Urban Lyme Disease: The Key Role of Connectivity of Greenspaces in the Urban Matrix

Although the risk of locally acquired Lyme disease cases is lower in medium-intensity developed (urban) areas compared with low-intensity developed areas within endemic regions (Cromley et al. 1998), green spaces in urban areas can facilitate the invasion of hosts, ticks, and pathogens (Fig. 4). Exposure to the enzootic hazard for park visitors or in neighborhoods connected to parks has become a growing public health threat (Gassner et al. 2016, Noden et al. 2017, Heylen et al. 2019). With high human densities in cities, emerging tick-borne infections can cause a significant public health burden. Although the positive effect of urban forests/

green spaces on human wellbeing (ecosystem service) is well established (Lee and Maheswaran 2011), those benefits need to be weighed against potential negative effects (ecosystems disservices), which are often overlooked (Escobedo et al. 2011). Urban ecosystems should be managed to minimize the likelihood of human contact with tick-infested areas. However, the majority of tick-borne disease studies have been conducted in fragmented suburban landscapes and natural areas due to their favorable habitat suitability for ticks, so there is limited understanding of the dynamics of ticks and tick-borne pathogens as well as the effectiveness of control strategies in urban landscapes.

As fragmentation increases in medium-intensity developed areas, the proportion of residences that contain or adjoin forested areas decreases. The resulting neighborhood configuration and differential access and use of green spaces causes variable exposure to tick-borne pathogens recreational or peridomestically. It is well established in urban planning that access to green spaces increases with proximity, which mostly describes the ease of walking to the park (Rigolon 2016). Access to green spaces declines if the park is located beyond convenient human walkable distance (400 m; Just 1989; Wolch et al. 2005, 2014; Auyeung et al. 2016). Two studies of users of a large urban park in Chicago found that users were also more likely to live nearby and to walk, rather than drive, to the park (Gobster 2002, Tinsley et al. 2002). The average distance to parks will, in turn, depend on urban design, with higher access (and potential exposure to tick habitat) for cities or neighborhoods with a ‘land sharing’ design—extensive sprawling urbanization where built land and natural space are interspersed—in contrast with a ‘land sparing’ design—intensive and extremely compact urbanization alongside separate, large, contiguous green space (Stott et al. 2015). However, the risk will decrease if the ‘land sparing’ design

results in parks that are too small or isolated to maintain ticks and pathogens. The specific design and fragmentation of urban green spaces may also influence human exposure risk. One study looking into human engagement with nature in fragmented landscapes found that engagement was highest in areas that have a mix of land cover (less than 40% urban land cover, between 20 and 50% core forest cover, and more than 40% perforation cover) and coincided with the edges of the core natural areas that have paths leading to them (Zambrano et al. 2019).

In highly anthropic areas, we still lack an understanding of how urban structure influences functional connectivity to humans in relation to their risk of exposure to tick-borne pathogens. Extensive datasets becoming available to track human movement (Facebook 2020, Google 2020, Huang et al. 2020, Oliver et al. 2020, SafeGraph 2020) can aid in understanding people's movement patterns in relation to areas of high enzootic risk. We also need to develop tools including citizen science approaches to quantify human-tick encounter rates and characterize exposure or preventive behaviors in peridomestic, neighborhood and recreational contexts (e.g., Fernandez et al. 2019, reviewed by Eisen and Eisen 2021).

Integration: A Coupled Natural-Human System

The inherent complexity of the Lyme disease system, which results from the multiplicity of interconnected relationships and levels, requires an integrative approach that not only recognizes the complex Lyme disease ecology involving multiple hosts, transmission pathways, and tick phenologies but also the interwoven nature of natural and human components (Fig. 1). The coupled natural and human system framework allows us to simultaneously study the natural and human components of Lyme disease transmission and their complex feedback loops (Liu et al. 2007, An 2012) that give rise to emergent properties that cannot be explained in a reductionist paradigm (Arthur 1993, Gell-Mann 1995, Meadows 2008). These feedback loops between the human and natural components of Lyme disease transmission occur also at different scales. At a regional-scale, one study found that higher Lyme disease incidence reduced the proportion of the county's population residing in the WUI in high Lyme disease incidence states, potentially leading to a negative feedback limiting exurban expansion and Lyme disease exposure (Larsen et al. 2014). At a local scale, the enzootic hazard might affect how humans interact with the environment, either through reducing visits to hazardous habitats, reducing the density of ticks or host-targeted interventions or increasing protective behaviors. The use of preventive behaviors such as wearing protective clothing and using tick repellent has been found to increase at high levels of awareness of tick-borne diseases as a health threat (Valente et al. 2015, Aenishaenslin et al. 2017) and for people more frequently performing recreational or gardening activities (Bron et al. 2020). These responses to the enzootic hazard or perceived risk may, in turn, indirectly affect Lyme disease incidence in humans and their behavior regarding Lyme disease prevention.

People also may have inadvertent effects on the enzootic hazard through their interactions with wildlife. Cox and Gaston (2018) identified a positive feedback loop that links anthropogenic urban resource provisioning with humans' positive experience with wildlife. This feedback may self-perpetuate as humans experience benefits through increased wellbeing, but people may not witness the negative effects of provisioning on wildlife and the enzootic hazard. At an individual level, investment choices on tick

reduction versus adaptive responses (personal protective measures) will determine the intensity of the coupling between the natural and human system, as well as the individual's choice on the type of intervention (implementing individual and household level interventions and/or supporting local level ones). These decisions will be determined by people's knowledge of the Lyme disease system, risk perception, governmental and political institutional policies, and educational messaging.

Legacies also are important in coupled natural-human systems and Lyme disease is no exception. Suburban development is well captured by the WUI index and frequently reflects zones of Lyme disease risk (Fig. 6), but the dominance of suburban land use is quite unique to the United States (Larsen et al. 2014, Kaup 2018, MacDonald et al. 2019). Although eventually spreading throughout the world, the pace of suburbanization was faster in the United States than Europe due to sustained industrialization in cities prior to World War I (Nijman and Clery 2015). As a result, European cities are still more centralized and concentrated than in the United States and Canada (Hesse and Siedentop 2018), reducing Lyme disease risk in periurban or suburban settings. For example, research examining the socioeconomic factors driving tick-borne encephalitis cases in various European countries showed high exposure risk to the public through time spent in forests due to occupation and outdoor recreation activities (hiking and mushroom gathering; Randolph et al. 2008, Godfrey and Randolph 2011, Stefanoff et al. 2012), not from peridomestic exposure. The land use legacies of Europe and North America intersect with ecological and sociological factors to construct Lyme disease emergence patterns more broadly (a 'pathogenic landscape' sensu, Lambin et al. 2010).

Conclusion

The apparent contradictory findings from different studies evaluating the effects of land use and habitat fragmentation on the enzootic hazard and Lyme disease risk may be partly due to differences in these key elements: spatial and temporal scales, organizational levels, the components of the system considered and their feedbacks, relevant landscape metrics, and the measured outcome (Pickett et al. 2005, Ellis and Wilcox 2009). Standardization of study designs would facilitate comparisons across studies but may be difficult because the relevant scales and organizational levels depend on the question and study system. Authors should, however, strive to provide clear and explicit definitions of the relevant elements, as well as measure multiple landscape fragmentation and disease risk metrics. While focusing on the effects of land use change and landscape structure on Lyme disease as a model system, we postulate that measuring the abovementioned elements is key to understanding the ecoepidemiology of most tick-borne pathogens transmitted by hard-bodied ticks. In sum, significant impact on tick-borne diseases will be achieved once we obtain a more complete understanding of 1) how the history of land use change has shaped landscapes in the United States, Europe, and Asia; 2) how the complex and dynamic process of land use change and habitat fragmentation may lead to different enzootic hazard and disease outcomes depending on habitat composition, host community assemblage, and host movement; 3) how host and human behavior and movement influences human exposure to tick-borne pathogens and disease risk; and 4) how study comparisons across spatial and temporal scales can deepen our understanding of the eco-bio-social determinants of tick-borne diseases.

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