**Title:**

Subjective health complaints and exposure to tick-borne infections in southern Norway

**Running title:**

Tick-borne infections and subjective health complaints

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**Conflict of interest**

The authors state that there is no conflict of interest.

**Data availability statement**
Research data are not shared due to ethical restrictions.

**Abstract**
Objectives: Whether tick-borne infections can cause chronic subjective health complaints is heavily debated. If such a causal connection exists, one would expect to find more health complaints among individuals exposed to tick-borne infections than among non-exposed. In this study, we aimed to assess if exposure to tick-borne infections earlier in life, evaluated by examination of serum for IgG-antibodies to tick-borne microbes, was associated with self-reported somatic symptom load.
Materials & Methods: All individuals with residential address in Søgne municipality in southern Norway, aged 18-69 years, were invited to participate in the study. Blood samples were analyzed for IgG-antibodies to different tick-borne microbes, and somatic symptom load was charted by the Patient Health Questionnaire-15 (PHQ-15).
Results: Out of 7424 invited individuals, 2968 (40.0%) were included in the study. We detected IgG-antibodies *to Borrelia burgdorferi* sensu lato (*Bb*) in 22.9% (95% CI 21.4 - 24.4). *Bb* seropositive individuals reported less frequently moderate to severe somatic symptom load (i.e. PHQ-15 sum score $\geq$10) than seronegative individuals (12.5% versus 17.7%, difference 5.2% (95% 2.1 - 8.0)). However, when adjusting for several other variables in a multivariable linear regression model, presence of serum IgG-antibodies to *Bb* was not associated with somatic symptom load. Presence of IgG-antibodies to other tick-borne microbes than *Bb*, or seropositivity to at least two microbes, were also not associated with somatic symptom load.
Conclusion: Presence of serum IgG-antibodies to tick-borne microbes was not associated with self-reported somatic symptom load.

**Keywords:**
Tick-borne diseases, Lyme borreliosis, seroepidemiologic studies, diagnostic self-evaluation, PHQ, medically unexplained symptoms

## Introduction

Subjective symptoms for which doctors cannot find a medical explanation, often termed "subjective health complaints" or "medically unexplained symptoms", represent a global health challenge [1]. The most common symptoms are fatigue, musculoskeletal pain, headache, gastrointestinal discomfort and dizziness. Such symptoms are frequently reported in European population studies [2-4], are frequent causes of consultations both in primary and secondary health care services [5,6], and are major causes of sick-leave and disability [1]. In several countries in northern Europe, the prevalence of medically unexplained symptoms has been reported to be up to 30% among patients referred to neurological outpatient clinics [7].

Patients with medically unexplained symptoms are often worried about undetected underlying disease despite thorough examination, and continue to search for a potential cause and treatment. Over the past years tick-borne diseases as borreliosis has been launched as a possible cause of chronic subjective health complaints, and many

want long-term antibiotic treatment despite evidence of no effect [8]. It has also been claimed that tick-borne diseases can trigger other neurological disorders, but also for this hypothesis evidence is lacking [9].

The tick *Ixodes ricinus* is widespread along the coastline in southern Norway [10], and borreliosis caused by *Borrelia burgdorferi* sensu lato (*Bb*) is the most common tick-borne disease [11]. A *Bb* infection can be asymptomatic, present as a local skin infection, or cause diseases as neuroborreliosis or borrelia arthritis. Furthermore, several "emerging" tick-borne pathogens (*Anaplasma, Babesia, Bartonella, Neoehrlichia* and *Rickettsia*) have been detected in ticks in northern Europe the last decades [12-15], but the knowledge about the human prevalence and clinical impact of these infections is still scarce. The clinical impact of simultaneous infections with more than one tick-borne pathogen is also largely unknown.

Exposure to tick-borne infections earlier in life can be charted retrospectively by examination of serum samples for presence of IgG-antibodies to specific microbes. If the hypothesis claiming a causal connection between tick-borne infections and subjective health complaints is correct, one would expect the group exposed to tick-borne infections earlier in life to have more health complaints than the non-exposed group. The aim of our study was to assess if presence of serum IgG-antibodies to tick-borne microbes was associated with increased self-reported somatic symptom load in a Norwegian population with high exposure to ticks.

## Materials & Methods

### *Recruitment area*

Søgne is a coastal area in Agder county, in the southernmost part of Norway. Søgne has a high abundance of ticks [10], and a high incidence of neuroborreliosis [16]. In January 2016, there was 11260 inhabitants in Søgne, of whom 7424 were aged from 18 to 69 years.

### *Recruitment strategies*

We invited all individuals aged 18-69 years, with residential address in Søgne municipality, to participate in the study. Two different recruitment strategies were used: From June 2015 to January 2016, eligible individuals who attended the general practitioner's center were invited to participate. Then, from January to June 2016, we sent an invitation letter to all eligible individuals not already enrolled in the study. Participants who did not respond to the questionnaire within 2-6 weeks after blood sampling were contacted once more by letter or phone for a reminder. Further details on the recruitment procedure have been published previously [4].

### *Serological tests*

Enzyme-linked immunosorbent assay (ELISA) tests were applied for detection of serum IgG antibodies to *B*b and Tick-borne encephalitis virus. Indirect immunofluorescent assay (IFA) tests were used for detection of serum IgG antibodies to *Anaplasma phagocytophilum*, *Babesia microti*, *Bartonella henselae*/B. q*uintana*, and *Rickettsia helvetica*/R. *conorii*. Because of substantial cross reactivity for IgG antibodies to *Bartonella henselae/B. quintana* and *Rickettsia helvetica/R. conorii*, the results are reported summarized for the *Bartonella* species and the *Rickettsia* species respectively. Analyzes and interpretation of results were performed according

to the manufacturer's instructions. All samples were analyzed for IgG-antibodies to *Bb*. A portion of the samples were analyzed for IgG-antibodies to other tick-borne infections, these samples were collected consecutively from the start of the study. Further details on the serological test procedures have been published previously[17].

*Questionnaire*

Participants were encouraged to answer the questionnaire online, but a paper version was also available on request. The questionnaire included questions about demographics, physical activity, exposure to tick-bites, previous tick-borne diseases, number of other diseases (0 - 22), Patient Health Questionnaire-15, Modern Health Worries-questionnaire [18] and Hospital Anxiety and Depression scale [19].

The Patient Health Questionnaire-15 (PHQ-15) charts prevalence and intensity of 15 symptoms during the last 4 weeks (www.phqscreeners.com), and the following sum score cut-off values have been stated for somatic symptom load; 0 - 4 points: normal, 5 - 9 points: mild, 10 - 14 points: moderate, 15 - 30 points: severe [20]. In a systematic review of questionnaires, the PHQ-15 questionnaire was recommended for assessing somatic symptoms in large scale studies [21]. The questionnaire has been validated in several studies and European languages [2,20,22], including Swedish.

*Sample size and statistics*

The hypothesis was that presence of serum IgG-antibodies to *Bb* is associated with increased somatic symptom load. Based on previous studies we assumed 20% prevalence of serum IgG-antibodies to *Bb*[23], and proportions with moderate to severe somatic symptom load in the seropositive and seronegative groups to be 20% and 15%, respectively [24]. On this background, a power- and sample size calculation (www.openepi.com) implied a required total sample size of 2832 to show an association between exposure to *Bb*-infection and moderate to severe somatic symptom load with 80% statistical power at a 5% significance level.

We did a multivariable regression analysis to adjust for various factors with possible association with somatic symptom load. No further power calculation was performed prior to the multivariable regression analysis. We chose linear model rather than a logistic model to avoid loss of power in the statistical processing. $P < 0.05$ was considered statistically significant. Statistical analyzes were performed using SPSS version 25.

*Ethics*

The study was approved by the Regional Committee for Medical and Health Research Ethics (approval number 2013/2082 and 2014/449), and the Research Unit at Sørlandet Hospital. All participants signed an informed consent, and they could withdraw their consent at any time. Seven randomly selected participants received a gift card valued NOK 500 for taking part in the study, otherwise there was no economic benefit of participation.

## Results

*Study participants and recruitment rates*

Out of 7424 invited individuals, 3571 responded. Serum and questionnaires were available from 2968, and they were included in the study. Demographic data and recruitment rates according to gender and age are described in table 1. Mean age was 48.6 years (95% CI 48.1 - 49.0) and the proportion of females was 54.6% (95% CI 52.8 -

56.4) in the study participants versus 41.9 years and 48.8% in the whole Søgne population aged 18-69 years. Further demographic characteristics have been published previously [4].

*Exposure to tick-bites and tick-borne infections*

Self-reported exposure to tick-bites and tick-borne diseases are described in table 2. Health complaints attributed to tick-borne disease by the responders themselves, or their general practitioner, were reported by 5.0% (95% CI 4.2 - 5.8) (147/2947). The prevalence of serum IgG-antibodies to different tick-borne pathogens are listed in table 3. Out of the 1058 responders tested for all six microbes, 5.7% (95% CI 4.3 - 7.1) (60/1058) were seropositive to at least two microbes. The prevalence of serum IgG-antibodies to *Bb* was higher among males than females (29.3% (394/1347) vs 17.6% (286/1621), difference 11.7% (95% CI 8.6 - 14.8)), and tended for both genders to increase with age. The seroprevalence of IgG-antibodies to *Bb* was 23.0% (283/1229) for samples tested to at least one other tick-borne pathogen than *Bb*, and 22.8% (397/1739) for samples tested only for *Bb*, difference 0.2% (95% CI -2.8 - 3.3). The prevalence of serum IgG-antibodies to *Bb* was 21.9% (267/1221) among participants recruited when visiting the general practitioner, and 22.9% (367/1606) among participants recruited by invitation, difference 1.0% (95% CI -2.1 - 4.1).

*Somatic symptom load*

PHQ-15 score was available for 2908 individuals. PHQ-15 mean score was 5.3 (95% CI 5.1-5.5). Moderate to severe somatic symptom load (i.e. PHQ-15 sum score $\geq$ 10) was reported by 16.5% (95% CI 15.1 - 17.8) (479/2908) of the responders. The most frequent single complaints were feeling tired/having low energy, pain in arms/legs/joints, back pain, headache and trouble sleeping. PHQ-15 sum score $\geq$ 10 was reported by 20.8% (248/1190) of the participants recruited when visiting the general practitioner's center, and by 13.2% (210/1592) of those recruited by invitation letter/phone, difference 7.6% (95% CI 4.8 - 10.5). Further characteristics of the somatic symptom load have been published previously[4].

*Somatic symptom load and exposure to tick-borne infections*

In univariable analysis (table 4) the prevalence of moderate to severe somatic symptom load was lower among individuals with serum IgG-antibodies to *Bb* than among individuals without. The prevalence of moderate to severe somatic symptom load was similar among individuals with serum IgG-antibodies to other tick-borne microbes than *Bb* and among individuals without.

Table 5 shows how various variables differed in *Bb* IgG-antibody seropositive and seronegative/equivocal participants. When these variables and *Bb* antibody status were entered into a multivariable regression model, presence of serum IgG-antibodies to *Bb* was not associated with somatic symptom load (table 6). In the multivariable model the following variables were associated with increased somatic symptom load: Anxiety and depression, number of other diseases, female gender, younger age, recruitment when attending the general practitioner's office, $\leq$ 6 years education after primary school, tick-bite earlier in life, erythema migrans earlier in life, less physical activity, and modern health worries (table 6). $R^2$ for the multivariable regression analysis was 0.393. Presence of IgG-antibodies to other tick-borne microbes than *Bb*, or seropositivity to at least two microbes, were not associated with somatic symptom load when entered in a multivariable regression model with other independent variables as listed in table 6 (data not shown, n = 1031).

**Discussion**

The main result of our study is that presence of serum IgG-antibodies to *Borrelia burgdorferi* sensu lato, Tick-borne encephalitis virus, *Anaplasma phagocytophilum*, *Babesia microti*, *Bartonella henselae/B. quintana* and *Rickettsia helvetica/R. conorii* were not associated with increased self-reported somatic symptom load. Neither was simultaneous seropositivity to at least two microbes. Also in previous studies exploring the association between IgG-antibodies to *Bb* and health complaints, no association was found [25,26]. However, these studies evaluated only serum IgG-antibodies to *Bb*, and in one [26], the participants were blood donors that might be a group with less health complaints than the general population.

Strengths of our study is the large number of participants from the general adult population, and that all serum samples were tested for IgG-antibodes to *Bb*. Weaknesses are potential biases as analysis of IgG-antibodies to other tick-borne microbes than *Bb* only in a selected portion, different recruitment strategies during the study-period, and higher mean age and a larger proportion of women in the study-population than in the whole Søgne population aged 18-69 years. However, the seroprevalence of IgG-antibodies to *Bb* did not differ between the group of samples tested only for *Bb*, and the group of samples tested for other tick-borne microbes. We therefore consider the selection of samples tested for antibodies to other microbes than *Bb* as serological representative. Most of the participants were recruited by invitation letter/phone, or when visiting the general practitioner's center. The participants recruited when visiting the general practitioner's center reported higher somatic symptom load than those recruited by invitation, but the seroprevalence of IgG-antibodies to *Bb* did not differ between these groups. Although if the recruitment procedure may have caused an overestimation of health complaints in the population, we will not expect such a bias to influence the association between presence of antibodies to tick-borne microbes and self-reported somatic symptom load. The skewed age and gender distribution in our sample may also have caused a bias since seroprevelence of IgG-antibodies to tick-borne pathogens and PHQ-15 score both show variation according to age and gender groups[4,17]. These factors are therefore adjusted for in the multivariable regression model.

In the regression analyses, self-reported exposure to tick-bite earlier in life, and erythema migrans earlier in life, were both weakly associated with increased somatic symptom load. This result is in contrast to a previous Norwegian study of blood donors in a region with somewhat lower prevalence of tick-borne infections, were no association between self-reported exposure to tick-bite and load of subjective health complaints was found [26]. Possible explanations for this discrepancy may be a greater tendency to attribute present somatic symptoms to previous tick-borne diseases in our high endemic region, or/and an overrepresentation in the study of individuals who attribute their symptoms to assumed tick-borne disease. A recall bias regarding exposure to tick-bite (and tick-borne diseases) more than one year ago can also be present since reporting tick-bite the last year was not associated with increased somatic symptom load. However, we cannot completely exclude that the association between reporting exposure to tick-bite or/and erythema migrans earlier in life, and increased somatic symptom load, may be due to previous tick-borne diseases not identified by the serological testing.

In conclusion, our study showed no association between presences of serum IgG-antibodies to tick-borne microbes and self-reported somatic symptom load. Although there was a weak association between self-reported somatic symptom load and self-reported previous exposure to tick-bites and erythema migrans, the result of our study does not support the hypothesis claiming a causal connection between tick-borne diseases and subjective health complaints.

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**Table 1: Study participants and recruitment rates**

| | Study participants n (%) | Recruitment rates % |
|---|---|---|
| All participants | 2968 | 40.0 |
| Gender | | |
| Male | 1347 (45.4) | 35.4 |
| Female | 1621 (54.6) | 44.7 |
| Age (years) | | |
| 18-29 | 275 (9.3) | 14.6 |
| 30-39 | 491 (16.5) | 35.9 |
| 40-49 | 736 (24.8) | 43.9 |
| 50-59 | 709 (23.9) | 51.1 |
| 60-69 | 757 (25.5) | 67.7 |
| Recruitment | | |
| Invitation | 1606 (54.1) | |
| Visit GP center | 1221 (41.1) | |
| Other[a] | 141 (4.8) | |
| Living with | | |
| Partner | 2287 (77.1) | |
| Children | 1294 (43.6) | |
| Alone | 392 (13.2) | |
| Education after primary school | | |
| ≤ 3 years | 1097 (37.0) | |
| > 3 - ≤ 6 years | 1117 (37.6) | |
| > 6 years | 636 (21.4) | |
| Net household income/month | | |
| > 20 000 NOK | 2606 (87.8) | |

[a]Own initiative or more than one answer to the question. Abbreviations: GP: General Practitioner

**Table 2: Self-reported exposure to tick-bites and tick-borne diseases**

| | % (95% CI) | n/N |
|---|---|---|
| Tick-bite earlier in life | 85.1 (83.8 - 86.4) | 2508/2947 |
| Three or more tick-bites earlier in life | 63.9 (62.2 - 65.6) | 1883/2947 |
| Tick-bite the last year | 33.4 (31.7 - 35.2) | 984/2942 |
| EM earlier in life | 24.6 (23.0 - 26.1) | 723/2942 |
| Other TBD than EM earlier in life | 5.0 (4.2 - 5.8) | 148/2942 |

Abbreviations: EM: erythema migrans, TBI: tick-borne disease

**Table 3: Prevalence of serum IgG antibodies to different tick-borne pathogens[a]**

| | % (95% CI) | n/N |
|---|---|---|
| *Borrelia burgdorferi* sensu lato | 22.9 (21.4 - 24.4) | 680/2968 |
| Tick-borne encephalitis virus[b] | 3.2 (2.2 - 4.2) | 37/1164 |
| *Anaplasma phagocytophilum* | 10.8 (9.0 - 12.5) | 125/1162 |
| *Babesia microti* | 2.1 (1.3 - 2.9) | 26/1229 |
| *Bartonella henselae* or/and *B. quintana* | 0.2 (0.0 - 0.4) | 2/1162 |
| *Rickettsia helvetica* or/and *R. conorii* | 4.1 (2.9 - 5.2) | 47/1157 |

[a]All 2968 samples were analyzed for antibodies to *Bb*, and 1157 - 1229 samples for antibodies to the other pathogenes, [b]Prevalence 1.4 % (95% CI 0.3 - 2.6) (6/419) when assessing only participants not reporting being vaccinated against tick-borne encephalitis virus or yellow-fever.

**Table 4: Proportion with PHQ-15 sum score ≥ 10 according to prevalence of serum IgG antibodies to different tick-borne pathogens**

| | Proportion with PHQ-15 score ≥ 10 % (n/N) | | Difference in proportion between groups % (95% CI) |
|---|---|---|---|
| | IgG seropositive | IgG seronegative or equivocal | |
| *Borrelia burgdorferi* sensu lato | 12.5 (83/665) | 17.7 (396/2243) | 5.2 (2.1 - 8.0) |
| Tick-borne encephalitis virus | 22.2 (8/36) | 20.0 (219/1094) | 2.2 (-8.6 - 18.2) |
| *Anaplasma phagocytophilum* | 17.4 (21/121) | 19.5 (197/1009) | 2.1 (-6.0 - 8.4) |
| *Babesia microti* | 19.2 (5/26) | 19.9 (233/1169) | 0.7 (-18.1 - 11.7) |
| *Bartonella henselae* or/and *B. quintana* | 0 (0/2) | 20.1 (226/1126) | 20.1 (-45.7 - 22.5) |
| *Rickettsia helvetica* or/and *R. conorii* | 24.4 (11/45) | 19.8 (214/1079) | 4.6 (-5.9 - 19.0) |
| ≥ 2 out of the 6 tested pathogens | 13.3 (8/60) | 19.7 (197/998) | 6.4 (-4.7 - 13.3) |

**Table 5: Characteristics and comparison of *Bb* IgG-antibody seropositive and seronegative/equivocal participants**

| | *Bb* IgG seropositive | *Bb* IgG seronegative or equivocal | Difference between groups (95% CI) |
|---|---|---|---|
| Male gender (%) | 57.9 | 41.7 | 16.2 (11.9 - 20.4) |
| Age (mean years) | 53.1 | 47.2 | 5.9 (4.8 - 7.0) |
| Recruitment GP (%) | 39.3 | 41.7 | 2.4 (-1.8 - 6.5) |
| Number of diseases (mean) | 1.0 | 1.0 | 0.0 (-0.1 - 0.1) |
| Living alone (%) | 13.2 | 13.3 | 0.1 (-3.0 - 2.9) |
| Education after primary school > 6 years (%) | 22.8 | 21.3 | 1.5 (-2.0 - 5.2) |
| Net household income > 20 000 NOK/month (%) | 90.6 | 87.5 | 3.1 (0.3 - 5.5) |
| Physical activity $\geq$ 6 hour/week (%) | 19.4 | 13.4 | 6.0 (2.8 - 9.4) |
| Tick bite earlier in life (%) | 91.3 | 83.3 | 8.0 (5.2 - 10.5) |
| Tick-bite the last year (%) | 33.1 | 17.8 | 15.3 (11.5 - 19.2) |
| Erythema migrans earlier in life (%) | 32.7 | 22.1 | 10.6 (6.7 - 14.6) |
| Modern health worries scale score (mean) | 2.0 | 2.0 | 0.0 (-0.1 - 0.1) |
| Hospital anxiety and depression scale sum score (mean) | 7.1 | 7.7 | 0.7 (0.1 - 1.2) |

Abbreviations: *Bb*: *Borrelia burgdorferi* sensu lato

**Table 6: Linear regression with PHQ-15 sum score as dependent variable[a]**

| Independent variable | | B | Standardized Beta | p-value |
|---|---|---|---|---|
| Anxiety and depression[b] | | 0.283 | 0.371 | <0.001 |
| Number of diseases[c] | | 1.040 | 0.271 | <0.001 |
| Male gender | | -1.677 | -0.181 | <0.001 |
| Age (years) | | -0.041 | -0.117 | <0.001 |
| Recruitment GP[d] | | 0.835 | 0.089 | <0.001 |
| Education after primary school | ≤ 3 years | 0.168 | 0.018 | 0.287 |
| | > 6 years | -0.656 | -0.059 | <0.001 |
| | Unknown | 0.137 | 0.005 | 0.757 |
| Tick bite earlier in life | | 0.733 | 0.056 | <0.001 |
| Erythema migrans earlier in life | | 0.409 | 0.038 | 0.014 |
| Physical activity[e] | | -0.175 | -0.032 | 0.031 |
| Modern health worries[f] | | 0.006 | 0.031 | 0.046 |
| Borrelia IgG seropositive | | -0.257 | -0.024 | 0.125 |
| Net household income[g] | | -0.181 | -0.016 | 0.343 |
| Tick-bite the last year | | -0.038 | -0.004 | 0.807 |
| Living alone | | 0.020 | 0.001 | 0.928 |

[a]n = 2846, [b]Hospital Anxiety and Depression scale sum score, [c]Number of diseases reported by the participant, [d]Recruited when visiting the GP center, [e]Mean hours physical activity/week (< 1 / ≥ 1 - < 3/ ≥ 3 - < 6 / ≥ 6), [f]Modern Health Worries questionnaire sum score, [g]Net household income/month (NOK < 10 000 / 10 000 - 20 000 / >20 000). Abbreviations: PHQ-15: Patent Health Questionnaire-15, B: Regression coefficient, GP: General Practitioner