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Predictors of Lyme Arthritis Diagnosis in Lyme Disease Cases

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PREDICTORS OF LYME ARTHRITIS DIAGNOSIS IN LYME DISEASE CASES

A Thesis Presented

by

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DEDICATION

To my loving parents.

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I would like to give my sincerest thanks to my thesis chair, Dr. Brian Whitcomb. Without his endless patience, motivation, and good humor I would never have completed this project. Thanks are also due to my other committee member, Dr. Stephen Rich, for piquing my interest in Lyme disease.

ABSTRACT

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Lyme disease is the most common vector-borne disease in the United States with over 20,000 cases reported yearly. A common and sometimes severe symptom of Lyme disease is Lyme arthritis, which has clinical and etiological similarities to rheumatoid arthritis. While risk factors for Lyme disease are established, there have been no studies exploring risk factors for Lyme arthritis. To assess this relationship a cross-sectional study was conducted, using data from confirmed cases of Lyme disease reported to the Massachusetts Department of Public Health (MDPH) from 2000 to 2006. Bivariate analyses and ANOVA tests were conducted to assess the relationship between age, sex and Lyme arthritis, as well as other symptoms of Lyme disease. Results showed that those in the lowest quartile of age were more likely to be diagnosed with Lyme arthritis alone than those in higher age quartiles ($p < 0.001$). No significant difference was seen in the proportion of Lyme arthritis diagnosis between males and females ($p = 0.61$). By recognizing that younger patients with Lyme disease are more likely to be diagnosed with Lyme arthritis, measures may be taken to improve early identification and treatment of Lyme disease in this group. We recommend that a future prospective study be conducted to further elucidate the true relationships between age, sex, and Lyme arthritis.

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CHAPTER I

INTRODUCTION

Lyme disease (LD), caused by the bacteria *Borrelia burgdorferi*, is the most common vector-borne disease in the United States, with an average of over 20,000 cases reported annually since 2002 [1]. Many of these cases occur in the New England and Mid-Atlantic regions, as well as in Wisconsin and Minnesota [1]. In 2007, Massachusetts had an incidence rate of 46.3 cases per 100,000 people, compared to the national rate of 9.1 cases per 100,000 [1]. Due to the highly endemic nature of LD in Massachusetts it is vital that we recognize the risks of contracting this disease and the benefits of diagnosing it early.

A major symptom of LD is Lyme arthritis (LA), which is reported in roughly one-third of all LD cases and up to 60% of untreated cases [1, 2]. The manifestations of this form of arthritis include swelling and pain in the large joints, especially the knees [2]. These symptoms typically take place in the late stage of infection, arising weeks to years after initial infection [18]. Due to LA being a late stage symptom it is clear that early diagnosis and treatment are essential to LA prevention. Most LD and LA cases can be treated effectively with antibiotics in the early stages of infection. However, about 10% of individuals may experience bouts of chronic inflammation lasting months to years [3]. This long-term repercussion of LD infection has been termed chronic LA or antibiotic-treatment-resistant LA [4].

Lyme arthritis closely mimics rheumatoid arthritis (RA) in two ways. First, the inflammatory symptoms associated with LA closely resemble those of RA as they can flare up and then be followed by periods of remission [3, 4]. Secondly, particular antigen-presenting HLA class II molecules that are associated with treatment-resistant LA have also been implicated with increased susceptibility and severity of RA [5-7]. These two forms of arthritis differ in that *B. burgdorferi* is the initial cause of LA, while the true cause of RA remains unclear.

Due to the similar clinical pathology and genetic risk factors of these two forms of arthritis (particularly in the case of chronic LA), LA cases may have similar risk factors to those for RA cases. While high-risk groups have been identified for RA, risks for LA have been largely disregarded. Because of this discrepancy in established knowledge, coupled with variability and difficulty associated with LD diagnosis, my hypotheses for LA are to an extent, based on what is known about age and sex as risk factors of RA.

To assess this relationship a cross-sectional study design was used, utilizing Lyme disease case data obtained from the Massachusetts Department of Public Health (MDPH) from 2000 to 2006 to assess the relationship between age, sex and LA.

CHAPTER II

LITERATURE REVIEW

Physiology of Exposure-Outcome Relationship:

While it is recognized that RA is an autoimmune disease, its cause remains unclear [4]. On the other hand, the initial cause of LA is the presence of *B. burgdorferi* in the joints, though chronic or treatment-resistant forms of LA may be caused by autoimmune responses [5].

Age is a well-established risk factor for RA, with the majority of cases arising between the ages of 40-60 years old [4]. There is limited evidence, however, to assess if age is also a risk factor for LA in LD cases. In older populations more individuals may have weakened immune systems due to chronic illness, immunosuppressive chemotherapy, or simply due to advanced age. As a corollary, those individuals will be more prone to disseminating *B. burgdorferi* infection, and therefore LA, compared to their younger and healthier counterparts. Also, as people advance in age they may become more likely to experience chronic LA due to autoimmune reaction, as is the case with RA [4, 13].

Sex is another recognized risk factor for RA that has garnered little attention with LA. In the case of RA, women have up to four times the risk as men in some populations [8, 9]. While there is no clear reason for this, it is hypothesized that hormonal factors play a role in female susceptibility [10]. Genetic predisposition is also a factor in RA as the presence of HLA-DRB1 alleles have shown to increase susceptibility and severity of

disease [6]. Distribution of these alleles may differ, or appear in different combinations, between men and women, leading to varying outcomes between sexes [6, 11, 12].

In summary, due to the similar biological similarities between LA and RA, age and sex may be analogous risk factors between these two forms of arthritis, especially in cases of treatment-resistant LA.

Epidemiology of Exposure-Outcome Relationship:

Epidemiological data concerning LA in particular are quite sparse. While a number of studies have been performed on the topic of LD, research has seldom evaluated the distribution of LA among those cases. Because age and sex are established risk factors for RA, these variables are rarely the main exposures of interest in recent studies. Indeed, in the majority of studies age and sex are controlled for to determine the effects of other variables. Therefore, due to the lack of epidemiological studies directly pertaining to age and gender as risk factors for LA, we will present studies evaluating age and gender as risk factors for LD and RA to make indirect inferences on LA [13-15].

A prospective cohort study conducted by Chan et al. was designed to determine the incidence of RA according to age and sex in central Massachusetts from 1987 to 1990 [13]. The study included members of the Fallon Community Health Plan (FCHP), primarily residing in Worcester County, MA. Over the course of the study, FCHP membership increased from 77,000 individuals in 1987 to 126,000 in 1990. Potential cases were queried from the research database by identifying all FCHP members with at least 1 provisional or hospital diagnosis of RA during the study period. A case of RA was defined as an adult (older than 18) member of FCHP whose symptoms fit the criteria for

either the 1958 or 1987 American College of Rheumatology definition of RA. Because incident, not prevalent, cases were the object of the study, any members identified as RA cases at the beginning of the study were dropped from the analysis. Incidence rates were calculated by dividing the number of new cases in each age-sex category by membership-years at risk. Calculations were based on the assumption that case counts followed a Poisson distribution and all results were age- and sex-standardized to the 1980 US white population. Over the course of the study period, 81 members (22 men and 59 women) were diagnosed as having incident RA. Age-specific annual incidence was highest among the 60-69 year old age group at 97 cases per 100,000. This varied sharply from an incidence rate of 5 cases per 100,000 in the18-29 age group. Women had 2-3 times the risk of RA as compared to men at all levels of age. The overall age-standardized incidence rates per 100,000 were 22 (95% CI 13-32) for men and 60 (95% CI 46-75) for women. This study reinforces the finding that age and sex are established and important risk factors for RA.

In a prospective cohort study conducted around Paris, France, Dhote et al. aimed to determine the clinical and epidemiological features of Lyme borreliosis in the area between 1989 and 1997 [14]. Patients were recruited from various wards in a public hospital in Paris and cases were verified by assessing a combination of clinical symptoms and serological tests. Lyme arthritis was defined in this cohort as the presence of synovial inflammation, with chronic LA defined as synovitis persisting at least 6 months. Of the 170 patients that were diagnosed with Lyme borreliosis, 34 (20%) were also diagnosed with LA, which is somewhat lower than the percentage typically seen in the United States [1]. The mean age of cases with LA was 44 (SD = 18.8) years old. In terms of the gender

distribution, 9 (26%) were females and the other 25 (74%) were males. Though this difference found between males and females is considerable, Dhote provides no theories to explain this finding. A possible reason for this gender difference may be that the pathogen interacts differently between male and female host environments due to hormonal factors. While this study assessed the distribution of LA, it must be noted that European forms of Lyme borreliosis are caused by different species of *B. burgdorferi* than are found in the US, so results may lack generalizability. Also, due to the relatively small sample size, the study lacks the power to make significant conclusions.

A study was performed by Petersen et al. in which LD cases identified by active surveillance were analyzed to assess the incidence and epidemiology of LD and its symptoms [15]. The study was carried out in Connecticut during 1984 and 1985, and obtained a total of 1,149 defined LD cases. Data on patients were gathered by the Connecticut State Department of Health Services from physician case report forms paired with specimens sent to the state laboratory. To meet the case definition an individual had to have at least one clinical manifestation commonly associated with LD and at least one positive serological test result. Serological laboratory tests included either an indirect immunofluorescence assay (IFA) or an enzyme-linked immunofluorescence assay (ELISA). Results showed that 252 (24%) of LD cases presented the symptom of LA. Of these 252 cases, 113 were under the age of 20 and the remaining 129 were 20 or older. Persons less than 20 years old were nearly twice as likely to be diagnosed with LA as those 20 or older (RR = 1.9; 95% CI 1.5-2.3). This finding may be the result of surveillance bias due to a heightened awareness of LA among children, who are less likely to have joint aches and pains than older people.

In general, the studies cited here found that women and older people were at higher risk of contracting RA, which is not the same disease as LA, though they share some etiological similarities, especially in the case of chronic LA. Also, men and those under 20 years old were at higher risk of experiencing LA. Failure to adjust for potential confounding and effect modifying variables may have hidden or skewed the interpretation of the relationships found in these studies. They may also be subject to biases that were not controlled for in the designs. Due to these shortcomings, the true associations between age, sex, and LA remain unknown.

CHAPTER III

SUMMARY

Lyme disease is a growing concern in the United States with over 20,000 cases occurring annually. Of these LD cases, many suffer from arthritis due to *B. burgdorferi* infection. Despite the considerable morbidity caused by LA, little attention has been paid to understanding its risk factors. From what scant data has been collected it appears that LA has a tendency to affect males more often than females. However, when looking at the incidence of RA, which shares biological similarities with LA, rates are much higher in women. Also, while increasing age has been shown to increase the risk of RA, the opposite has been found for LA in at least one instance. The lack of definitive epidemiological evidence suggests that more research is needed to assess what roles age and sex play in the manifestation of LA. In light of the paucity of quality studies on this topic, an accurate analysis focusing on LA, as opposed to LD, is necessary to better elucidate the relationships between age, sex, and LA.

CHAPTER IV

AIM AND HYPOTHESES

Specific Aim:

To evaluate age and sex as predictors of Lyme arthritis diagnosis in patients who have contracted Lyme disease.

Hypotheses:

1. Among those with Lyme disease, age will be positively correlated to diagnosis of Lyme arthritis.
2. Among those with Lyme disease, females will be diagnosed with Lyme arthritis more often than males.

CHAPTER V

METHODS

Study Design:

To examine the associations between age, sex, and the diagnosis of LA in patients with LD, a cross-sectional study was conducted utilizing data obtained from the Massachusetts Department of Public Health (MDPH) that encompassed the years 2000 to 2006. Massachusetts state regulations place LD on its list of reportable diseases (105 CMR 300.100) and require that local boards of health promptly report any cases or suspected cases to the MDPH (105 CMR 300.110) [16]. Physicians generally contact local health agents to notify them of suspected cases, at which point it is the health agents' responsibility to fill out a case report form using information from the physician or the case, and send it to the MDPH. At the MDPH, report forms are compiled, reviewed, and transcribed into a database. Case report forms include patient information on demographics and clinical information relating to LD, as well as symptom onset and diagnosis dates (Figure 1). Due to the lack of reliable biological information obtained from the case report forms it was impossible to make substantial claims about how age and sex truly affect the risk of acquiring LA. However, with the data available, I aimed to assess how these variables play a role in the diagnosis of LA.

Population and Eligibility:

This study was based on LD cases reported to the MDPH between the years 2000 and 2006. Lyme disease is endemic throughout the state, so exposure was not limited to any specific group. However, those living in metropolitan areas are less likely to contract LD around their homes due to the sylvatic nature of tick and their usual hosts.

Each year the MDPH receives an average of 10,000 LD reports from local health agents and physicians, which are then validated by a team of epidemiologists and assigned a case status of "confirmed," "probable," "suspect," or "revoked," based on a combination of clinical and laboratory results. In this study we included only cases that were deemed as "confirmed" by the MDPH. Also, LD cases with unknown LA status and those with incomplete covariate data were excluded from analysis.

Outcome Assessment:

Lyme arthritis is recorded in LD case report forms that have been filled out by town health agents or physicians. On the form, LA can be coded as yes, no, or unknown, though individuals with unknown status were excluded from the study as noted earlier (Table 1). The symptom is used as an element in the diagnostic assessment of LD, so physicians should be alert to the potential for LA in suspected LD cases. Clinical features of LA are typified by recurrent, brief (weeks to months) bouts of swelling and pain in the joints, particularly the knees.

Outcome validation:

Lyme arthritis is generally diagnosed by clinical means and is dependent on having a primary diagnosis of LD. Lyme disease is validated by physician diagnosis and is based on an algorithm that includes the presence of an erythema migrans rash of at least 5cm in diameter, or by a combination of late-manifesting LD symptoms in addition to a positive laboratory test. Laboratories test serum for the presence of diagnostic levels of IgG or IgM antibodies to Borrelial antigen. Initial testing is done using ELISA or IFA techniques, and samples with positive or equivocal results are then re-tested using Western blot procedure [16, 17]. Unfortunately, these tests are not always accurate. For example, they are particularly insensitive in the early stages of infection and cannot distinguish between past and present infection. Also, false positives may occur due to cross-reactivity with antibodies being produced against diseases such as RA, lupus, and mononucleosis, among others. Another diagnostic method is to isolate *B. burgdorferi* itself from a clinical specimen [18].

Exposure Assessment:

Assessment of the exposures of age and sex is also based on data from case report forms. In this study, age in years will be divided into quartiles and sex will be classified as male or female (Table 1).

Exposure validation:

Reporting of these variables should be accurate in forms submitted by physicians due to their access to patient medical charts. For local health agents it may be more challenging to accurately characterize features of LD cases, as they may not meet all cases face to face.

Covariate Assessment:

A number of covariates were included in the analysis based on their roles as diagnostic elements for LD and their temporal relation to LA. These variables include the presence of erythema migrans rash, Bell's palsy, and the number of months between symptom onset date and diagnosis date (Table 1). Again, data for these variables were obtained from a compilation of MDPH Lyme disease case report forms.

Data Analysis:

Univariate Analysis:

We first determined the total number of study participants and made exclusions due to missing or unknown LA status, as well as missing or unknown covariate data leading to the final study population of individuals having complete data (Table 2). Because the study population was obtained via case report forms, patient refusal was not a concern. Next, the number and percentage of people in the exposure (age, sex) and outcome (LA) groups for our study population was calculated (Table 3). The total number and percent of people with each symptom, or combination of symptoms, was also determined (Table 4).

Bivariate Analysis:

Analyses were conducted to specifically determine if the proportion of individuals with each symptom, or group of symptoms, differed across strata of age, sex, and number of months between symptom onset and diagnosis (Table 5-7). Chi-squared tests were used to assess significance, as well as Fischer's Exact test where cell counts were less than 5.

Additional Analyses:

Least squares means were calculated using ANOVA to determine the mean ages of individuals having each symptom, or combination of symptoms. P-values were obtained for Dunnett post-hoc comparisons of means, with erythema migrans used as the referent against which the means of all other symptoms were compared (Table 8). The same analysis was run to assess the mean number of months between onset of symptoms and diagnosis for each symptom, both with and without individuals having a time difference of 36 months or more (Table 9).

CHAPTER VI

SIGNIFICANCE

Risk factors for LA have largely been overlooked in prior studies involving LD. This study aimed to elucidate the role that age and sex play in the diagnosis of LA. From our findings we may be able to heighten awareness about LD in high-risk groups or even target these people for more aggressive anti-arthritis treatment at first onset of LD, thus reducing morbidity due to LD. These measures could be especially effective in highly endemic areas such as southeastern Massachusetts.

CHAPTER VII

HUMAN SUBJECT PROTECTION AND PERMISSION TO ACCESS DATA

Human Subjects Protection:

All potential case-identifying information was removed from the data set, as overseen by members in the Privacy and Data Access Office and the Office of Integrated Surveillance and Informatics Services at the Massachusetts Department of Public Health.

Permission to Access Data:

Permission to access data was granted by the Massachusetts Department of Public Health.

CHAPTER VIII

RESULTS

The original study base included all individuals recorded by the MDPH as being diagnosed with LD from the year 2000 to 2006 (n = 12500). Of these LD cases, 4074 were excluded due to missing or unknown LA status, and an additional 4187 were excluded due to missing exposure variable data, leaving 4329 individuals for inclusion in the final analysis (Table 2). The age of this population ranged from 0 to 99 years old, with a mean age of 35.9 (SD = 23.1). The study included 2366 males and 1873 females, accounting for 55.8% and 44.2% of the population respectively. Of these individuals, 1680 (39.6%) were diagnosed with LA (Table 3). The distribution of symptoms among the entire population showed that 2055 (49.6%) had erythema migrans as their only symptom, 282 (6.8%) had Bell's palsy as their only symptom, and 1087 (26.3%) had LA as their only symptom. Only 59 (1.4%) individuals diagnosed with LD were also diagnosed with all three of the main symptoms of interest (Table 4).

Symptoms were broken down into seven specific categories to distinguish those with single symptoms (3 groups) and those presenting multiple symptoms (4 groups). Stratification by age showed no change between quartiles for erythema migrans ($p=0.563$), but significant changes for Bell's palsy and LA ($p<0.001$ for each) with those in the lower quartiles having a higher proportion of being diagnosed with these symptoms than their older counterparts. For those with multiple symptoms results were variable, however, those in the first age quartile consistently had lower proportions of these grouped symptoms than all others (Table 5). When all symptoms were stratified by sex there were no significant differences seen except for in the case of Bell's palsy, in which

females were diagnosed with this more often than males ($p = 0.011$) (Table 6). Stratifying symptoms by time from symptom onset to diagnosis with LD yielded some significant results. As the number of months between onset and diagnosis increased for erythema migrans and Bell's palsy the proportions of individuals presenting those symptoms decreased ($p<0.001$). The opposite was seen for LA, where only 21.6 percent had LA where diagnosed with LD occurred in the same month as symptom onset, while 36.6 percent had LA in those where LD diagnoses occurred at least 7 months after symptom onset ($p<0.001$). For those presenting the combinations of EM+LA and BP+LA similar trends were seen as that for LA only (Table 7).

Comparing the mean age of individuals at the time of LD diagnosis based on their symptoms showed that those with Bell's palsy only or LA only were significantly younger than those with erythema migrans only ($p<0.001$ and 0.011 respectively). Also, individuals with multiple symptoms tended to be older than those diagnosed with only a single symptom, as individuals with erythema migrans, Bell's palsy, and LA combined were an average of 44.0 years old (Table 8).

Statistically significant differences were not initially seen when mean number of months between symptom onset and diagnosis of LD was looked at between erythema migrans and other symptoms, except for in the EM+LA group ($p = 0.015$). A sensitivity analysis was then done removing 33 individuals who had a difference of 36 or more months between symptom onset and diagnosis. After removal of these individuals similar means were still seen between erythema migrans and Bell's palsy ($p = 0.642$) while LA became significantly different ($p<0.001$) (Table 9).

Individuals with complete data (n = 4329) differed significantly from those with incomplete data (n = 4187) in many respects, including the presence of LA, Bell's palsy, erythema migrans, and mean age. Months between symptom onset and diagnosis was significant among the two groups (p = 0.049) and male-female distribution was not found to be significantly different (p = 0.457) (Table 10).

CHAPTER IX

DISCUSSION

The findings of this cross-sectional study suggest that children in the first age quartile (aged 0-14) who contract LD are more likely to be diagnosed with LA than older individuals. This finding is the opposite of what was hypothesized at the beginning of the study. It does, however, support the findings by Petersen et al., who had previously suggested that those under 20 years old had twice the risk of LA compared to those over 20. The other main exposure of interest, sex, did not seem to have any appreciable effect on LA diagnosis, as the proportions of LA diagnosis were nearly identical between men and women.

Though we found similar results to Petersen et al. regarding LA in children, the true cause of this remains to be seen. Like Petersen, we were limited by the surveillance data collected and were unable to discover and true biological relations between age and LA. While children with LD may truly be more susceptible to LA, the same bias may have been present in this study as I suggested for Petersen; that LA would be detected more readily in children as it is an unusual symptom in that age group, whereas it may be overlooked if it is the only symptom present in an older individual where arthritis is more common. This hypothesis may be supported by the fact that for individuals with LA in combination with another symptom the proportions are higher in older age groups, suggesting that LD diagnosis is more dependent on the presence of another symptom to go along with LA in older people than it is for children.

Whether LD cases were male or female, they were diagnosed with LA at similar rates. There is no obvious reason why actual physician diagnosis should be differential

between males and females, as the diagnostic criteria is the same for both sexes. Though we do not know if there is a true difference in susceptibility between males and females due to genetic or hormonal factors, we can infer from our results that such a difference is unlikely.

Whereas being female dramatically increases the risk of having RA, the same does not appear to hold true for LA. Though LA and RA do share some clinical and biological similarities, they are truly two different diseases with different causes; LA being resultant of a bacterial infection and RA resulting from autoimmunity. Because of this, gender may have had less of an effect than originally hypothesized. While the findings of Dhote et al. suggested that females had roughly one-third the risk of presenting LA as males, a logical conclusion may be that the gender distribution found by Dhote was a product of chance, due to the small sample size of the study.

The mean age at diagnosis for erythema migrans (36.2 years) being so close to the mean age of the total population (35.9 years) provides further evidence that erythema migrans is diagnosed uniformly across all age strata. An interesting feature regard mean ages was that those with multiple symptoms tended to be older than those with single symptoms. This may be a product of the fact the younger people exhibiting the symptoms of Bell's palsy or arthritis may be recognized as LD cases more readily based on a single symptom than in older people, where these symptoms are generally more common, and may necessitate a supplementary symptom to arise before a doctor is willing to diagnose them with LD.

The results from looking at the mean number of months between symptom onset and LD diagnosis suggest that those with LA, whether alone or in concert with other

symptoms, significantly delays diagnosis time. One explanation for this is that LA typically takes a number of weeks to months to manifest itself, which is usually longer than it takes for erythema migrans or Bell's palsy to be diagnosed.

Limitations:

This study is limited by the incomplete nature of the data. With nearly two-thirds of the initial study base excluded from the final analysis there is a large potential for bias in the results, especially as those with complete data and those with incomplete data are significantly different in the distribution of LA, Bell's palsy, and erythema migrans as well as age.

Non-differential misclassification of exposure:

On the case report forms sent to the MDPH, patient date of birth is recorded instead of age. In this data set, patient age was derived from date of birth by the MDPH. Age may be misclassified if the person converting date of birth information into age made a typological or mathematical error. This is unlikely to be an issue, however, because age is stratified into four levels in this study, so only those whose age changed them from one group to another due to rounding error are of concern. Another potential for misclassification of age is if people falsely reported their date of birth to the medical doctor or local health agent filling out the case report form. In the case of a report from a doctor, this seems to be an unlikely scenario as a doctor would have had access to the patients' medical charts at the time of diagnosis and therefore, would have been able to accurately report date of birth. Reports taken by health agents may have been more prone

to misclassification as they may not have bothered, or have had the means, to validate patient date of birth. Once again this would have only been an issue in the event that misreporting of date of birth caused the individual to change from one of the age quartiles into another. It is believed that rounding error and false patient reporting were rare occurrences and did not have significant effect on the outcome.

Sex is an unlikely source of misclassification. This may have occurred if a physician or health agent made a mistake while filling out the case report form and the error was not identified.

Non-differential misclassification of outcome:

Misclassification of LA may have been a fairly common occurrence for a variety of reasons. First, there is no diagnostic tool for LA, and the ones for LD are not perfect. This alone may have lead to highly variable diagnoses from one doctor to the next. Second, some LD patients may have had a case report form sent in before the symptom of LA developed, so true cases would have been counted as non-cases. Another likely source of misclassification is that those experiencing LA may have been more likely to be diagnosed with LD than those without LA, because the symptom helps to elucidate the disease. This means that individuals with LD who had the symptom of LA may be over-represented. It is likely that misclassification of LA is common in this population and has lead to some bias in the results.

Selection Bias:

One possible form of bias is that older people who truly have LA may have been more likely to be misdiagnosed with rheumatoid (or other) arthritis more often than younger people, as this is a relatively common disease in those who fall into the highest age quartile of this study. If this has occurred it would yield an underestimate of true cases of LA in the highest age group.

In a similar scenario, women may also have been more likely to be misdiagnosed with rheumatoid arthritis compared to men. This could be attributed to the higher rates of rheumatoid arthritis seen in women compared to men, which would lead a doctor to more readily make that diagnosis. A diagnosis of RA would make it less likely for that person to be also diagnosed with LD, so they would be missing from the cohort. Again, if this has occurred it would lead to an underestimate of true cases of LA in women and would result in biased data.

Information Bias:

While it is clear that diagnosis of LA will differ among LD patients it is not clear if this will be a product of differing age or sex. One possibility is that general physicians may be more likely to recognize the signs of arthritis more readily than a pediatrician, which could cause an overestimation of the true relationship between age and LA. It seems less likely that sex would play a role in differential diagnosis of LA as men and women see the same doctors and currently neither sex is recognized as being at a higher risk of LA than the other.

Confounding:

Though information was collected on a number of variables, some potential confounders may exist that we were not able to obtain data for. One factor that likely had an effect on the results is treatment status and use of medication. There are multiple courses of treatment that doctors may prescribe based on patient age, symptoms, and medical history. These differences in treatment regimens may result in varied outcomes for the progression of the disease and its symptoms. As a result, there could be either an over- or an underestimate of the true relative risk for the associations between age and LA, as well as sex and LA. Also, some individuals may have already been taking antibiotics that are used to combat LD, such as doxycycline or amoxicillin, before they were even bit by a tick as they were being treated for another ailment. This would likely have a prophylactic effect and prevent individuals from contracting LD in the first place, excluding them from the study population altogether.

Another potential confounder is cigarette smoking, which has been shown to significantly increase the risk of rheumatoid arthritis [20]. As treatment-resistant LA has some biological relation to RA, it is predicted that smoking may also lead to higher rates of LA. It is expected that those in the upper age groups have had more exposure to smoking, meaning that people who are older may be more likely to be (or to have been) smokers, which would increase their risk of LA.

Generalizability:

The results of this study can likely be generalized to other endemic areas of LD in the United States. Lyme disease is mostly present along the East Coast from Virginia northward to Maine, as well as in the Northern Central states of Wisconsin and Minnesota. In these areas the population demographics are similar enough to those of Massachusetts that it is not unreasonable to assume generalizability. The findings may not be generalizable, however, to non-endemic areas of the United States, as suggested by the CDC after conducting a national LD surveillance summary [21]. In non-endemic areas population demographics may be significantly different based on age or race. Reporting and diagnosis of LD may also differ in areas where the disease is uncommon. Lastly, LD in non-endemic areas may be caused by different *Borrelia* species than are found in areas of endemicity. These species may have different tissue tropisms and could be more or less likely to cause LA, as in Europe where LA is not a common symptom of Lyme borreliosis.

Temporality:

While temporality is not of great concern in this study in terms of age and sex, it is a considerable issue regarding diagnosis for LD, LA, erythema migrans, and Bell's palsy. Because this study was cross-sectional, all data was collected at a single point in time, so we do not know what outcomes the patients may have encountered following their entrance into the study. For example, an individual who presented erythema migrans and was diagnosed with LD may have had a case report sent to the MDPH with that information recorded. However, that same person may have later developed LA, though

we would have no way of knowing as no additional case report form would have been submitted. To be able to truly associate the risk that early symptoms have on LA a prospective cohort study would have to be conducted, which followed patients past the time of LD diagnosis until the point where symptoms have subsided.

Survival Bias:

While LD is associated with substantial morbidity its mortality rate is negligible. Due to the extremely rare nature of death due to LD we do not believe that survival bias was an issue in this study.

CHAPTER X

CONCLUSION

In conclusion, this study found that a significantly higher proportion of children 14 years old and younger were diagnosed with LA only, as compared those over 14 years old. Our finding was consistent with those of previous LD surveillance studies [15, 21]. This consistency, however, may be a product of surveillance or diagnostic bias. Gender did not appear to be a significant factor for predicting LA, as males and females had nearly identical risks, though a significant difference was seen for Bell's palsy.

There were a number of limitations to this study that prevented us from being able to uncover any truly meaningful biological findings. First, we were limited to using data provided by the MDPH, which was collected using passive surveillance and did not include many variables, such as race, co-infection with other tick-borne diseases, serological test results, or any personal or medical information that may have helped to elucidate the true relationships between age, sex, and LA. The second issue was that many cases had missing data, which drastically reduced the power and validity of the study, as those with complete data differed significantly from those with missing data in many respects. Lastly and most importantly was the issue of temporality, as patients were not followed after their initial LD diagnosis, causing us to miss any LA cases that may have developed after a case report form had been submitted to the MDPH.

To appropriately assess the risk factors for developing LA we recommend that a prospective cohort study be done in the future, following individuals from time of infection until abatement of symptoms, and including a larger number of potentially confounding medical and lifestyle variables.

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TABLE 1: Classification of study variables; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

Name	Description	Type
LA	Lyme arthritis 0 = No 1 = Yes	Dichotomous
AGE	Age in years 1 = Quartile 1 2 = Quartile 2 3 = Quartile 3 4 = Quartile 4	Categorical
SEX	Sex 0 = Male 1 = Female	Dichotomous
EM	Erythema migrans rash 0 = No 1 = Yes	Dichotomous
BP	Bell's Palsy 0 = No 1 = Yes	Dichotomous
SD_DIFF2	Months between symptom onset and diagnosis 0 = Same month 1 = 1-6 months 2 = More than 6 months	Categorical

TABLE 2: **Study population size and exclusions; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000 - 2006.**

	Total
Initial study base	12500
Exclusions	
Unknown Lyme arthritis status	4074
Incomplete covariate data	4187
Final study base	4239

TABLE 3: Percent distribution of exposure and outcome characteristics in the study population; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Total
Age†	35.9 (23.1)
Sex‡	
Male	2366 (55.8)
Female	1873 (44.2)
Lyme arthritis‡	
Yes	1680 (39.6)
No	2559 (60.4)

†Recorded as mean (standard deviation)
‡Recorded as number (%)

TABLE 4: Distribution of symptoms among study population; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	N (%)
Erythema migrans	2055 (49.6)
Bell's palsy	282 (6.8)
Lyme arthritis	1087 (26.3)
EM+BP	124 (3.0)
EM+LA	450 (10.9)
BP+LA	84 (2.0)
EM+BP+LA	59 (1.4)

TABLE 5: Percentage of individuals diagnosed with each symptom by age quartile; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Age [Quartile (years)]				
	Q1 (0-14)	Q2 (15-41)	Q3 (42-55)	Q4 (56+)	p-value
Erythema migrans	47.4	47.6	49.5	49.8	0.56
Bell's palsy	8.0	8.5	5.1	4.4	<0.001
Lyme arthritis	32.6	21.9	22.9	23.8	<0.001
EM+BP	2.3	4.2	2.8	2.5	0.04
EM+LA	6.3	10.5	12.7	14.2	<0.001
BP+LA	1.1	2.1	2.9	2.1	0.04
EM+BP+LA	0.3	2.1	1.7	1.6	0.01

TABLE 6: Percentage of individuals diagnosed with each symptom by sex; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Sex		
	Female	Male	p-value
Erythema migrans	47.7	49.4	0.27
Bell's palsy	7.5	5.6	0.01
Lyme arthritis	26.0	25.3	0.61
EM+BP	3.3	2.5	0.11
EM+LA	10.1	11.3	0.22
BP+LA	2.0	2.0	0.98
EM+BP+LA	1.5	1.3	0.58

TABLE 7: Percentage of individuals diagnosed with each symptom by time from symptom onset to Lyme disease diagnosis; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Months from symptom onset to diagnosis of LD			
	<1	1 to 6	7+	p-value
Erythema migrans	53.4	43.4	30.3	<0.001
Bell's palsy	7.9	5.5	0.7	<0.001*
Lyme arthritis	21.6	30.3	36.6	<0.001
EM+BP	2.8	3.1	2.1	0.76*
EM+LA	9.9	10.9	19.0	<0.001
BP+LA	1.2	2.7	6.3	<0.001
EM+BP+LA	1.2	1.7	0.7	0.35*

*Denotes use of Fischer's Exact test due to small cell sizes

TABLE 8: Comparison of means age at diagnosis for each symptom category; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Mean Age at Diagnosis (years)	p-value[#]
Erythema migrans	36.2	-
Bell's palsy	30.1	<0.001
Lyme arthritis	33.6	0.011
EM+BP	35.4	0.999
EM+LA	42.3	<0.001
BP+LA	41.9	0.147
EM+BP+LA	44.0	0.064

[#]p-value from Dunnett post-hoc comparison of means with EM as the reference

TABLE 9: Comparison of mean number of months between symptom onset and diagnosis for each symptom category; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

	Mean Months Between Symptom Onset and LD Diagnosis			
	All Included	p-value[#]	Without 36+ Months Difference	p-value[#]
Erythema migrans	-1.12	-	-0.68	-
Bell's palsy	-0.47	0.272	-0.47	0.642
Lyme arthritis	-1.54	0.193	-1.40	<0.001
EM+BP	-0.81	0.988	-0.81	0.988
EM+LA	-1.96	0.015	-1.25	<0.001
BP+LA	-2.62	0.066	-2.01	<0.001
EM+BP+LA	-0.81	0.998	-0.81	0.998

[#]p-value from Dunnett post-hoc comparison of means with EM as the reference

TABLE 10: Comparison of variables between population with complete data to that with incomplete data; Predictors of Lyme arthritis diagnosis in Lyme disease cases, 2000-2006.

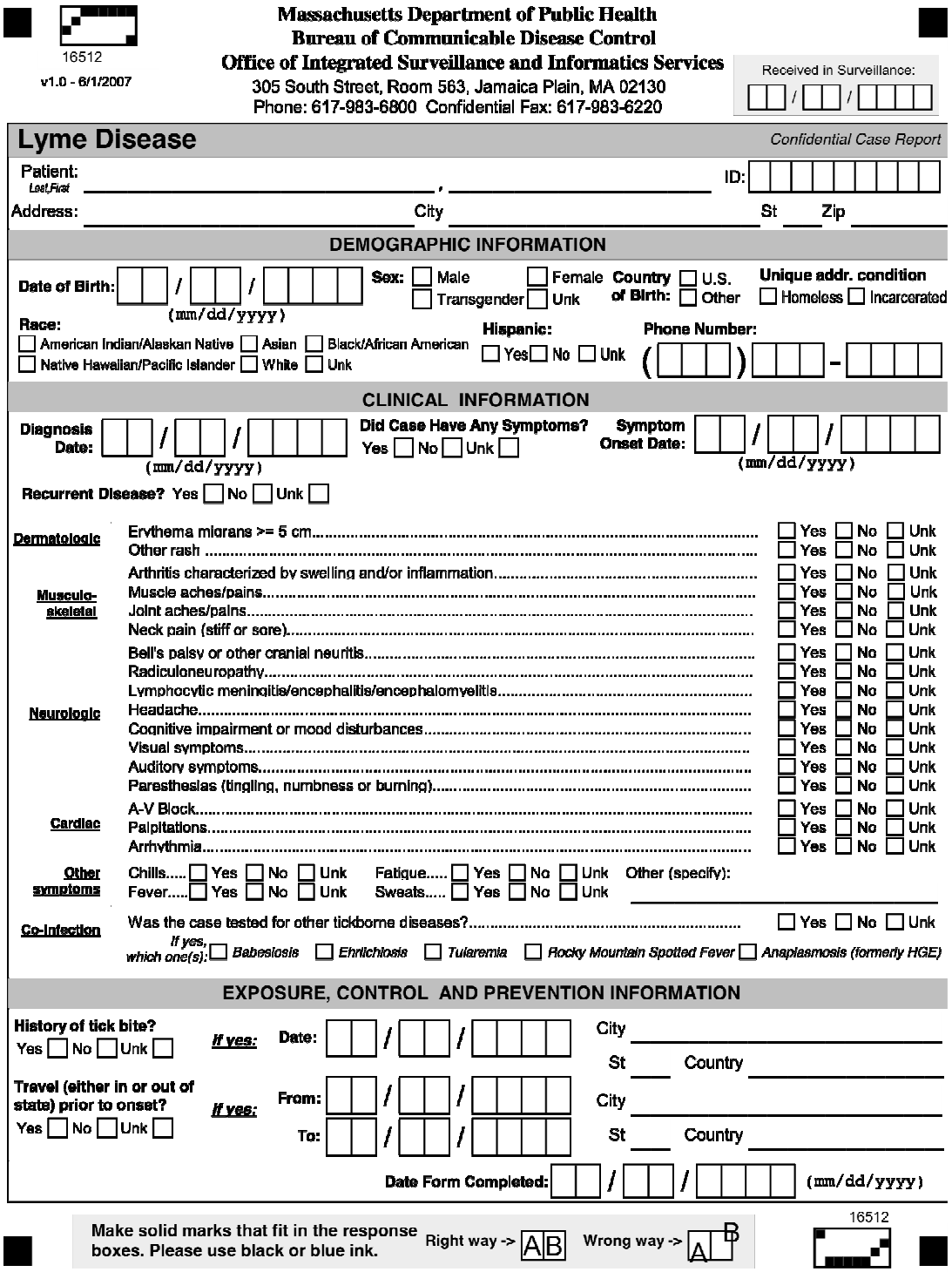
	Complete data (n = 4239)	Missing data	p-value
Lyme arthritis	1680 (39.6)	2361 (56.4) [n = 4187]	<0.001
Age†	35.95 (23.1)	39.67 (22.5) [n = 3321]	<0.001
Sex‡	1873 (44.2)	1800 (45.0) [n = 4000]	0.457
Bell's palsy	549 (13.0)	319 (10.6) [n = 2999]	0.003
Erythema migrans	2688 (63.4)	2170 (66.7) [n = 3252]	0.003
Months between symptom onset and diagnosis†	-1.31 (5.29)	-1.06 (3.93) [n = 1669]	0.049

†Recorded as mean (standard deviation)

‡Recorded as number (%) male

All other variables recorded as number (%) yes

FIGURE 1: MDPH Lyme Disease case report form



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Received in Surveillance: ☐☐ / ☐☐ / ☐☐☐☐

Lyme Disease

Confidential Case Report

Patient: *Last,First* _____, _____ ID: ☐☐☐☐☐☐☐☐☐☐

Address: _____ City _____ St ___ Zip _____

DEMOGRAPHIC INFORMATION

Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

Sex: ☐ Male ☐ Female ☐ Transgender ☐ Unk

Country of Birth: ☐ U.S. ☐ Other

Unique addr. condition ☐ Homeless ☐ Incarcerated

Race:
☐ American Indian/Alaskan Native ☐ Asian ☐ Black/African American
☐ Native Hawaiian/Pacific Islander ☐ White ☐ Unk

Hispanic: ☐ Yes ☐ No ☐ Unk

Phone Number: (☐☐☐) ☐☐☐-☐☐☐☐

CLINICAL INFORMATION

Diagnosis Date: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

Did Case Have Any Symptoms? Yes ☐ No ☐ Unk ☐

Symptom Onset Date: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

Recurrent Disease? Yes ☐ No ☐ Unk ☐

Dermatologic	Erythema migrans >= 5 cm	☐ Yes ☐ No ☐ Unk
	Other rash	☐ Yes ☐ No ☐ Unk
Musculo-skeletal	Arthritis characterized by swelling and/or inflammation	☐ Yes ☐ No ☐ Unk
	Muscle aches/pains	☐ Yes ☐ No ☐ Unk
	Joint aches/pains	☐ Yes ☐ No ☐ Unk
	Neck pain (stiff or sore)	☐ Yes ☐ No ☐ Unk
Neurologic	Bell's palsy or other cranial neuritis	☐ Yes ☐ No ☐ Unk
	Radiculoneuropathy	☐ Yes ☐ No ☐ Unk
	Lymphocytic meningitis/encephalitis/encephalomyelitis	☐ Yes ☐ No ☐ Unk
	Headache	☐ Yes ☐ No ☐ Unk
	Cognitive impairment or mood disturbances	☐ Yes ☐ No ☐ Unk
	Visual symptoms	☐ Yes ☐ No ☐ Unk
	Auditory symptoms	☐ Yes ☐ No ☐ Unk
	Paresthesias (tingling, numbness or burning)	☐ Yes ☐ No ☐ Unk
Cardiac	A-V Block	☐ Yes ☐ No ☐ Unk
	Palpitations	☐ Yes ☐ No ☐ Unk
	Arrhythmia	☐ Yes ☐ No ☐ Unk

Other symptoms
Chills..... ☐ Yes ☐ No ☐ Unk Fatigue..... ☐ Yes ☐ No ☐ Unk Other (specify): _____
Fever..... ☐ Yes ☐ No ☐ Unk Sweats..... ☐ Yes ☐ No ☐ Unk

Co-Infection
Was the case tested for other tickborne diseases? ☐ Yes ☐ No ☐ Unk
If yes, which one(s): ☐ *Babesiosis* ☐ *Ehrlichiosis* ☐ *Tularemia* ☐ *Rocky Mountain Spotted Fever* ☐ *Anaplasmosis (formerly HGE)*

EXPOSURE, CONTROL AND PREVENTION INFORMATION

History of tick bite? Yes ☐ No ☐ Unk ☐
If yes: **Date:** ☐☐ / ☐☐ / ☐☐☐☐ City _____ St ___ Country _____

Travel (either in or out of state) prior to onset? Yes ☐ No ☐ Unk ☐
If yes: **From:** ☐☐ / ☐☐ / ☐☐☐☐ City _____
To: ☐☐ / ☐☐ / ☐☐☐☐ St ___ Country _____

Date Form Completed: ☐☐ / ☐☐ / ☐☐☐☐ (mm/dd/yyyy)

Make solid marks that fit in the response boxes. Please use black or blue ink. Right way -> AB Wrong way -> A B

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