

Lyme Borreliosis and Associations With Mental Disorders and Suicidal Behavior: A Nationwide Danish Cohort Study

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Objective: Lyme borreliosis is a tick-borne infectious disease that may confer an increased risk of mental disorders, but previous studies have been hampered by methodological limitations, including small sample sizes. The authors used a nationwide retrospective cohort study design to examine rates of mental disorders following Lyme borreliosis.

Methods: Using Denmark's National Patient Register and the Psychiatric Central Research Register, and including all persons living in Denmark from 1994 through 2016 (N=6,945,837), the authors assessed the risk of mental disorders and suicidal behaviors among all individuals diagnosed with Lyme borreliosis in inpatient and outpatient hospital contacts (N=12,156). Incidence rate ratios (IRRs) were calculated by Poisson regression analyses.

Results: Individuals with Lyme borreliosis had higher rates of any mental disorder (IRR=1.28, 95% CI=1.20, 1.37), of affective disorders (IRR=1.42, 95% CI=1.27, 1.59), of suicide

attempts (IRR=2.01, 95% CI=1.58, 2.55), and of death by suicide (IRR=1.75, 95% CI=1.18, 2.58) compared with those without Lyme borreliosis. The 6-month interval after diagnosis was associated with the highest rate of any mental disorder (IRR=1.96, 95% CI=1.53, 2.52), and the first 3 years after diagnosis was associated with the highest rate of suicide (IRR=2.41, 95% CI=1.25, 4.62). Having more than one episode of Lyme borreliosis was associated with increased incidence rate ratios for mental disorders, affective disorders, and suicide attempts, but not for death by suicide.

Conclusions: Individuals diagnosed with Lyme borreliosis in the hospital setting had an increased risk of mental disorders, affective disorders, suicide attempts, and suicide. Although the absolute population risk is low, clinicians should be aware of potential psychiatric sequelae of this global disease.

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Infection and inflammation have been linked to increased risk of mental disorders and suicidal behaviors (1, 2). Lyme borreliosis is one such infectious disease, which has been associated with psychiatric manifestations, including depression, suicidal ideation, obsessive-compulsive disorder, mania, psychosis, and mild to severe cognitive impairment (3–12). These have been reported among individuals with acute untreated infection (5, 6), and months to years after antibiotic therapy (7, 8). Despite the multisystem involvement of *Borrelia burgdorferi* infection, evidence on the relationship between mental disorders and Lyme borreliosis is inconsistent, and previous studies have been hampered by small sample sizes.

To our knowledge, the largest outpatient psychiatric study assessing persistent mental symptoms attributed to Lyme borreliosis was a retrospective psychiatric office chart review without a control comparison group, which noted that

43.5% of the 253 patients reported suicidal thoughts (12). While some controlled studies have reported higher rates of depression in children and adults after Lyme borreliosis (8–10), other controlled studies did not find elevated rates of depressive symptoms (13–15). One cross-sectional study (16) noted rates of depression among hospitalized individuals with neuroborreliosis similar to rates for Lyme arthritis, and higher rates of depressive symptoms were reported after neuroborreliosis compared with erythema migrans in a follow-up study (mean follow-up, 32 months) after antibiotic treatment (11). In contrast, other follow-up studies of Lyme borreliosis found no difference in depressive symptoms 6 months after erythema migrans (17) or 10–20 years after erythema migrans, facial palsy, or arthritis (13). Supporting an association, a controlled study reported a significantly higher rate of seropositivity for *B. burgdorferi* antibodies among 499 psychiatric

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inpatients compared with age- and gender-matched healthy participants (18). Suicidal thoughts have been less frequently studied, with two controlled studies of patients with persistent posttreatment Lyme symptoms reporting elevated rates of suicidal thoughts compared with non-medically ill control subjects (9, 10). Several of these studies were hampered by small sample size, ascertainment bias, lack of an appropriate control group, use of poorly specified or nonstandard criteria for the diagnosis of Lyme borreliosis, reliance on clinical samples, use of unvalidated measures, lack of control for confounding variables, or a cross-sectional design. Given the methodological limitations of previous studies, the relationship between acute or posttreatment Lyme borreliosis and mental disorders and suicide remains uncertain. A recent Danish cohort study using elevated production of *Borrelia* antibodies in CSF as a proxy diagnosis of neuroborreliosis reported no association with mental diagnoses but found that psychiatric medication prescriptions were increased during the subsequent year (19). While improving on previous research, that study relied on a laboratory proxy rather than a clinical diagnosis of neuroborreliosis and did not include the nonneurologic manifestations of Lyme borreliosis.

We conducted a nationwide, population-based cohort study comparing the rate of new-onset mental disorders among persons diagnosed with Lyme borreliosis through a hospital contact (inpatient, emergency department, or outpatient) to those with no such diagnosis, a design that bypasses many of the limitations of previous studies. Our secondary aims were to examine whether individuals who had hospital contacts with a recorded diagnosis of Lyme borreliosis had higher rates of subsequent affective disorders, suicide attempts, and death by suicide than individuals without a diagnosis of Lyme borreliosis.

METHODS

The study was approved by the Danish Data Protection Agency (journal number RHP-2012-021). An anonymized data set was used for research purposes, and according to Danish legislation, informed consent from participants was not required.

Study Population

All Danish residents age 3 or older living in Denmark from 1994 through 2016 were included in our analyses. Linkage of data between various national registries was possible, as each Danish resident has a unique personal identification number. We accessed data from the Danish Civil Registration System (20), the Database for Integrated Labor Market Research (21), the National Patient Register (22), the Psychiatric Central Research Register (23), and the Register of Causes of Death (24). All registers are based on continuously updated administrative data on all residents living in Denmark. Diagnoses in the National Patient Register (22) and the Psychiatric Central Research Register (23) were recorded according to ICD-10's diagnostic system.

Measures

Exposure variables. Lyme borreliosis was identified as recorded in the National Patient Register since 1994 using ICD-10 (see Table S1 in the online supplement); this includes all hospital contacts—inpatient, outpatient, and emergency department visits. A description of the clinical assessment, laboratory tests, and treatment of Lyme borreliosis in Denmark is available online (25). Inpatient diagnoses of Lyme borreliosis have been recorded in the register since 1994, and outpatient and emergency department diagnoses have been available since 1995. From the date of a first diagnosis, the individual was considered exposed. To assess whether neuroborreliosis was more likely to be associated with psychiatric disorders than nonneuroborreliosis, Lyme borreliosis was grouped into three mutually exclusive categories: Lyme general and other nonneurologic; other neurologic Lyme manifestations; and Lyme meningitis. The number of registered medical contacts and of new episodes of Lyme borreliosis served as indicators of severity. A medical contact was defined as a hospital-based visit with a diagnosis of Lyme borreliosis, regardless of whether it was for a new episode or a prior episode. A new episode was operationally defined as at least a 2-month interval without hospital-based contacts for Lyme borreliosis.

Outcome variables. The primary outcome variable was any mental disorder, which was defined by an individual being newly registered in the Psychiatric Central Research Register since 1994 with a mental disorder diagnosis (ICD-10 codes F00–F99). The secondary outcome variables were affective disorders, defined by ICD-10 codes F30–F39; suicide attempt, as determined by registration in the National Patient Register and the Psychiatric Central Research Register (ICD-10 codes X60–X84) or where the reason for contact was indicated to be suicide attempt; and suicide, as determined from the Cause of Death Register (24) (ICD-10 codes X60–X84, Y87.0).

Follow-Up

Participants were included from January 1, 1994. Individuals who reached age 3 or who migrated into the country were included as of the dates of those events. The follow-up ended on the date of examined outcome, death, emigration from Denmark, or December 31, 2016, whichever came first.

Statistical Analysis

The associations between Lyme borreliosis and the examined outcomes were estimated in SAS, version 9.4, using adjusted Poisson regression models to obtain incidence rate ratios and population attributable risks with 95% confidence intervals. Statistical significance was determined by a *p* value below 0.05 using two-sided tests. The association with Lyme borreliosis was explored further in a range of adjusted models: number of new episodes; overall number of contacts; contact setting for Lyme borreliosis, ordered according to highest level of seriousness (inpatient, emergency department, outpatient); time since first diagnosis; and age at first diagnosis.

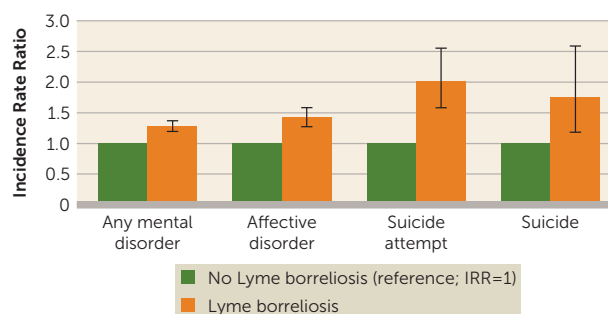
We excluded all individuals who had been recorded as having either a mental disorder or a suicide attempt prior to 1994. From 1994 onward, individuals with a first episode of Lyme borreliosis were excluded from the Lyme borreliosis group if a mental disorder or suicide attempt occurred prior to the Lyme borreliosis diagnosis. First, we estimated the rate of having a mental disorder among individuals diagnosed with Lyme borreliosis relative to those without this diagnosis. Basic models were adjusted for calendar period, sex, and age in 5-year intervals. Fully adjusted models were further adjusted for marital status, educational level, socioeconomic status, and chronic medical comorbidity (based on Charlson comorbidity index [26] scores of 0, 1, or ≥ 2). In addition, we adjusted for pre-Lyme borreliosis mental disorders occurring after 1994 in the analyses of suicide attempts and suicides. Because the number of Lyme-exposed individuals who died by suicide was relatively small ($N=25$), we restricted these analyses to basic adjusted models.

To validate the association found between Lyme borreliosis and the primary outcome of mental disorders, we carried out additional sensitivity analyses. First, we examined the association with mental disorders in a subcohort of individuals who had full register follow-up from birth (born after 1993); this was conducted because the registry prior to 1994 did not include Lyme borreliosis as a diagnosis. Second, we tested the association in a subcohort excluding all individuals with a Charlson comorbidity index score above zero to rule out undiagnosed mental disorders associated with other somatic illnesses. Third, we tested whether different results appeared if individuals with a history of mental disorders and/or a suicide attempt before 1994 were included in analyses, as they were excluded in our primary analyses. Fourth, because tools for the diagnosis of Lyme borreliosis modestly improved over the course of the 22-year study period, we tested whether the association with mental disorders was higher in those diagnosed with Lyme borreliosis from 2005 onward as opposed to before 2005. Fifth, we tested whether rates of mental disorders differed if a Lyme borreliosis diagnosis was given before the age of 40 as compared with later. Sixth, we tested whether incidence rate ratios were elevated after Lyme borreliosis compared with the non-Lyme population in age-stratified younger and older cohorts. Seventh, to examine whether a 2-month interval between hospital contacts for Lyme borreliosis was too short a period to define a new episode, we also calculated the incidence rate ratio for mental disorders using a longer duration (6 months) between hospital contacts for Lyme borreliosis. Finally, to address specificity, we calculated the incidence rate ratios for fractures not involving the skull or spine after Lyme diagnoses.

RESULTS

Among the 6,945,837 individuals (3,471,769 of them male) who were observed for a total of 111,952,876 person-years between 1994 and 2016, 12,616 individuals (6,528 of them male) received a hospital-based diagnosis of Lyme borreliosis (see

FIGURE 1. Incidence rate ratios for any mental disorder, affective disorder, suicide attempt, and suicide among individuals with Lyme borreliosis compared with individuals with no Lyme borreliosis in Denmark (1994–2016)^a



^a Estimates for any mental disorder, affective disorder, and suicide attempt were adjusted for calendar period, sex, age group, civil status, educational level, socioeconomic status, and chronic medical comorbidity. The model examining the outcome of suicide attempt was further adjusted for pre-Lyme mental disorders. Because there were few observed events, the estimate for suicide was adjusted for calendar period, sex, and age group. Error bars indicate 95% confidence interval. IRR=incidence rate ratio.

Table S1 in the online supplement), leaving 6,933,221 individuals in the comparison group. The national cohort spanned ages 3 years to 104 years. The mean age at first hospital-based diagnosis of Lyme borreliosis was 41 years ($SD=23$) and the median age was 44 years (interquartile range=20–59). Among those diagnosed (see Table S1), 11,256 (90%) had general Lyme borreliosis and other nonneurologic manifestations, while 360 (3%) had Lyme meningitis and 1,000 (7%) had other neuroborreliosis manifestations. Among those with Lyme borreliosis, 831 were subsequently registered with a mental disorder (see characteristics in Table S2 in the online supplement), 324 with an affective disorder, 67 with suicide attempt, and 25 with suicide.

Any Mental Disorder

The incidence rate of a new mental disorder among individuals with a Lyme borreliosis diagnosis was 733 per 100,000 person-years (95% CI=683, 782), compared with 567 (95% CI=565, 568) among individuals with no such diagnosis. The fully adjusted model showed that the rate of mental disorder diagnoses was 28% higher (incidence rate ratio [IRR]=1.28, 95% CI=1.20, 1.37) among individuals with Lyme borreliosis compared with those with no such diagnosis (Figure 1). A dose-response relationship was noted with respect to number of episodes (one episode: IRR=1.24, 95% CI=1.15, 1.33; two or more episodes: IRR=1.79, 95% CI=1.44, 2.22) (Table 1 and Figure 2). Compared with individuals with no history of Lyme borreliosis, the first 6 months after the first diagnosis was associated with a 96% higher rate of mental disorder diagnoses (IRR=1.96, 95% CI=1.53, 2.52), which fell gradually over time; however, even 5 years after first diagnosis, the IRR remained elevated (IRR=1.19; CI=1.09, 1.31; $p<0.0001$). Elevated rates were noted for

TABLE 1. Association between Lyme borreliosis and mental disorders in Denmark (1994–2016), basic and fully adjusted incidence rate ratios

Characteristic	Cases With Diagnosis	Incidence Rate per 100,000 Person-Years	95% CI	Basic Adjusted Model ^a		Fully Adjusted Model ^a	
				IRR	95% CI	IRR	95% CI
Number of episodes (defined as more than 2 months between hospital contacts)							
No Lyme	633,973	567	565, 568	1		1	
1	748	712	661, 763	1.16	1.08, 1.24	1.24	1.15, 1.33
>1	83	989	776, 1,202	1.63	1.32, 2.03	1.79	1.44, 2.22
Number of contacts for hospital services							
No Lyme	633,973	567	565, 568	1		1	
1	534	719	658, 780	1.17	1.07, 1.27	1.26	1.16, 1.37
2	202	742	639, 844	1.21	1.05, 1.39	1.28	1.11, 1.47
3	59	749	558, 940	1.22	0.95, 1.58	1.33	1.03, 1.71
≥4	36	888	598, 1,179	1.48	1.06, 2.05	1.62	1.17, 2.25
Time since first diagnosis							
No Lyme	633,973	567	565, 568	1		1	
<1 year	61	1,053	789, 1,318	1.82	1.42, 2.34	1.96	1.53, 2.52
1–2 years	56	1,010	746, 1,275	1.74	1.34, 2.26	1.88	1.45, 2.44
2–3 years	125	618	510, 727	1.06	0.89, 1.27	1.15	0.96, 1.37
3–4 years	131	753	624, 882	1.27	1.07, 1.51	1.37	1.15, 1.62
>4 years	458	710	645, 775	1.12	1.02, 1.22	1.19	1.09, 1.31
Age at first diagnosis							
No Lyme	633,973	567	565, 568	1		1	
<10 years	202	903	778, 1,027	1.35	1.17, 1.55	1.25	1.09, 1.44
10–19 years	117	1,254	1,027, 1,481	1.92	1.60, 2.30	1.47	1.22, 1.76
20–29 years	89	1,063	842, 1,283	1.7	1.38, 2.10	1.72	1.40, 2.12
30–39 years	106	754	611, 898	1.22	1.01, 1.48	1.65	1.36, 1.99
40–49 years	94	496	396, 597	0.83	0.68, 1.02	1.16	0.95, 1.42
50–59 years	78	394	306, 481	0.67	0.53, 0.83	0.89	0.71, 1.11
60–69 years	88	630	498, 762	1.09	0.89, 1.35	1.11	0.90, 1.37
≥70 years	57	869	644, 1,095	1.57	1.21, 2.04	1.28	0.98, 1.66
Setting type							
No Lyme	633,973	567	565, 568	1		1.0	
Inpatient	531	737	675, 800	1.2	1.10, 1.31	1.3	1.15, 1.37
Emergency department	103	721	582, 860	1.18	0.98, 1.44	1.4	1.11, 1.64
Outpatient	197	726	624, 827	1.17	1.02, 1.34	1.3	1.14, 1.50

^a The basic adjusted model adjusted for sex, age, and calendar period; the fully adjusted model adjusted for sex, age, calendar period, educational level, socioeconomic status, civil status, and Charlson comorbidity index score. IRR=incidence rate ratio.

those whose first Lyme borreliosis diagnosis was before age 40 and were highest in the age range of 20–29 years (IRR=1.72; CI=1.40, 2.12). No significant differences between rates of mental disorders were noted when we assessed for severity of Lyme borreliosis by the clinical setting where the initial diagnosis was made.

Affective Disorders

A 42% higher rate of affective disorders (IRR=1.42, 95% CI=1.27, 1.59) was noted among individuals with Lyme borreliosis compared with individuals with no such history (Figure 1). The rate of affective disorders by number of episodes of Lyme borreliosis was 1.37 (95% CI=1.22, 1.54) after one episode and 2.07 (95% CI=1.49, 2.87) after two or more episodes (Table 2). The highest rate of affective disorders was noted 6–12 months after diagnosis of Lyme borreliosis (IRR=2.59, 95% CI=1.77, 3.81), yet the rate remained elevated 5 or more years after first diagnosis (IRR=1.34, 95% CI=1.16, 1.55). The highest rate of affective disorders among individuals

with Lyme borreliosis occurred in the age range of 10–19 years (IRR=2.15, 95% CI=1.59, 2.90).

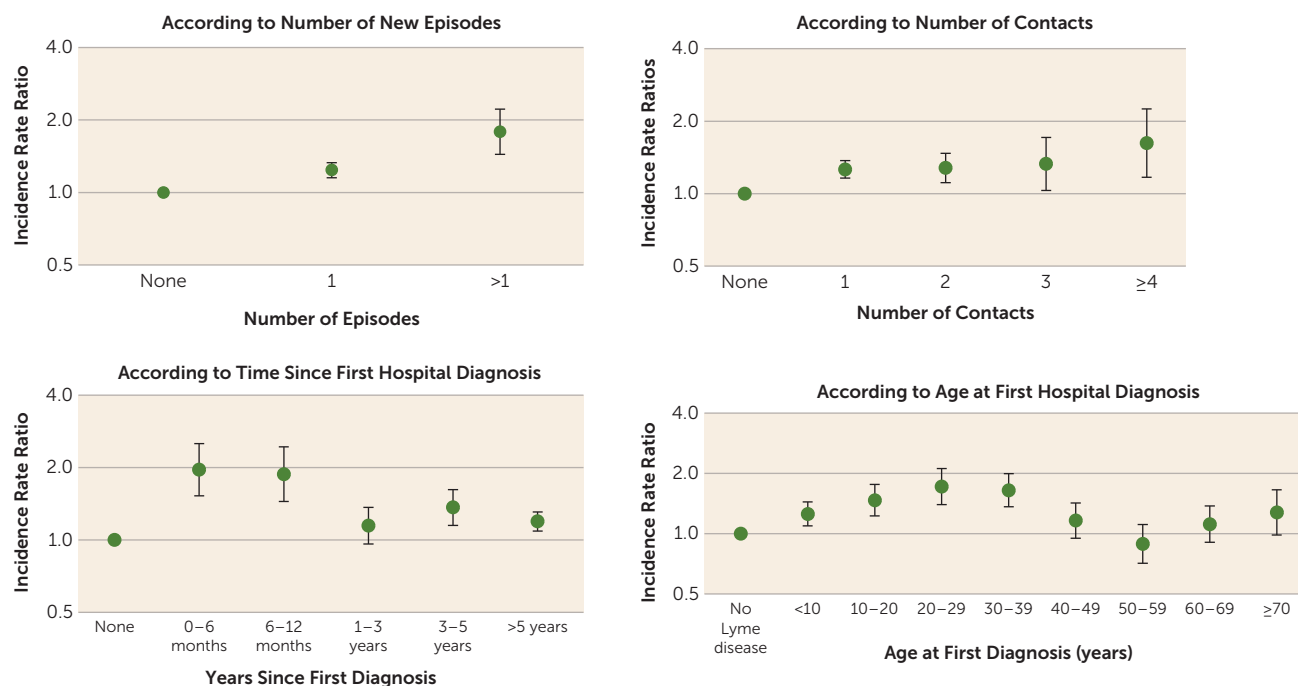
Suicide Attempt

A higher rate of suicide attempt was found among individuals diagnosed with Lyme borreliosis (IRR=2.01, 95% CI=1.58, 2.55) than among those with no such diagnosis (Figure 1). Regarding temporal effects, only the period 3 years after Lyme borreliosis diagnosis was associated with an increased rate of suicide attempt (IRR=2.45, 95% CI=1.87, 3.22) (Table 3). With respect to age, those diagnosed with Lyme borreliosis before age 10 had the highest IRR for later suicide attempt, at 4.01 (95% CI=2.58, 6.21), while those older than 30 had an IRR of 2.85 (95% CI=1.77, 4.59).

Death by Suicide

When we adjusted for period, sex, and age group, individuals diagnosed with Lyme borreliosis were found to have a 75% higher rate of suicide (IRR=1.75, 95% CI=1.18, 2.58)

FIGURE 2. Incidence rate ratios for any mental disorder with respect to Lyme borreliosis and according to number of new episodes, number of contacts, time since first hospital diagnosis, and age at first hospital diagnosis in Denmark (1994–2016)^a



^a Estimates for any mental disorder were adjusted for calendar period, sex, age group, civil status, educational level, socioeconomic status, and chronic medical comorbidity. Error bars indicate 95% confidence interval.

compared with those with no such diagnosis. A higher IRR was also noticed within 3 years of first diagnosis (IRR=2.41, 95% CI=1.25, 4.62) (Table 3).

Population Attributable Risks

Population attributable risks associated with mental disorders, affective disorders, suicide attempt, and suicide were low: 0.03% (95% CI=0.02, 0.04), 0.04% (95% CI=0.03, 0.06), 0.11% (95% CI=0.06, 0.16), and 0.08% (95% CI=0.02, 0.16), respectively.

Analysis by Neurologic Classification

Compared with the population not diagnosed with Lyme borreliosis, those classified specifically with neuroborreliosis did not have a significantly increased rate of mental disorders, affective disorders, or death by suicide; however, the rate of suicide attempt was increased (IRR=2.40, 95% CI=1.00, 5.77, N=5) (see Table S3 in the online supplement). When we combined the two neurologic classifications (meningitis and other neurologic manifestations), there was no significant difference in rates of mental disorders compared with the population not diagnosed with Lyme borreliosis (IRR=1.17, 95% CI=0.91, 1.52), or in rates of affective disorders (IRR=1.29, 95% CI=0.82, 2.03). Also, there was no significant difference in the rates of mental disorders between those with Lyme meningitis and those with other neurologic manifestations (IRR=0.99, 95% CI=0.59, 1.66, $p=0.980$).

Sensitivity Analysis

Compared with our primary analysis, similar rate ratios of mental disorders were found 1) when we restricted the sample to individuals with complete follow-up data since birth (IRR=1.32, 95% CI=1.12, 1.66); 2) when we restricted the sample to individuals without other somatic comorbidities as measured by a Charlson comorbidity index score of zero (IRR=1.29, 95% CI=1.20, 1.39); and 3) when we did not exclude those with a history of mental disorders and/or suicide attempt before 1994 (IRR=1.26, 95% CI=1.18, 1.35) (see Table S4 in the online supplement). Further, those diagnosed with Lyme borreliosis later than 2004 did not have a significantly different rate of mental disorders compared with those diagnosed before 2005 ($p=0.186$).

We further examined the impact of age. Individuals diagnosed with Lyme borreliosis before age 40 had a higher rate of mental disorders (IRR=1.33, 95% CI=1.15, 1.53, $p<0.0001$) compared with those age 40 or older. In age-stratified analyses, compared with individuals without a Lyme borreliosis diagnosis, the IRR for mental disorders for individuals with Lyme borreliosis younger than age 40 was 1.36 (95% CI=1.24, 1.49), whereas it was 1.27 (95% CI=1.13, 1.41) for individuals age 40 or older.

When we redefined a new episode to require at least a 6-month interval between clinical contacts for Lyme borreliosis, the IRR for mental disorders was 1.25 (95% CI=1.17, 1.34) for one episode and 2.05 (95% CI=1.55, 2.72) for two or more episodes. There were no statistically significant

TABLE 2. Association between Lyme borreliosis and affective disorders in Denmark (1994–2016), basic and fully adjusted incidence rate ratios

				Basic Adjusted Model ^a		Fully Adjusted Model ^a	
Characteristic	Cases With Affective Diagnosis	Incidence Rate per 100,000 Person-Years	95% CI	IRR	95% CI	IRR	95% CI
Number of episodes (more than 2 months between)							
No Lyme	218,358	189	189, 190	1		1	
1	288	261	231, 292	1.19	1.06, 1.34	1.37	1.22, 1.54
>1	36	407	274, 541	1.85	1.33, 2.56	2.07	1.49, 2.87
Number of contacts for hospital services							
No Lyme	218,358	189	189, 190	1		1	
1	210	269	233, 306	1.21	1.06, 1.39	1.37	1.20, 1.57
2	77	270	209, 330	1.26	1.00, 1.57	1.47	1.17, 1.84
3	22	268	156, 380	1.23	0.81, 1.86	1.5	0.99, 2.28
≥4	15	354	175, 534	1.65	0.99, 2.73	1.85	1.12, 3.07
Time since first diagnosis							
No Lyme	218,358	189	189, 190	1		1	
<1 year	16	267	136, 398	1.36	0.84, 2.23	1.53	0.94, 2.50
1–2 years	26	453	279, 627	2.3	1.56, 3.38	2.59	1.77, 3.81
2–3 years	47	224	160, 288	1.13	0.85, 1.50	1.29	0.97, 1.72
3–4 years	49	270	195, 346	1.32	1.00, 1.75	1.51	1.14, 2.00
>4 years	186	273	234, 312	1.16	1.01, 1.34	1.34	1.16, 1.55
Age at first diagnosis							
No Lyme	218,358	189	189, 190	1		1	
<10 years	56	237	175, 299	1.18	0.91, 1.53	1.84	1.42, 2.40
10–19 years	42	419	292, 546	2.04	1.50, 2.75	2.15	1.59, 2.90
20–29 years	37	400	271, 529	1.94	1.40, 2.67	1.55	1.13, 2.15
30–39 years	54	363	266, 460	1.67	1.28, 2.18	1.73	1.32, 2.25
40–49 years	46	233	166, 300	1.06	0.79, 1.41	1.21	0.91, 1.62
50–59 years	33	161	106, 216	0.68	0.49, 0.96	0.81	0.58, 1.14
60–69 years	42	293	205, 382	1.23	0.91, 1.67	1.41	1.04, 1.91
≥70 years	14	209	99, 318	0.87	0.51, 1.46	0.97	0.58, 1.64
Setting type							
No Lyme	218,358	189	189, 190	1		1	
Inpatient	209	277	239, 314	1.29	1.12, 1.47	1.5	1.31, 1.72
Emergency department	47	313	223, 402	1.43	1.07, 1.90	1.71	1.28, 2.27
Outpatient	68	239	182, 296	1.03	0.81, 1.30	1.11	0.88, 1.41

^a The basic adjusted model adjusted for sex, age, and calendar period; the fully adjusted model adjusted for sex, age, calendar period, educational level, socioeconomic status, civil status, and Charlson comorbidity index score. IRR=incidence rate ratio.

interactions between sex and Lyme borreliosis for any of the four outcomes.

Finally, compared with those without Lyme borreliosis, those with Lyme borreliosis had a small increased rate of fractures not involving the skull or spine after a hospital-based diagnosis of Lyme borreliosis (IRR=1.14, 95% CI=1.09, 1.20) (see Table S5 in the online supplement).

DISCUSSION

Our study represents the first nationwide epidemiologic investigation of mental disorders and suicidal behaviors after Lyme borreliosis. The results reveal that rates of any mental disorder, affective disorder, suicide attempt, and suicide are each higher after the diagnosis of Lyme borreliosis compared with no history of Lyme borreliosis. As the number of episodes of Lyme borreliosis increased, the rates of mental disorders, affective disorders, and suicidal behaviors increased. Temporal proximity to diagnosis also increased the rates of mental disorders, affective disorders, and

suicide. Rates of mental disorders remained significantly higher after adjustment for important confounding variables, including age, sex, calendar period, marital status, socioeconomic status, and medical comorbidity. These results support the early clinical reviews suggesting that Lyme borreliosis is associated with psychiatric manifestations (3, 4). The population attributable risks demonstrate that although mental disorders and suicidal behaviors may be increased after Lyme borreliosis, hospital-based cases of Lyme borreliosis are not a major contributor to the overall frequency of mental disorders or suicide in the general population.

A 42% higher rate of affective disorders and a 75% higher rate of suicide (in basic adjusted analyses) among people with Lyme borreliosis are of concern. Notably, the rate for affective disorders was highest during the first year after diagnosis and highest for completed suicide during the first 3 years after diagnosis. Although the IRR for suicide was elevated, our study also clarifies that, in Denmark, the absolute rate for suicide after Lyme borreliosis was low, accounting for 25

TABLE 3. Association between Lyme borreliosis and suicide attempt and suicide in Denmark (1994–2016), basic and fully adjusted incidence rate ratios

				Basic Adjusted Model ^a		Fully Adjusted Model ^a	
	Cases With Suicidal Behavior	Incidence Rate per 100,000 Person-Years	95% CI	IRR	95% CI	IRR	95% CI
Characteristic							
Suicide attempt							
Number of episodes (more than 2 months between)							
No Lyme	58,144	50	50, 50	1		1	
1	61	54	41, 68	1.18	0.91, 1.51	1.96	1.52, 2.52
>1	6	66	13, 119	1.56	0.70, 3.47	2.71	1.22, 6.03
Number of contacts to hospital services							
No Lyme	58,144	50	50, 50	1		1	
1	46	58	41, 75	1.26	0.95, 1.69	2.03	1.52, 2.71
>1	21	50	29, 72	1.09	0.71, 1.67	1.97	1.28, 3.02
Time since first diagnosis							
No Lyme	58,144	50	50, 50	1		1	
<3 years	15	45	22, 68	0.93	0.56, 1.54	1.23	0.74, 2.04
≥3 years	52	59	43, 75	1.31	1.00, 1.72	2.45	1.87, 3.22
Age at first diagnosis							
No Lyme	58,144	50	50, 50	1		1	
<10 years	17	71	37, 105	3.08	1.98, 4.77	4.01	2.58, 6.21
10–30 years	27	137	86, 189	0.94	0.66, 1.34	1.34	0.94, 1.91
>30 years	23	30	17, 42	0.98	0.61, 1.58	2.85	1.77, 4.59
Setting type							
No Lyme	58,144	50	50, 50	1		1	
Inpatient	43	56	39, 73	1.18	0.88, 1.60	2.02	1.50, 2.72
Emergency department	12	78	34, 123	1.76	1.00, 3.10	3.02	1.72, 5.32
Outpatient	12	41	18, 65	0.95	0.54, 1.68	1.48	0.84, 2.61
Suicide ^b							
Number of episodes (more than 2 months between)							
No Lyme	12,644	11	11, 11	1			
1	22	20	11, 28	1.68	1.10, 2.55		
>1	3	33	−4, 70	2.52	0.81, 7.82		
Number of contacts for hospital services							
No Lyme	12,644	11	11, 11	1			
1	16	20	10, 30	1.73	1.06, 2.83		
>1	9	21	7, 35	1.77	0.92, 3.40		
Age at first diagnosis							
No Lyme	12,644	11	11, 11	1			
<50 years	11	14	6, 22	1.71	0.95, 3.10		
≥50 years	14	33	16, 50	1.77	1.05, 2.99		
Time since first diagnosis							
No Lyme	12,644	11	11, 11	1			
<3 years	9	27	9, 45	2.41	1.25, 4.62		
≥3 years	16	18	9, 27	1.51	0.93, 2.47		
Setting type							
No Lyme	12,644	11	11, 11	1			
Inpatient	17	22	12, 32	1.87	1.16, 3.01		
Emergency department	3	19	−3, 42	1.64	0.53, 5.09		
Outpatient	5	17	2, 32	1.47	0.61, 3.53		

^a The basic adjusted model adjusted for sex, age, and calendar period; the fully adjusted model adjusted for sex, age, calendar period, educational level, socioeconomic status, civil status, Charlson comorbidity index score, and pre-Lyme psychiatric disorders. IRR=incidence rate ratio.

^b Because there were too few suicide cases (N=25), no fully adjusted model was carried out for suicide.

fatalities over a 22-year period, representing less than 0.2% of all suicides. Our findings are consistent with findings from previous studies, which demonstrated an increased rate of depression and suicidality after infection in general (1, 2) and after spirochetal and *B. burgdorferi* infections in particular (8–12, 27). The absence of an association with neuroborreliosis is also consistent with previous studies (13–15, 19). However, a

recent study raised the question of whether mental disorders may emerge in the first year after a laboratory diagnosis of neuroborreliosis, as psychiatric prescriptions were elevated during that period, presumably for pain and/or psychiatric indications (19).

Infection with *B. burgdorferi* can occur at any time in the life span; however the incidence peaks in childhood, with a

second peak in later middle age (28, 29). Similarly, the peak incidence of many major mental disorders occurs earlier in life, with nearly three-fourths starting by age 24 (30). Compared with individuals without Lyme borreliosis, we found the highest incidence rate ratios for mental disorders after Lyme borreliosis during each of the first four decades of life (<10, 10–19, 20–29, 30–39 years). Compared with those age 40 or older, our younger cohort had an approximately 33% higher rate of mental disorders after diagnosis of Lyme borreliosis. Our age-stratified analyses furthermore demonstrated increased incidence rate ratios in both the younger and older Lyme cohorts when compared with the non-Lyme population. This suggests that the mechanisms by which *Borrelia* infection may influence mental disorders are not limited to specific factors associated with childhood.

Our study demonstrated an increased rate of mental disorders after hospital-based diagnosis of Lyme borreliosis. The strength of this association further increased with number of episodes and temporal proximity to the original diagnosis. Still, our findings should not be considered specific to Lyme borreliosis infection, as hospital-based diagnoses of infections have previously been reported to be associated with an increased risk of mental disorders and suicidal behaviors (2, 31). To address specificity, we additionally examined the rate of fractures not involving the skull or spine (a non-mental health outcome) after exposure to Lyme borreliosis. Compared with the incidence rate ratios for such fractures after Lyme borreliosis, the incidence rate ratios were two-, three-, and sevenfold higher for mental disorders, affective disorders, and suicide attempts, respectively, after Lyme borreliosis, suggesting a higher risk of mental disorders than the examined proxy of a non-mental disorder. The 14% increased rate of fractures after hospital-based diagnosis of Lyme borreliosis might not be surprising if individuals receive prescriptions for psychiatric medications after hospitalization, as reported recently for neuroborreliosis (19), given that use of psychotropic medications is associated with an increase in risk of fractures (32).

Although our study design cannot establish causality, plausible mechanisms may link Lyme borreliosis to mental disorders and suicide. Infections and autoimmune diseases have been shown to increase the risk of subsequent mental disorders (1, 2). Inflammation, which has been associated with psychiatric disorders and suicidal behaviors (33, 34), is a natural component of the host response to *Borrelia* infection (29). Ongoing immune activation may result from either persistent infection or postinfectious processes. Elevated biomarkers of inflammation and immune activation have been demonstrated in posttreatment Lyme borreliosis, including IL-23 (35), CCL19 (36), and CRP (37). Microglial activation—a marker of central inflammatory processes—was demonstrated in a positron emission tomography brain imaging study of post-treatment Lyme borreliosis (38). Autoimmunity may play a role as well, as *B. burgdorferi*-triggered cross-reactive antibodies can target peripheral and central neural tissue (39, 40), and repeated infection may trigger a more robust

antineuronal antibody and neuronal activation response (41). Dysbiosis, due either to the disease itself or to the impact of antibiotics, may play a role in infection-related mood disorders (42) and in posttreatment Lyme borreliosis (43). Psychological factors may also contribute to mood disorders and suicide, possibly due to having a chronic painful or debilitating illness associated with uncertainty, economic stressors, and disability.

We hypothesized that patients with neuroborreliosis might have higher rates of mental disorders than the “general Lyme and other nonneurologic” group, largely because CNS infection with *B. burgdorferi* may lead to encephalitis, which can have psychiatric manifestations (5, 6). However, higher rates of mental disorders were not found in the neuroborreliosis group. Possible explanations include the following. First, if clinicians used the general code for Lyme borreliosis when diagnosing neurologic manifestations instead of the more specific code for neuroborreliosis, our ability to test this hypothesis with a registry-based data set would have been impaired. Nonspecific codes would also be used for individuals with Lyme borreliosis who have neuropsychiatric or other atypical manifestations of neuroborreliosis (44), as clinicians may not recommend a lumbar puncture. Third, a diagnosis of neuroborreliosis may lead clinicians not to record an evolving psychiatric diagnosis, as the neurologic diagnosis would be considered primary. Finally, the “general Lyme and other nonneurologic” group may experience increased mental distress due to other factors, such as the chronic pain that accompanies Lyme arthritis and posttreatment Lyme disease syndrome (45).

It is important to emphasize that the vast majority of mental disorders are unrelated to infection with *B. burgdorferi*. Nevertheless, in the case of, for example, an individual from a Lyme-endemic area with a new-onset affective disorder that is accompanied by a recent history of multisystem nonspecific signs and symptoms, such as an expanding rash or a viral-like syndrome followed by severe fatigue, asymmetric or migrating arthritis, myalgias, neuropathies, and/or cognitive problems, the medical history should be expanded to include Lyme borreliosis as one of the potential general medical conditions to rule out (45–47).

Borrelia genospecies and strains can differ by geographic region. Our report focuses on Lyme borreliosis in Denmark, where the predominant genospecies of *Borrelia* sensu lato consist of *Borrelia afzelii* and *Borrelia garinii*, similar to the rest of Europe. Our findings may therefore be generalizable to Europe but not to the United States, where *B. burgdorferi* sensu stricto causes virtually all cases of Lyme borreliosis. Because *B. burgdorferi* sensu stricto elicits a more robust host inflammatory response than the other genospecies (48), rates of mental disorders and suicidal behavior after Lyme borreliosis could potentially be higher in the United States than those reported for Denmark.

Strengths and Limitations

The strengths of this study are several. First, our population-based cohort study was large, and the data were collected

prospectively, covering 22 years of follow-up with little or no loss to follow-up. Second, the data in the analyses were adjusted for time-varying important and well-known risks for mental disorders and suicide. Third, the inclusion of various temporal and severity covariates adds strength to the examined associations. Fourth, because diagnoses of mental disorders are not recorded in the Danish National Patient Register, our study made use of the Psychiatric Central Research Register, thereby relying on a registered mental disorder diagnosis rather than inference based on other methods such as use of prescription medications.

First among the study's limitations is that because our sample identification relied on the National Danish Registry, which only records diagnoses made in the hospital setting, our results may not be generalizable to less severe cases of Lyme borreliosis that do not require hospital contact, as their care is provided in the community setting by general practitioners. This limitation also applies to mental disorders, as less severe mental disorders may be managed entirely in the community setting. Second, because our study design entailed counting mental disorders that emerged only after Lyme borreliosis, cases for which a mental disorder was a prodromal manifestation of borrelia infection would have been missed. Third, we cannot know for certain whether a clinical contact after 2 months marked a new episode or was related to persistent or recurrent symptoms from prior infection; it seems likely, however, that this marked a new episode, given the similar findings in the sensitivity analysis where we redefined a new episode as at least 6 months between hospital contacts. Fourth, given the predominance of nonspecific coding, it is not possible to assess whether rates differed by system involvement. Fifth, we were not able to address the question of whether delay in detection and treatment played a mediating role in the rate of subsequent mental disorders or suicidality. Sixth, because until 1994 the Danish Registries used ICD-8, which did not have a code for Lyme borreliosis, our study design excluded all individuals who had a history of mental disorders prior to 1994, as before that year, we were unable to determine associations between Lyme borreliosis and subsequent mental disorders. Sensitivity analysis that did not exclude individuals with mental disorders prior to 1994 revealed incidence rate ratios for mental disorders after Lyme borreliosis nearly identical to those in the original, more restrictive study sample; this was also the case for the sensitivity analysis, which included only the younger cohort of those born between 1994 and 2016.

CONCLUSIONS

In this nationwide registry-based retrospective cohort study, individuals with hospital contacts for Lyme borreliosis, compared with the general population without Lyme borreliosis, had increased rates of mental disorders, affective disorders, suicide attempts, and suicide. Although the absolute population risk is low, clinicians should be aware of potential psychiatric sequelae of this global disease.

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Examination Questions: Fallon et al.

1. Which best describes the association between Lyme disease and mental disorders?
 - a. The first six months after the diagnosis of Lyme disease is associated with the highest rate of mental disorders.
 - b. After adjustment for multiple confounding variables, this nationwide cohort study found no association between Lyme disease and mental disorders.
 - c. The rates of mental disorder are not associated with the number of episodes of Lyme disease.
 - d. Female gender was associated with higher rate of mental disorders after Lyme disease.
2. Which best describes the association between Lyme disease and suicidal behaviors?
 - a. Suicide after Lyme disease diagnosis accounts for a large proportion of the suicides in Denmark.
 - b. Lyme disease is unusual because other serious hospital-diagnosed infections have not been found to have increased rates of suicidal behaviors.
 - c. Although rates of affective disorders are increased after Lyme borreliosis, the rates of suicidal behaviors and completed suicide are not increased.
 - d. This nationwide study found a 75% higher rate of suicide after a hospital-based diagnosis of Lyme disease compared to those without this diagnosis.
3. What clinical findings below might alert the clinician to consider evaluating a patient further for Lyme borreliosis?
 - a. A recent history of multiple flea bites
 - b. A recent history of drinking unpasteurized milk
 - c. A recent history of migrating arthralgias, neuropathies, fatigue, and/or cognitive problems after exposure to a Lyme endemic area
 - d. A recent history of a small non-expanding rash with multiple pustules