Received: 7 March 2023 | Revised: 14 June 2023 | Accepted: 30 June 2023

DOI: 10.1111/zph.13073

ORIGINAL ARTICLE

WILEY

Demographic patterns in Lyme borreliosis seasonality over 25 years

Asena Goren[1] | Atle Mysterud[1] | Solveig Jore[2] | Hildegunn Viljugrein[1,3] | Haakon Bakka[3] | Yngvild Vindenes[1]

[1]Department of Biosciences, Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo, Oslo, Norway

[2]Zoonotic, Food & Waterborne Infections, The Norwegian Public Health Institute, Oslo, Norway

[3]Norwegian Veterinary Institute, Ås, Norway

Correspondence
Asena Goren, Department of Biosciences, Centre for Ecological and Evolutionary Synthesis (CEES), University of Oslo, P.O. Box 1066 Blindern, Oslo NO-0316, Norway.
Email: asena.goren@ibv.uio.no

Funding information
Research Council of Norway, Grant/Award Number: 313286; University of Oslo

Abstract

Lyme borreliosis, the most common vector-borne disease in Europe and North America, is attracting growing concern due to its expanding geographic range. The growth in incidence and geographic spread is largely attributed to climate and land-use changes that support the tick vector and thereby increase disease risk. Despite a wide range of symptoms displayed by Lyme borreliosis patients, the demographic patterns in clinical manifestations and seasonal case timing have not been thoroughly investigated and may result from differences in exposure, immunity and pathogenesis. We analysed 25 years of surveillance data from Norway, supplemented by population demography data, using a Bayesian modelling framework. The analyses aimed to detect differences in case seasonality and clinical manifestations of Lyme borreliosis across age and sex differentiated patient groups. The results showed a bimodal pattern of incidence over age, where children (0–9 years) had the highest incidence, young adults (20–29 years) had low incidence and older adults had a second incidence peak in the ages 70–79 years. Youth (0–19 years) presented with a higher proportion of neuroborreliosis cases and a lower proportion of arthritic manifestations compared to adults (20+ years). Adult males had a higher overall incidence than adult females and a higher proportion of arthritis cases. The seasonal timing of Lyme borreliosis consistently occurred around 4.4 weeks earlier in youth compared to adults, regardless of clinical manifestation. All demographic groups exhibited a shift towards an earlier seasonal timing over the 25-year study period, which appeared unrelated to changes in population demographics. However, the disproportionate incidence of Lyme borreliosis in seniors requires increased public awareness and knowledge about this high-risk group as the population continues to age concurrently with disease emergence. Our findings highlight the importance of considering patient demographics when analysing the emergence and seasonal patterns of vector-borne diseases using long-term surveillance data.

KEYWORDS
demography, Lyme borreliosis, Lyme disease, seasonality, surveillance, vector-borne diseases

1 | INTRODUCTION

Lyme borreliosis, also known as Lyme disease, is the most common vector-borne disease in the northern hemisphere (Steinbrink et al., 2022). There is increasing evidence of the geographic expansion of Lyme borreliosis, particularly into higher latitude and elevation areas in Europe and North America (Jore et al., 2011; Mysterud et al., 2017; van Oort et al., 2020; Vandekerckhove et al., 2019). This tick-vectored bacterial (spirochete) infection is caused by several genospecies in the *Borrelia burgdorferi* sensu lato (sl) complex, with *B. burgdorferi* sensu stricto most common in North America and *Borrelia afzelii* and *Borrelia garinii* in Europe (Nelder et al., 2016; Steere et al., 2016). The emergence and geographic expansion of Lyme borreliosis have primarily been attributed to climate and land-use changes impacting the tick vector and thereby increasing disease hazard (Brownstein et al., 2005; Couper et al., 2021; Li et al., 2019; Lindgren & Jaenson, 2006; Simon et al., 2014). While many studies focus on spatial changes in Lyme borreliosis cases linked to climate change, far fewer explore long-term temporal and seasonal changes in the disease system (Goren et al., 2023; Monaghan et al., 2015; Moore et al., 2014). Little is known about how human demography impacts Lyme borreliosis incidence and seasonality through differences in exposure, immunity and pathogenesis among age and sex groups. Demographic changes in the population could impact the future burden of Lyme borreliosis and other vector-borne diseases, and a deeper understanding of disease demography is necessary for managing the risk of emerging diseases.

The pathogenesis of Lyme borreliosis is highly variable among individuals, but the typical presentation of a localized infection is an initially expanding skin lesion, termed *erythema migrans*, located at the site of the bite of an infected tick. The lesion usually appears around 2–30 days after the bite and may be accompanied by flu-like symptoms (Johnson et al., 2018; Steinbrink et al., 2022). If left untreated, a localized infection can progress into a disseminated form of disease (Steere et al., 2016). Early disseminated infections can result in neurological manifestations involving the central and/or peripheral nervous systems (Cadavid et al., 2016; MacDonald et al., 2016; Steere et al., 2016; Steinbrink et al., 2022). Late dissemination can result in long-term sequelae and can include arthritis, *acrodermatitis chronica atrophicans* and carditis (Cadavid et al., 2016; Coburn et al., 2021). It has been estimated that 15%–20% of untreated localized infections progress to the early disseminated form (Koedel et al., 2015; Ornstein et al., 2001; Strnad & Rego, 2020). Age- and sex-based differences in immune markers have been found to impact *Borrelia* sp. seroconversion and pathogenesis in patients, but little is known about how this impacts disease trends on a population scale (Carlsson et al., 2018; Steere et al., 2003; Woudenberg et al., 2020).

To better understand the causes of population-level trends in Lyme borreliosis over time, we need a deeper understanding of the role of patient demography. The goal of this study is to investigate demographic differences in clinical manifestations, as well as in temporal trends of annual incidence and seasonal case timing. We take advantage of a unique dataset encompassing 25 years of Norwegian Lyme borreliosis surveillance data, at the expanding northern limit of the disease's biogeographical range in Europe.

Impacts

- Analysis of 25 years of Lyme borreliosis surveillance data from Norway revealed differences across age and sex groups in annual incidence, seasonal timing and clinical manifestations.
- Youth (0–19 years old) exhibited a 4.4 weeks earlier seasonal timing of cases compared to adults (20+ years), irrespective of clinical manifestation. There was a higher proportion of neuroborreliosis and a lower proportion of arthritis cases among youth compared to adults.
- There was a bimodal incidence pattern across age, with children (0–9 years) having the highest incidence, low incidence in young adults (20–29 years) and a second incidence peak in older adults aged 70–79 years. In adults (20+ years), males had a higher overall incidence compared to females and a higher proportion of arthritic manifestations.

2 | METHODS

2.1 | Surveillance data

This study is based on Lyme borreliosis surveillance data from Norway, which is curated by the Norwegian Institute of Public Health through the Norwegian Surveillance System for Communicable Diseases (MSIS). Since 1991, Lyme borreliosis has been a notifiable disease in Norway, with consistent notification criteria since 1995 (MacDonald et al., 2016). For this reason, this analysis covers the 25 year period from 1995 to 2019. There have been a few changes in case reporting and diagnostic testing methods for Lyme borreliosis during this time. Only disseminated forms of Lyme borreliosis are notifiable in Norway, by both clinicians and medical laboratories. Notification is based on a clinically compatible case with laboratory confirmation of *B. burgdorferi* sl by isolation, polymerase chain reaction (PCR) nucleic acid test or enzyme-linked immunosorbent assay (ELISA) antibody test (Mysterud et al., 2019; Norwegian Public Health Institute, 2023). Some notable changes in diagnostics over the study period include the introduction of improved ELISA methods in 2005–2008 and the introduction of standardized use of spinal puncture for diagnosis in children under 9 years old since 2011 (Berstad et al., 2017; Hunfeld et al., 2005; Mysterud et al., 2019). These changes in diagnostics, combined with increased disease awareness, could have resulted in higher overall detection rates as these new methods were implemented. A more detailed account of

reporting criteria can be found elsewhere (MacDonald et al., 2016; Mysterud et al., 2019).

The timing of cases in this study is determined by the date of diagnostic testing, which is available for every patient. This date usually occurs several weeks after the tick bite when symptoms of disseminated disease have emerged (Coburn et al., 2021). Clinical manifestations were grouped into three categories: neuroborreliosis, arthritis or other. Neuroborreliosis was defined as any neurological manifestation of the disease, while arthritis was categorized as all clinical manifestations affecting the joints. Any other manifestations, such as *acrodermatitis chronica atrophicans*, carditis and multiple *erythema migrans*, were categorized as 'other'. The incidence comparisons among demographic groups were based on cases per 100,000 persons (per year or week, depending on the model) in the population, where population data (Statistics Norway, 2022) were differentiated by sex and age. Initial explorations of Lyme borreliosis incidence trends across age and sex groups were based on 10-year age intervals for ages 0–80, with the oldest individuals pooled into the '80–99 years' group (Figure 1). Because of the bimodal incidence distribution over age (Figure 1c), temporal trends in incidence were analysed by comparison of three demographic groups: youth, adult males and adult females, with youth defined as individuals aged 0–19 years old and adults as individuals aged 20 years old or more.

2.2 | Statistical analysis

The statistical R package INLA (http://www.r-inla.org) was used to fit Bayesian models to investigate differences in case timing, incidence, and clinical manifestations across demographic groups, as well as explore differences in temporal trends within and between years (Rue et al., 2009). We first fitted a set of models to annual incidence rates stratified by demographic groups. We then fitted another set of models to annual values for the proportion of cases in each demographic group presenting with neurological, arthritic or other clinical manifestations. A third set of models was fitted to weekly incidence rates, accounting for seasonal effects. Incidence rates were defined as the number of cases per 100,000 persons in the selected demographic group for the specified time period (week or year). The R code for fitting the models and defining priors is provided as Appendix S2, without the underlying data as these are restricted.

To estimate differences in clinical manifestation (neuroborreliosis, arthritis or other) within each demographic group (youth, adult males, and adult females), a Poisson distribution was used to model the number of cases y_{jk} in year j and clinical manifestation type k,

$$y_{jk} \sim Poisson(\lambda_{jk}), \tag{1}$$

where λ_{jk} is the expected annual number of cases with manifestation k. The annual incidence was modelled with a logarithmic link function, including a population offset (size of demographic group) and year as an autoregressive term:

$$\ln(\lambda_{jk}) = \beta_0 + G_k + \ln(N_j) + Y_j + \varepsilon_{jk}. \tag{2}$$

Here β_0 is the intercept (reference level representing neuroborreliosis), and G_k is a fixed effect factor representing the effect of clinical manifestation (arthritis or other, compared to the reference), $\ln(N_j)$ is the population offset, Y_j is the year effect, and ε_{jk} is a Gaussian random effect used to account for overdispersion (Bakka et al., 2019; Goren et al., 2023). The population offset accounts for any changes in the number of observed cases due to changes in population size. The year effects are modelled as random intercepts following an autoregressive model of order 1 constrained to mean zero to avoid confounding with the reference level β_0. The model was run separately for each demographic group.

Differences in clinical manifestation were also quantified based on the proportion of cases within each demographic group. Letting y_{jk} be the number of cases in year j of manifestation type k, this variable has a binomial distribution

$$y_{jk} \sim Binomial(y_j, p_{jk}), \tag{3}$$

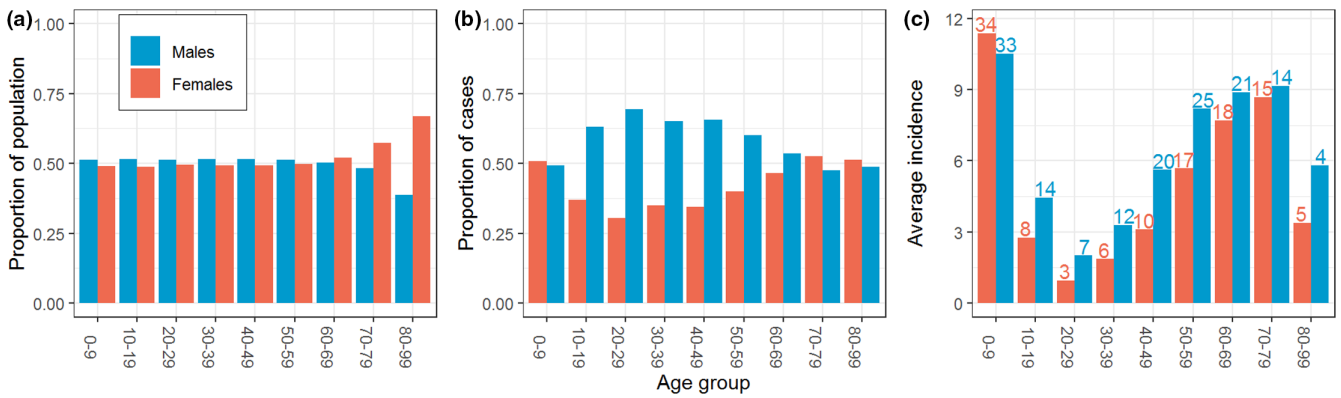

FIGURE 1 (a) Proportion of males and females in each age group in the population data over the study period. (b) Proportion of males and females in each age group in the Lyme borreliosis surveillance data over the study period. (c) Annual incidence (per 100,000) of Lyme borreliosis averaged over the study period, for each sex and age group. The numbers above the bars represent average annual case numbers.

where p_{kj} is the probability that each of the y_j cases in the demographic group presents with the clinical manifestation k. This probability was modelled on the logit scale as

$$\text{logit}(p_{kj}) = \beta_0 + G_k + Y_j + \varepsilon_{jk} \quad (4)$$

with the same interpretation and definition of the model components ($\beta_0, G_k, Y_j, \varepsilon_{jk}$) as for the model in Equation (2) (defined on another scale). The model was run separately for each demographic group. Results of the models are presented as point estimates of incidence or proportion in each group with the corresponding 95% credible intervals calculated from the posterior distributions. We consider two point estimates to be significantly different if each lies outside the credible interval of the other.

To compare seasonal case timing between demographic groups and clinical manifestations, the above models for incidence (Equations 1 and 2) were expanded to a weekly scale, adding a seasonal component following the approach of Goren et al. (2023). This weekly model captures changes in seasonality over time by separating long term (inter-annual) from seasonal trends (intra-annual). A Poisson distribution was used to model the number of cases y_{ij} in week i (from 1 to 52) and year j,

$$y_{ij} \sim Poisson(\lambda_{ij}) \quad (5)$$

where λ_{ij} is the expected number of cases, described by a logarithmic link function:

$$\ln(\lambda_{ij}) = \beta_0 + \ln(N_j) + Y_j + W_{ij} + \varepsilon_{ij}. \quad (6)$$

Here β_0 is the intercept, Y_j is the year effect estimated for year j, W_{ij} is the seasonal effect modelled using a sinusoidal wave function, $\ln(N_j)$ is the population offset and ε_{ij} is a Gaussian random effect used to account for overdispersion (Bakka et al., 2019; Goren et al., 2023). By including the population offset term $\ln(N_j)$, we are in effect modelling the weekly incidence rate (per capita). The sinusoidal wave function used to model the seasonal effect ensures that case seasonality is uniquely described by the week in which cases peak. Changes in within-year case timing are measured by extracting the annual peak week from the fitted models, and any shifts observed apply to all seasonal features (Goren et al., 2023). The year trend and seasonal effects were modelled using a first-order random walk to (i) account for autocorrelations in the time series and (ii) allow for the seasonal pattern to change (slowly) over the years.

A seasonal model was fit independently to the number of weekly cases for each demographic group, for weekly cases of all clinical manifestations together and for neuroborreliosis cases only. The seasonal model was also fit independently to the total number of weekly cases for each clinical manifestation. For arthritis cases and other clinical manifestations, there were too few cases to fit a model with flexible seasonality. Instead, the seasonal part of the model (W_{ij} in Equation (6) above) was modelled using fixed effects for the sinusoidal wave function so that the seasonality was restricted to be the same for each year (Goren et al., 2023). The model with fixed seasonality outperformed the flexible seasonality model by DIC for arthritis and other clinical manifestations, but not for neuroborreliosis (see Appendix S2). All analyses were done using the statistical software R version 4.0.3 (R Core Team, 2022).

3 | RESULTS

Over the study period, there was a demographic shift towards an ageing population in Norway (Figure S1). The sex ratio did not change much across age groups during the study period, except in the oldest age groups that had an initially high but decreasing proportion of females (Figure S2). Overall, the age groups had slightly more males in the younger and intermediate age groups and more females in the older age groups (Figure 1a). The overall Lyme disease annual incidence distribution, expressed as annual incidence (per 100,000) averaged over the study period, was bimodal over age both for males and females (Figure 1c), with the highest incidence at age 0–9 years (11 per 100,000), and a smaller peak at age 70–79 years (9 per 100,000). Although the 70–79 years group had the highest incidence of adults, the majority of adult cases were in the 50–59 years group (Figure 1c).

The proportion of youth compared to adults in the population of Norway showed a minimal decrease during the study period (Figure S3). Geographic patterns were not investigated in this study, but the proportions of the youth and adult populations in different regions remained relatively unchanged over the study period (Figure S4). The youth had a higher incidence of Lyme borreliosis than adults, and adult males had a higher incidence compared to adult females (Figure 1c). Males had a higher incidence than females in all except the youngest age group (0–9 years old), where there was a higher incidence in females (Figure 1c). Compared to the proportion of males in each age group in the underlying population, there was an excess of male cases in all age groups except the youngest (Figure S5).

The statistical models fitted to annual data showed that patterns of clinical manifestation were significantly different between youth and adults, and more similar among adult males and females (Figure 2). In all demographic groups, neuroborreliosis was the most common clinical manifestation, with the highest incidence as well as the proportion of cases. Adult males had a higher annual incidence (per 100,000) of neuroborreliosis (3.67 [3.47, 3.87]) and arthritis (1.12 [0.94, 1.30]) compared to adult females (neuroborreliosis: 2.61 [2.45, 2.78]; arthritis: 0.59 [0.48, 0.73]; Figure 2a, Table S1). The proportion of neuroborreliosis cases was very similar in adult males (0.55 [0.53, 0.57]) and females (0.56 [0.53, 0.58]), while the proportion of arthritis cases was estimated to be somewhat higher (0.17 [0.14, 0.20]) compared to adult females (0.13 [0.10, 0.16]; Figure 2b, Table S1). The youth had a higher proportion of neuroborreliosis (0.79 [0.78, 0.81]) and a lower proportion of arthritis (0.08 [0.06, 0.10]) and other manifestations (0.08 [0.06, 0.10]) compared to adult males and females (Figure 2b, Table S1).

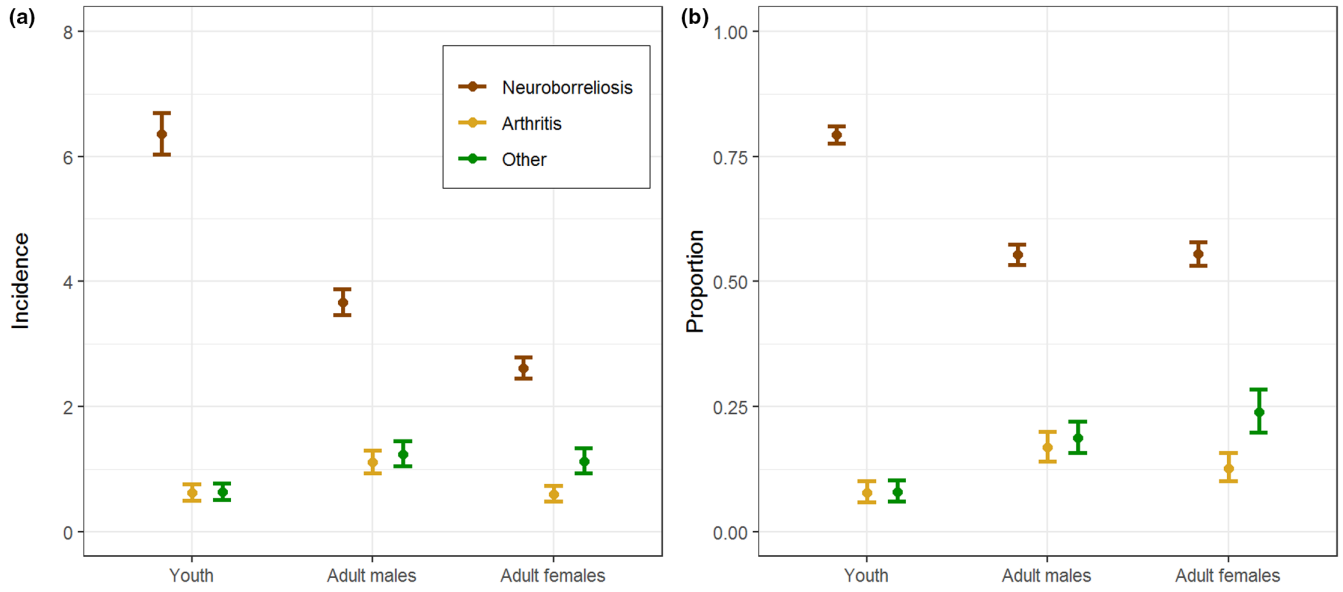

FIGURE 2 Comparison of Lyme borreliosis clinical manifestations between demographic groups, based on INLA models fitted to annual data for each clinical manifestation, with a random effect year component and no seasonal component. (a) Mean annual incidence (per 100,000) with 95% credible intervals. (b) Per cent of cases with each clinical manifestation within each demographic group, with 95% credible intervals.

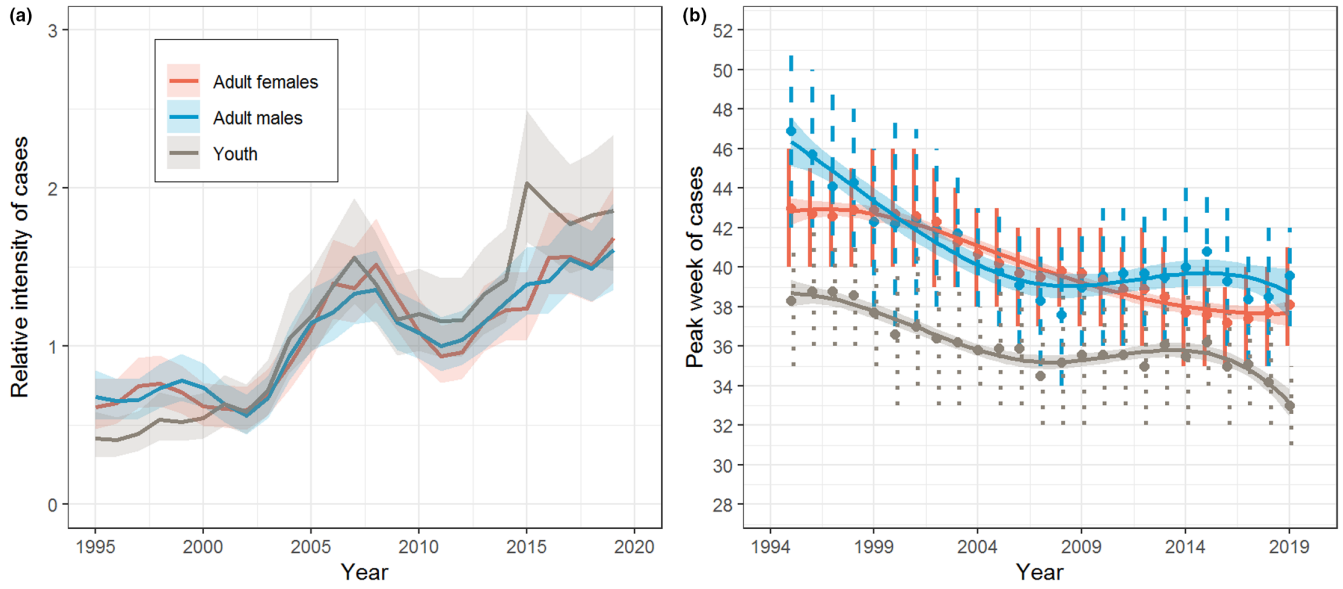

FIGURE 3 Temporal trends in Lyme borreliosis cases for demographic groups (youth, adult females, and adult males) based on seasonal INLA models. (a) Inter-annual trend comparison based on the annual components of the models, with shaded 95% credible intervals. The annual components describe the relative intensity of cases (not incidence) over the study period. (b) Comparison of changing seasonality measured by predicted seasonal incidence peak. The ribbons represent the 95% confidence intervals on the fitted splines, while the vertical lines represent error margins on the estimated peak incidence weeks based on repeated sampling from the posterior distribution.

The inter-annual trends were similar across demographic groups, with youth exhibiting a slightly greater increase in incidence over the study period (Figure 3a). The inter-annual trends were also similar across clinical manifestations, with neuroborreliosis showing a slightly greater increase in incidence than arthritis over the study period (Figure 4a). Differences in case seasonality were larger between youth and adults than between adult males and females (Figure 3b), with the seasonal incidence peak on average 4.4 weeks earlier in youth than adults. The difference in case timing between youth and adults was also observed when the analysis was restricted to neuroborreliosis cases (Figure S6), indicating the difference is not driven by differences in clinical manifestation. There was limited difference in case seasonality across clinical manifestations, however, low annual case numbers for arthritis resulted in large error margins for the seasonal peaks and necessitated the use of a simplified model with fixed seasonality across years.

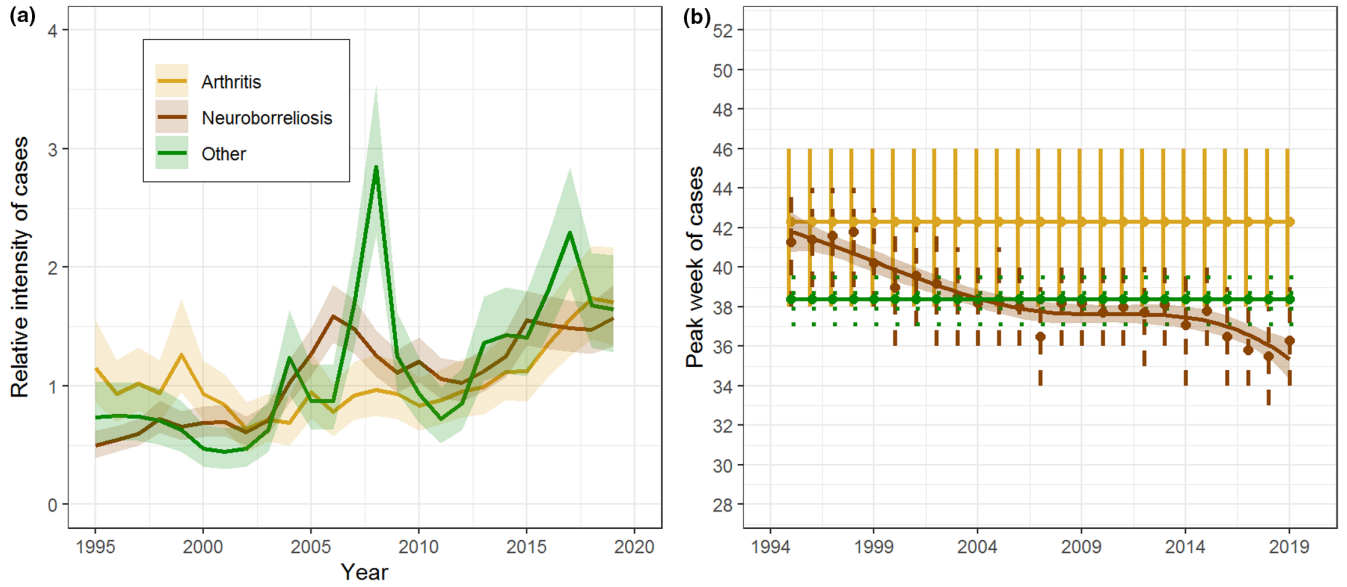

FIGURE 4 Temporal trends in Lyme borreliosis cases for different clinical manifestations (neuroborreliosis, arthritis and other) based on seasonal INLA models. (a) Inter-annual trend comparison based on annual components of the seasonal models, with 95% credible intervals. The annual components describe the relative intensity of cases (not incidence) over the study period. (b) Comparison of the seasonality of the different clinical manifestations of Lyme borreliosis measured by the seasonal incidence peak. The ribbons represent the 95% confidence intervals on the fitted splines, while the vertical lines represent error margins on the estimated peak weeks based on repeated sampling from the posterior distribution. Note that due to low case numbers, arthritis and other clinical manifestations were modelled with a fixed seasonal effect across years, while neuroborreliosis was modelled with a flexible seasonality that can vary across years.

4 | DISCUSSION

Based on long-term surveillance data from Norway, we analysed demographic differences in incidence, clinical manifestation, and seasonality of Lyme borreliosis using a Bayesian framework for statistical analysis. We found that youth (0–19 years) had a higher overall incidence, a larger proportion of neuroborreliosis cases, and an earlier seasonal peak by 4.4 weeks compared to adults. Adult males had a higher overall incidence of Lyme borreliosis with a higher proportion of arthritis compared to adult females. The overall demographic trends identified in this analysis, including the bimodal incidence distribution over age and overrepresentation of males in most age groups, are predominantly in concordance with prior studies in Norway and other countries (Berglund et al., 1995; Eliassen et al., 2017; Nygård et al., 2005; Schwartz et al., 2017; Skufca et al., 2022; Stanek & Strle, 2018; Steere et al., 2016; Sundheim et al., 2021; Tulloch et al., 2019, 2020; Tveitnes & Øymar, 2015). This study is the first to provide insight into how the seasonality of Lyme borreliosis varies among demographic groups.

The bimodal distribution of incidence over patient age suggests that children and older adults are at higher risk of developing disseminated Lyme borreliosis, compared to young adults in the age range 18–30. The reasons for these differences are not yet clear and may be due to a combination of factors such as exposure to vectors, care-seeking behaviour and biological and immunological differences. In Norway, youth tend to have a higher proportion of neurological manifestations compared to other forms of the disease (Figure 2), which is typical in Europe but contrasts with North America, where arthritis is commonly seen in both youth and adult patients (Christen et al., 1993; Marques et al., 2021; Stanek et al., 2012).

While it is known from prior studies that the seasonal timing of Lyme borreliosis cases has shifted significantly over the study period (Goren et al., 2023), this analysis demonstrated consistent differences in case seasonality between demographic groups (Figure 3b). The current analysis demonstrated that the overall shift in case seasonality observed prior was unlikely to be caused by changes in patient or population demography. The 4.4 weeks earlier case timing in youth compared to adults was not attributable to adults having a higher incidence of arthritis and other late disseminated clinical manifestations compared to youth (Stanek & Strle, 2018), as the difference persisted even when restricting the analysis to only neuroborreliosis cases (Figure 3, Figure S6). The difference in case timing between youth and adults could indicate that youth have more rapid pathogenesis of Lyme borreliosis than adults. While there is evidence of some differences in pathogenesis between adults and children (Feder Jr, 2008), there is yet insufficient clinical evidence to determine if more rapid pathogenesis actually occurs in youth. Differences in Lyme borreliosis trends between adults and children could also be related to behavioural factors resulting in differential tick exposure (Cull et al., 2020). A combination of other factors could also impact case timing, such as differences in healthcare-seeking behaviour between youth and adults and patient handling in hospitals. Demographic differences in healthcare-seeking behaviour and patient handling have not been sufficiently investigated for Lyme borreliosis, in particular, but have been broadly acknowledged in public health literature (Giasson & Chopik, 2020; Thompson

et al., 2016). Further investigation into infection dynamics between the *Borrelia* genospecies and the immune system across ages could yield deeper insight into the observed trends.

This study found an overrepresentation of males in the Lyme borreliosis surveillance data, which is expected because only disseminated cases are reported in the national surveillance data in Norway. Gender differences in accessing healthcare are well recognized (Dias et al., 2022; Govender & Penn-Kekana, 2008). For Lyme borreliosis, females typically represent a higher proportion of localized infections and *erythema migrans*, whereas males comprise a higher proportion of disseminated disease cases (Eliassen et al., 2017; Nygård et al., 2005; Skufca et al., 2022; Tulloch et al., 2019, 2020). A prior study in an overlapping time period in Norway used general practitioner data instead of surveillance data and found an overrepresentation in females presenting with *erythema migrans*, indicating early localized Lyme borreliosis infection (Eliassen et al., 2017). This trend has been attributed to gender-related differences in healthcare-seeking behaviour (Bennet et al., 2007; Doyal, 2001; Eliassen et al., 2017), but insufficient investigation has been conducted into whether there could also be a biological explanation for the increased incidence of disseminated Lyme borreliosis in males (Schwarzwalder et al., 2010; Strle et al., 2013). In this study, some of the elevated overall incidence in adult males compared to females was attributable to a higher incidence of Lyme arthritis. More research is needed to confirm this pattern and disentangle the causes. It is known that females have a higher incidence of auto-immune rheumatoid arthritis than males (Kvien et al., 2006), but little research has been done into sex differences in non-rheumatoid arthritides to determine if other types of septic arthritis show a similar trend as Lyme arthritis of elevated incidence in males.

This study explores demographic patterns in Lyme borreliosis clinical manifestation and is the first study to investigate differences in the seasonality of Lyme borreliosis case timing across demographic groups. Further research into disease pathogenesis is needed to understand the causal explanations of the demographic patterns observed in surveillance data.

FUNDING INFORMATION

This project is funded by the University of Oslo (PhD grant) and the Research Council of Norway (project TimeLyme, 313286).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data used for this analysis are maintained by the Norwegian Institute of Public Health and cannot be made publicly available due to patient confidentiality. The R script for analyses is provided as Appendix S2.

ETHICS STATEMENT

The project was approved by the Regional Committee for Medical and Health Research Ethics (REK sør-øst B; Reference 115365).

ORCID

Asena Goren https://orcid.org/0000-0003-1042-3413
Atle Mysterud https://orcid.org/0000-0001-8993-7382
Solveig Jore https://orcid.org/0000-0001-8527-4892
Hildegunn Viljugrein https://orcid.org/0000-0002-3798-5267
Haakon Bakka https://orcid.org/0000-0001-8272-865X
Yngvild Vindenes https://orcid.org/0000-0003-1197-5818

REFERENCES

Bakka, H., Vanhatalo, J., Illian, J. B., Simpson, D., & Rue, H. (2019). Non-stationary gaussian models with physical barriers. *Spatial Statistics*, *29*, 268–288. https://doi.org/10.1016/j.spasta.2019.01.002

Bennet, L., Stjernberg, L., & Berglund, J. (2007). Effect of gender on clinical and epidemiologic features of Lyme borreliosis. *Vector-Borne and Zoonotic Diseases*, *7*(1), 34–41. https://doi.org/10,1089/vbz.2006.0533

Berglund, J., Eitrem, R., Ornstein, K., Lindberg, A., Ringnér, Å., Elmrud, H., Carlsson, M., Runehagen, A., Svanborg, C., & Norrby, R. (1995). An epidemiologic study of Lyme disease in southern Sweden. *New England Journal of Medicine*, *333*(20), 1319–1324. https://doi.org/10.1056/NEJM199511163332004

Berstad, A. K. H., Døllner, H., & Eikeland, R. (2017). *Generell veileder i pediatri*, *3.7 Borreliose*. Norsk barnelegeforening. January 01. First published 2006, updated 2011 and 2017. https://www.helsebiblioteket.no/innhold/retningslinjer/pediatri/generell-veileder-i-pediatri/3.infeksjoner-vaksiner-og-undersokelse-av-adoptivbarn/3.7-borreliose#-helsebiblioteket-innhold-retningslinjer-pediatri-generell-veileder-i-pediatri-3infeksjoner-vaksiner-og-undersokelse-av-adoptivbarn-37-borreliose

Brownstein, J. S., Holford, T. R., & Fish, D. (2005). Effect of climate change on Lyme disease risk in North America. *EcoHealth*, *2*(1), 38–46. https://doi.org/10.1007/s10393-004-0139-x

Cadavid, D., Auwaerter, P. G., Rumbaugh, J., & Gelderblom, H. (2016). Antibiotics for the neurological complications of Lyme disease. *Cochrane Database of Systematic Reviews*, *2016*(12), CD006978. https://doi.org/10.1002/14651858.cd006978.pub2

Carlsson, H., Ekerfelt, C., Henningsson, A. J., Brudin, L., & Tjernberg, I. (2018). Subclinical Lyme borreliosis is common in South-Eastern Sweden and may be distinguished from Lyme neuroborreliosis by sex, age and specific immune marker patterns. *Ticks and Tick-Borne Diseases*, *9*(3), 742–748. https://doi.org/10.1016/j.ttbdis.2018.02.011

Christen, H. J., Hanefeld, F., Eiffert, H., & Thomssen, R. (1993). Epidemiology and clinical manifestations of Lyme borreliosis in childhood: A prospective multicentre study with special regard to neuroborreliosis. *Acta Paediatrica*, *82*, 1–76. https://doi.org/10.1111/j.1651-2227.1993.tb18082.x

Coburn, J., Garcia, B., Hu, L. T., Jewett, M. W., Kraiczy, P., Norris, S. J., & Skare, J. (2021). Lyme disease pathogenesis. *Current Issues in Molecular Biology*, *42*, 473–518. https://doi.org/10.21775/cimb.042.473

Couper, L. I., MacDonald, A. J., & Mordecai, E. A. (2021). Impact of prior and projected climate change on US Lyme disease incidence. *Global Change Biology*, *27*(4), 738–754. https://doi.org/10.1111/gcb.15435

Cull, B., Pietzsch, M. E., Gillingham, E. L., McGinley, L., Medlock, J. M., & Hansford, K. M. (2020). Seasonality and anatomical location of human tick bites in the United Kingdom. *Zoonoses and Public Health*, *67*(2), 112–121. https://doi.org/10.1111/zph.12659

Dias, S. P., Brouwer, M. C., & van de Beek, D. (2022). Sex and gender differences in bacterial infections. *Infection and Immunity*, *90*(10), e0028322. https://doi.org/10.1128/iai.00283-22

Doyal, L. (2001). Sex, gender, and health: The need for a new approach. *BMJ*, *323*(7320), 1061–1063. https://doi.org/10.1136/bmj.323.7320.1061

Eliassen, K. E., Berild, D., Reiso, H., Grude, N., Christophersen, K. S., Finckenhagen, C., & Lindbæk, M. (2017). Incidence and antibiotic treatment of erythema migrans in Norway 2005–2009. *Ticks and Tick-Borne Diseases*, *8*(1), 1–8. https://doi.org/10.1016/j.ttbdis.2016.06.006

Feder, H. M., Jr. (2008). Lyme disease in children. *Infectious Disease Clinics of North America*, *22*(2), 315–326. https://doi.org/10.1016/j.idc.2007.12.007

Giasson, H. L., & Chopik, W. J. (2020). Geographic patterns of implicit age bias and associations with state-level health outcomes across the United States. *European Journal of Social Psychology*, *50*(6), 1173–1190. https://doi.org/10.1002/ejsp.2707

Goren, A., Viljugrein, H., Rivrud, I. M., Jore, S., Bakka, H., Vindenes, Y., & Mysterud, A. (2023). The emergence and shift in seasonality of Lyme borreliosis in northern Europe. *Proceedings of the Royal Society B. Biological Sciences*, *290*, 20222420. https://doi.org/10.1098/rspb.2022.2420

Govender, V., & Penn-Kekana, L. (2008). Gender biases and discrimination: A review of health care interpersonal interactions. *Global Public Health*, *3*(S1), 90–103. https://doi.org/10.1080/17441690801892208

Hunfeld, K., Fingerle, V., Stanek, G., Daghofer, E., Brade, V., Wilske, B., & Peters, H. (2005). *European multicenter study for evaluation of a new enzyme immunoassay for detection of IgG antibodies against Borrelia burgdorferi sensu lato*. 10th international conference on Lyme borreliosis and other tick-borne diseases.

Johnson, K. O., Nelder, M. P., Russell, C., Li, Y., Badiani, T., Sander, B., Sider, D., & Patel, S. N. (2018). Clinical manifestations of reported Lyme disease cases in Ontario, Canada: 2005–2014. *PLoS One*, *13*(6), e0198509. https://doi.org/10.1371/journal.pone.0198509

Jore, S., Viljugrein, H., Hofshagen, M., Brun-Hansen, H., Kristoffersen, A. B., Nygård, K., Brun, E., Ottesen, P., Sævik, B. K., & Ytrehus, B. (2011). Multi-source analysis reveals latitudinal and altitudinal shifts in range of *Ixodes ricinus* at its northern distribution limit. *Parasites & Vectors*, *4*(1), 84. https://doi.org/10.1186/1756-3305-4-84

Koedel, U., Fingerle, V., & Pfister, H.-W. (2015). Lyme neuroborreliosis—Epidemiology, diagnosis and management. *Nature Reviews Neurology*, *11*(8), 446–456. https://doi.org/10.1038/nrneurol.2015.121

Kvien, T. K., Uhlig, T., Ødegård, S., & Heiberg, M. S. (2006). Epidemiological aspects of rheumatoid arthritis: The sex ratio. *Annals of the new York Academy of Sciences*, *1069*(1), 212–222. https://doi.org/10.1196/annals.1351.019

Li, S., Gilbert, L., Vanwambeke, S. O., Yu, J., Purse, B. V., & Harrison, P. A. (2019). Lyme disease risks in Europe under multiple uncertain drivers of change. *Environmental Health Perspectives*, *127*(6), 67010. https://doi.org/10.1289/EHP4615

Lindgren, E., & Jaenson, T. G. (2006). *Lyme borreliosis in Europe: Influences of climate and climate change, epidemiology, ecology and adaptation measures*. World Health Organization, Regional Office for Europe. https://apps.who.int/iris/handle/10665/107800

MacDonald, E., Vestrheim, D. F., White, R. A., Konsmo, K., Lange, H., Aase, A., Nygård, K., Stefanoff, P., Aaberge, I., & Vold, L. (2016). Are the current notification criteria for Lyme borreliosis in Norway suitable? Results of an evaluation of Lyme borreliosis surveillance in Norway, 1995-2013. *BMC Public Health*, *16*(1), 729. https://doi.org/10.1186/s12889-016-3346-9

Marques, A. R., Strle, F., & Wormser, G. P. (2021). Comparison of Lyme disease in the United States and Europe. *Emerging Infectious Diseases*, *27*(8), 2017–2024. https://doi.org/10.3201/eid2708.204763

Monaghan, A. J., Moore, S. M., Sampson, K. M., Beard, C. B., & Eisen, R. J. (2015). Climate change influences on the annual onset of Lyme disease in the United States. *Ticks and Tick-Borne Diseases*, *6*(5), 615–622. https://doi.org/10.1016/j.ttbdis.2015.05.005

Moore, S. M., Eisen, R. J., Monaghan, A., & Mead, P. (2014). Meteorological influences on the seasonality of Lyme disease in the United States. *The American Journal of Tropical Medicine and Hygiene*, *90*(3), 486–496. https://doi.org/10.4269/ajtmh.13-0180

Mysterud, A., Heylen, D. J. A., Matthysen, E., Garcia, A. L., Jore, S., & Viljugrein, H. (2019). Lyme neuroborreliosis and bird populations in northern Europe. *Proceedings of the Royal Society B: Biological Sciences*, *286*(1903), 20190759. https://doi.org/10.1098/rspb.2019.0759

Mysterud, A., Jore, S., Østerås, O., & Viljugrein, H. (2017). Emergence of tick-borne diseases at northern latitudes in Europe: A comparative approach. *Scientific Reports*, *7*(1), 16316. https://doi.org/10.1038/s41598-017-15742-6

Nelder, M. P., Russell, C. B., Sheehan, N. J., Sander, B., Moore, S., Li, Y., Johnson, S., Patel, S. N., & Sider, D. (2016). Human pathogens associated with the blacklegged tick *Ixodes scapularis*: A systematic review. *Parasites & Vectors*, *9*(1), 265. https://doi.org/10.1186/s13071-016-1529-y

Norwegian Public Health Institute. (2023). *Meldingskriterier for Sykdommer i MSIS*. https://www.fhi.no/publ/informasjonsark/meldingskriterier-for-sykdommer-i-msis/

Nygård, K., Brantsæter, A. B., & Mehl, R. (2005). Disseminated and chronic Lyme borreliosis in Norway, 1995–2004. *Eurosurveillance*, *10*(10), 1–2. https://doi.org/10.2807/esm.10.10.00568-en

Ornstein, K., Berglund, J., Nilsson, I., Norrby, R., & Bergström, S. (2001). Characterization of Lyme borreliosis isolates from patients with erythema Migrans and neuroborreliosis in southern Sweden. *Journal of Clinical Microbiology*, *39*(4), 1294–1298. https://doi.org/10.1128/jcm.39.4.1294-1298.2001

R Core Team. (2022). *R: A language and environment for statistical computing*. Foundation for Statistical Computing.

Rue, H., Martino, S., & Chopin, N. (2009). Approximate Bayesian inference for latent gaussian models by using integrated nested Laplace approximations. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *71*(2), 319–392. https://doi.org/10.1111/j.1467-9868.2008.00700.x

Schwartz, A. M., Hinckley, A. F., Mead, P. S., Hook, S. A., & Kugeler, K. J. (2017). Surveillance for Lyme disease—United States, 2008–2015. *MMWR Surveillance Summaries*, *66*(22), 1–12. https://doi.org/10.15585/mmw.ss6622a1

Schwarzwalder, A., Schneider, M. F., Lydecker, A., & Aucott, J. N. (2010). Sex differences in the clinical and serologic presentation of early Lyme disease: Results from a retrospective review. *Gender Medicine*, *7*(4), 320–329. https://doi.org/10.1016/j.genm.2010.08.002

Simon, J. A., Marrotte, R. R., Desrosiers, N., Fiset, J., Gaitan, J., Gonzalez, A., Koffi, J. K., Lapointe, F. J., Leighton, P. A., & Lindsay, L. R. (2014). Climate change and habitat fragmentation drive the occurrence of *Borrelia burgdorferi*, the agent of Lyme disease, at the northeastern limit of its distribution. *Evolutionary Applications*, *7*(7), 750–764. https://doi.org/10.1111/eva.12165

Skufca, J., De Smedt, N., Pilz, A., Vyse, A., Begier, E., Blum, M., Riera-Montes, M., Gessner, B., Skovdal, M., & Stark, J. H. (2022). Incidence of Lyme neuroborreliosis in Denmark: Exploring observed trends using public surveillance data, 2015–2019. *Ticks and Tick-Borne Diseases*, *13*(6), 102039. https://doi.org/10.1016/j.ttbdis.2022.102039

Stanek, G., & Strle, F. (2018). Lyme borreliosis–from tick bite to diagnosis and treatment. *FEMS Microbiology Reviews*, *42*(3), 233–258. https://doi.org/10.1093/femsre/fux047

Stanek, G., Wormser, G. P., Gray, J., & Strle, F. (2012). Lyme borreliosis. *The Lancet*, *379*(9814), 461–473. https://doi.org/10.1016/S0140-6736(11)60103-07

Statistics Norway. (2022). https://www.ssb.no/en

Steere, A. C., Sikand, V. K., Schoen, R. T., & Nowakowski, J. (2003). Asymptomatic infection with *Borrelia burgdorferi*. *Clinical Infectious Diseases*, *37*(4), 528–532. https://doi.org/10.1086/376914

Steere, A. C., Strle, F., Wormser, G. P., Hu, L. T., Branda, J. A., Hovius, J. W. R., Li, X., & Mead, P. S. (2016). Lyme borreliosis. *Nature Reviews Disease Primers*, *2*(1), 16090. https://doi.org/10.1038/nrdp.2016.90

Steinbrink, A., Brugger, K., Margos, G., Kraiczy, P., & Klimpel, S. (2022). The evolving story of *Borrelia burgdorferi* sensu lato transmission in Europe. *Parasitology Research*, *121*(3), 781–803. https://doi.org/10.1007/s00436-022-07445-3

Strle, F., Wormser, G. P., Mead, P., Dhaduvai, K., Longo, M. V., Adenikinju, O., Soman, S., Tefera, Y., Maraspin, V., & Lotrič-Furlan, S. (2013). Gender disparity between cutaneous and non-cutaneous manifestations of Lyme borreliosis. *PLoS One*, *8*(5), e64110. https://doi.org/10.1371/journal.pone.0064110

Strnad, M., & Rego, R. O. (2020). The need to unravel the twisted nature of the *Borrelia burgdorferi* sensu lato complex across Europe. *Microbiology*, *166*(5), 428–435. https://doi.org/10.1099/mic.0.000899

Sundheim, K. M., Levas, M. N., Balamuth, F., Thompson, A. D., Neville, D. N., Garro, A. C., Kharbanda, A. B., Monuteaux, M. C., & Nigrovic, L. E. (2021). Seasonality of acute Lyme disease in children. *Tropical Medicine and Infectious Disease*, *6*(4), 196. https://doi.org/10.3390/tropicalmed6040196

Thompson, A. E., Anisimowicz, Y., Miedema, B., Hogg, W., Wodchis, W. P., & Aubrey-Bassler, K. (2016). The influence of gender and other patient characteristics on health care-seeking behaviour: A QUALICOPC study. *BMC Family Practice*, *17*(1), 1–7. https://doi.org/10.1186/s12875-016-0440-0

Tulloch, J. S., Christley, R. M., Radford, A. D., Warner, J. C., Beadsworth, M. B., Beeching, N. J., & Vivancos, R. (2020). A descriptive epidemiological study of the incidence of newly diagnosed Lyme disease cases in a UK primary care cohort, 1998–2016. *BMC Infectious Diseases*, *20*(1), 1–13. https://doi.org/10.1186/s12879-020-05018-2

Tulloch, J. S., Semper, A. E., Brooks, T. J., Russell, K., Halsby, K. D., Christley, R. M., Radford, A. D., Vivancos, R., & Warner, J. C. (2019). The demographics and geographic distribution of laboratory-confirmed Lyme disease cases in England and Wales (2013–2016): An ecological study. *BMJ Open*, *9*(7), e028064. https://doi.org/10.1136/bmjopen-2018-028064

Tveitnes, D., & Øymar, K. (2015). Gender differences in childhood Lyme neuroborreliosis. *Behavioural Neurology*, *2015*, 1–6. https://doi.org/10.1155/2015/790762

van Oort, B. E. H., Hovelsrud, G. K., Risvoll, C., Mohr, C. W., & Jore, S. (2020). A mini-review of *Ixodes* ticks climate sensitive infection dispersion risk in the Nordic region. *International Journal of Environmental Research and Public Health*, *17*(15), 5387. https://doi.org/10.3390/ijerph17155387

Vandekerckhove, O., Buck, E. D., & Wijngaerden, E. V. (2019). Lyme disease in Western Europe: An emerging problem? A systematic review. *Acta Clinica Belgica*, *76*(3), 244–252. https://doi.org/10.1080/17843286.2019.1694293

Woudenberg, T., Böhm, S., Böhmer, M., Katz, K., Willrich, N., Stark, K., Kuhnert, R., Fingerle, V., & Wilking, H. (2020). Dynamics of *Borrelia burgdorferi*-specific antibodies: Seroconversion and Seroreversion between two population-based, cross-sectional surveys among adults in Germany. *Microorganisms*, *8*(12), 1859. https://doi.org/10.3390/microorganisms8121859

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Goren, A., Mysterud, A., Jore, S., Viljugrein, H., Bakka, H., & Vindenes, Y. (2023). Demographic patterns in Lyme borreliosis seasonality over 25 years. *Zoonoses and Public Health*, *00*, 1–9. https://doi.org/10.1111/zph.13073