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Somatic symptoms and fatigue in a Norwegian population with high exposure to ticks

Erik Thomas Thortveit[a,*], Åslaug Rudjord Lorentzen[a,b], Unn Ljøstad[a,c,1], Åse Mygland[a,c,d,1]

[a] Department of Neurology, Sørlandet Hospital Trust, PO Box 416, 4604, Kristiansand, Norway
[b] The Norwegian National Advisory Unit on Tick-Borne Diseases, Sørlandet Hospital Trust, Arendal, Norway
[c] Department of Clinical Medicine, University of Bergen, Bergen, Norway
[d] Department of Rehabilitation, Sørlandet Hospital Trust, Kristiansand, Norway

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ABSTRACT

Background: It is heavily debated whether tick-borne infections cause chronic subjective health complaints. If the hypothesis of a major causal connection is true, one would expect to find more subjective health complaints in a population with high exposure to ticks than in a population with less exposure. In the current study we aimed to assess somatic symptoms and fatigue in a Norwegian population with high exposure to ticks, compare our findings to normative data, and assess predictors of somatic symptom load.

Material and methods: All individuals aged 18–69 years with residential address in Søgne municipality in southern Norway were in the period June 2015 to June 2016 invited to participate in the study. Somatic symptoms were assessed by the Patient Health Questionnaire-15 (PHQ-15) and fatigue by the Fatigue Severity Scale (FSS). A multivariable regression analysis was performed to assess predictors of somatic symptom load.

Results: Out of 7424 invited individuals, 2971 (40.0%) returned the questionnaire. 85.1% of 2950 responders reported exposure to tick-bite. PHQ-15 mean sum score was 5.3, and 16.5% reported moderate to severe somatic symptom load (i.e. ≥ 10). FSS mean score was 3.2, and 29.8% scored above the cut-off value for fatigue (i.e. ≥ 4.0). All gender and age groups in our study population had equal or lower mean sum score on PHQ-15 than reported in Swedish normative data, and lower mean score on FSS than reported in Norwegian normative data. In multivariable regression the following factors were associated with higher somatic symptom load (listed in order of descending beta coefficient): Anxiety and depression, number of other diseases, female gender, younger age, recruitment when visiting general practitioner's office, ≤ 6 years education after primary school, tick-bite earlier in life, erythema migrans earlier in life, less physical activity, and modern health worries.

Conclusion: The study population reported high exposure to tick-bites, but less or equal level of somatic symptoms and less fatigue than found in normative data. There was a weak association between somatic symptom load and exposure to tick-bite and erythema migrans, possibly related to selection bias. Our findings do not support the hypothesis of a major causal connection between tick-borne infections and subjective health complaints.

1. Background

Health complaints as musculoskeletal pain, gastrointestinal discomfort, dizziness, headache and fatigue, are common (Aamland et al., 2012; Kjeldsberg et al., 2013; Kroenke, 2003). The prevalence and clinical presentation of these so-called subjective health complaints varies between countries and cultures (Wilhelmsen et al., 2007), but the phenomenon represents a global health care challenge and causes substantial economic and social costs. In Norway, subjective health complaints are one of the major causes of medical consultations and sick leave (Brage et al., 2013). In a cross-sectional study from 1996 with 1240 respondents, 80% reported musculoskeletal symptoms, and as many as 13% reported that the symptoms were substantial (Ihlebaek et al., 2002). The proportion of physicians-certified sick leave in Norway based on symptom diagnoses increased from 26% in 2000 to 39% in 2012 (Brage et al., 2013).

* Corresponding author.
E-mail addresses: erik.thomas.thortveit@sshf.no (E.T. Thortveit), aslaug.rudjord.lorentzen@sshf.no (Å.R. Lorentzen), unn.ljostad@sshf.no (U. Ljøstad), ase.mygland@sshf.no (Å. Mygland).
[1] These authors contributed equally to this work.

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Subjective health complaints often remain unexplained even after thorough medical examination. Consequently, there is a constant search, both among patients and health care providers, for potential etiologies. One of multiple theories is that the complaints may be caused by tick-borne infections. The tick *Ixodes ricinus* is endemic along most parts of the coastline in southern Norway (Jore et al., 2011), and various human pathogens can be transmitted by the tick. Lyme borreliosis, caused by *Borrelia burgdorferi* sensu lato, is the most prevalent human tick-borne infection (Eliassen et al., 2017). Borrelia infection can be asymptomatic, can present as a local skin infection, or more rarely, as disseminated disease. Other tick-borne microbes that can cause human infections are A*naplasma, Babesia, Bartonella, Neoehrlichia* and R*ickettsia*. The clinical impact and symptom burden of infections with these pathogens is largely unknown.

In the last decades it has been heavily debated whether tick-borne infections can cause chronic subjective health complaints (Auwaerter et al., 2011; Feder et al., 2007). Well-designed studies have neither found evidences of association between tick-borne infections and subjective health complaints (Feder et al., 2007), nor a benefit of long-time antibiotic therapy for subjective health complaints (Kaplan et al., 2003; Klempner et al., 2001; Krupp et al., 2003). Still, many patients with subjective health complaints receive long-time antibiotic treatment for assumed tick-borne infection. If the hypothesis of a causal connection between tick-borne infections and subjective health complaints is true, one would expect to find more subjective health complaints in a population with a high exposure to ticks, than in a population with less exposure. In this study we aimed to address this by assessing somatic symptoms and fatigue in a Norwegian population with high exposure to ticks, compare our findings to normative data, and assess predictors of somatic symptom load.

2. Material and methods

2.1. Recruitment area

Søgne is a coastal municipality in Vest-Agder County, in the southern part of Norway. The municipality has a high prevalence of ticks (Jore et al., 2011). *Borrelia burgdorferi* sensu lato was found in 22.3% of *Ixodes ricinus* ticks (adults and nymphs) collected in Søgne (Kjelland et al., 2010), and the municipality has a high incidence of Lyme neuroborreliosis (Ljostad et al., 2003). In January 2016, the municipality had 11,260 inhabitants, 7424 of whom were aged from 18 to 69 years.

2.2. Study participants and recruitment strategies

All individuals aged 18–69 years, with residential address in Søgne municipality, were invited to participate in a study of tick-borne infections and subjective health complaints. Participation entailed to give a blood sample (for biobanking) and to answer a questionnaire. We used two different recruitment strategies; From June 2015 to January 2016, eligible individuals who attended the general practitioner's center were informed about the study and invited to participate. Then, from January to June 2016, we sent a letter with study information to all eligible individuals not already enrolled in the study and announced that they would be contacted by phone within a few weeks. Invitation requests were then made by phone, and time for blood sampling agreed. Written informed consent was obtained prior to blood sampling and distribution of login key to a web-based questionnaire. Those 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. Recruitment and blood sampling were conducted by Søgne medical center, which is the only general practitioner center in the municipality.

2.3. Questionnaire and variables

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 infections, number of other diseases (0–22), regular medication, Patient Health Questionnaire-15, Fatigue Severity Scale, Modern Health Worries-questionnaire and Hospital Anxiety and Depression scale. The web-based questionnaire was designed so that each question had to be answered in order to proceed.

The Patient Health Questionnaire-15 (PHQ-15) charts prevalence and intensity of 13 somatic symptoms, fatigue/lack of energy, and difficulty sleeping during the last 4 weeks (www.phqscreeners.com). The answers are graded "not bothered at all" (0 points), "bothered a little" (1 point) and "bothered a lot" (2 points). Sum score ranges from 0 to 28 for men and from 0 to 30 for women (only women are asked about menstrual symptoms). 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 (Kroenke et al., 2002). A missing value for a PHQ-15 item was replaced with the average value of the other items if the number of missing values did not exceed 3 items (20%) (Kroenke et al., 2002; Spitzer et al., 1999). In a systematic review of questionnaires, the PHQ-15 questionnaire was recommended for assessing somatic symptoms in large scale studies due to well-established psychometric properties, relevant questions, and availability in many languages (Zijlema et al., 2013). A modified version of PHQ-15 was used for validation of the new diagnosis of somatic symptom disorder in the DSM V diagnostic manual (Dimsdale et al., 2013). The PHQ-15 has been validated in several studies and European languages (Kocalevent et al., 2013; Kroenke et al., 2002; Nordin et al., 2013), including Swedish. Normative data are also available from the Swedish population (Nordin et al., 2013). For the present study, we translated the PHQ-15 questionnaire into Norwegian based on the Swedish and English versions. Regarding culture and language, we consider the Norwegian and the Swedish population very similar.

The Fatigue Severity Scale (FSS) consists of nine statements assessing different aspects of fatigue. Each statement is scored on a 7-points scale ranging from "strongly disagree" (1 point) to "strongly agree" (7 points). A mean score is calculated, and cut-off for severe fatigue is usually set to a mean score $\geq$ 4.0 (Krupp et al., 1989). The FSS has been translated into Norwegian, validated in the general Norwegian population, and normative Norwegian data exists (Lerdal et al., 2005).

The Modern Health Worries-questionnaire (MHW) charts worries about different aspects of modernity on health, including toxic interventions, environmental pollution, tainted food and radiation (Indregard et al., 2013). It consists of 29 questions, and each answer is graded from "no concern" to "extreme concern" (0–5 points).

Hospital Anxiety and Depression Scale (HAD) assesses symptoms of anxiety and depression. It consists of 7 questions related to anxiety and 7 questions related to depression. Each question is scored from 0 to 3 points. Total scores range from 0 to 21 points for anxiety and depression, respectively (Bjelland et al., 2002).

2.4. Statistics

PHQ-15 and FSS scores were analyzed according to gender and age groups. Cronbach's α was calculated for PHQ-15 and FSS. Cronbach's $\alpha \geq 0.9$ indicates excellent, $0.9 > \alpha \geq 0.8$ good, and $0.8 > \alpha \geq 0.7$ acceptable internal consistency. Tests for categorical and continuous variables were used as appropriate. To compare continuous variables across groups we used independent samples t-test/one-way ANOVA for variables with a normal distribution, and Mann-Whitney U test/Kruskal-Wallis test for variables with a non-normal distribution. A multivariable linear regression model was used to assess predictors for somatic symptom load. Independent variables with $p < 0.20$ in univariable analysis were entered stepwise in the multivariable regression

Table 1
Study participant demographics and recruitment rates.

	n (%)	Recruitment rate (%)
All participants	2971	40.0
Gender		
Male	1350 (45.4)	35.5
Female	1621 (54.6)	44.7
Age		
18-34 years	506 (17.0)	19.6
35-54 years	1349 (45.4)	43.5
55-69 years	1116 (37.6)	63.9
Recruitment		
Invitation	1608 (54.1)	
Visit GP center	1222 (41.1)	
Other	141 (4.7)	
Nationality		
From Norway	2832 (95.3)	
Not from Norway	132 (4.4)	
Unknown	7 (0.2)	
Living with[1]		
Partner	2290 (77.1)	
Children	1296 (43.6)	
Alone	392 (13.2)	
Parents	96 (3.2)	
Others	52 (1.7)	
Education after primary school		
≤ 3 years	1098 (36.9)	
> 3 - ≤ 6 years	1117 (37.6)	
> 6 years	638 (21.5)	
Unknown	118 (4.0)	
Employment[1]		
Employed full time	1552 (52.2)	
Employed part time	572 (19.2)	
Retirement pension	302 (10.2)	
Disability pension full time	285 (9.6)	
Disability pension part time	131 (4.4)	
Unemployed	107 (3.6)	
Homemaker	95 (3.2)	
On sick leave full time	83 (2.8)	
On sick leave part time	70 (2.4)	
Net household income/month (NOK)		
< 10 000	67 (2.3)	
10 000 - 20 000	281 (9.5)	
> 20 000	2609 (87.8)	
Unknown	14 (0.5)	

[1] > 1 answer possible, Abbreviations: GP: General Practitioner.

model. A p-value < 0.05 was considered statistically significant. All statistical analyzes were performed using SPSS version 23.

2.5. Ethics

The study was approved by the regional committee for medical and health research ethics, and the Research Unit at Sørlandet Hospital. Written informed consent was obtained from all participants. Participants could at any time withdraw their consent. 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.

3. Results

3.1. Study participants and recruitment rates

Out of 7424 invited individuals, 3853 did not respond to the invitation and 600 did not return the questionnaire. 2971 individuals were included in the study. Recruitment rates according to gender and age groups are described in Table 1. Mean age in the study was 48.6 years (95% CI 48.1–49.0) versus 41.9 years (95% CI 41.5–42.2) in the whole Søgne population aged 18–69 years (p < 0.001). The proportion of females was 54.6% in the study versus 48.8% in the whole Søgne population aged 18–69 years (p < 0.001). Recruitment rates were lowest among younger age groups and males. Demographics are shown in Table 1.

Table 2
PHQ-15 mean sum score according to gender and age.

		Søgne		Swedish normative data	
Gender	**Age (years)**	**n**	**PHQ-15 mean sum score (95 % CI)**	**n**	**PHQ-15 mean sum score (95 % CI)**
Male	18 - 34	195	3.9 (3.3 - 4.5)	265	4.7 (4.3 - 5.1)
	35 - 54	613	4.2 (3.8 - 4.5)	455	5.1 (4.7 - 5.5)
	≥ 55[1]	516	3.8 (3.5 - 4.2)	788	5.5 (5.2 - 5.7)
Female	18 - 34	306	7.4 (6.9 - 8.0)	441	7.8 (7.4 - 8.2)
	35 - 54	719	6.6 (6.3 - 7.0)	597	6.8 (6.4 - 7.2)
	≥ 55[1]	562	5.5 (5.2 - 5.9)	860	7.1 (6.8 - 7.5)

[1] Age 55–69 years in data from Søgne and 55–79 years in Swedish normative data, Abbreviations: PHQ-15: Patent Health Questionnaire-15, CI: Confidence Interval.

3.2. Exposure to tick-bites and tick-borne infections

Out of 2950 responders, 2511 (85.1%) reported at least one tick-bite earlier in life, 1885 (63.9%) more than two tick-bites, and 985 out of 2945 (33.4%) tick-bite the last year. The proportion reporting at least one tick-bite earlier in life did not differ between men and women (p = 0.739), between age groups (p = 0.999), or between those recruited when attending the general practitioner's office and those recruited by invitation (p = 0.731). Out of 2945 responders, 723 (24.6%) reported erythema migrans earlier in life.

3.3. Somatic symptom load

PHQ-15 mean sum score was 5.3 (95% CI 5.1–5.5), and 16.5% had moderate to severe somatic symptom load (i.e. PHQ-15 sum score ≥ 10). Table 2 shows PHQ-15 mean sum scores in our population and Swedish normative data in relation to gender and age groups. Due to missing data for up to three PHQ-15 items, values were imputed for n = 17 (0.6%) to calculate sum scores. Women reported more somatic symptoms than men (PHQ-15 mean sum score 6.4 (95% CI 6.1–6.6) versus 4.0 (95% CI 3.8–4.2)), corresponding to mild symptom load for women and normal symptom load for men. PHQ-15 mean sum score was higher among women than among men in all age groups. The proportion with moderate to severe somatic symptom load was also higher among women (22.6%) than among men (9.1%) (p < 0.001). Individuals recruited when visiting general practitioner's center reported higher somatic symptom load than individuals invited by letter/phone, with PHQ-15 mean sum score 6.1 (95% CI 5.8–6.4) versus 4.7 (95% CI 4.5–4.9), respectively. Cronbach's α for PHQ-15 was 0.83.

The prevalence and intensity of the different somatic symptoms the last 4 weeks for men and women are shown in Fig. 1. Feeling tired or having low energy was the most prevalent symptom, followed by pain in arms/legs/joints, back pain, headache and trouble sleeping. The prevalence of each symptom in different age groups is shown in Fig. 2.

In the multivariable regression analysis, the following factors were associated with higher somatic symptom load (listed in order of descending standardized beta coefficient): Anxiety and depression, number of other diseases, female gender, younger age, recruitment when visiting general practitioner's office, ≤ 6 years education after primary school, tick-bite earlier in life, erythema migrans earlier in life, less physical activity, and modern health worries. The impact of each factor and corresponding p-values are shown in Table 3. R square was 0.39. Exposure to tick-bite the last year was not entered in the multivariable model (p = 0.969 in univariable analysis).

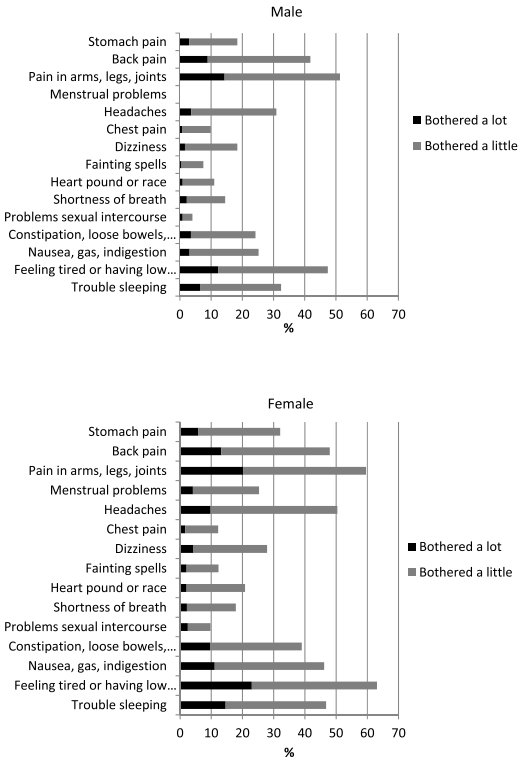

Fig. 1. Prevalence and intensity of somatic symptoms according to PHQ-15. Abbreviations: PHQ-15: Patient Health Questionnaire-15.

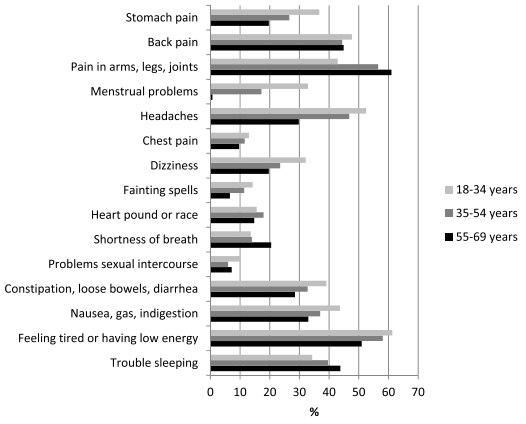

Fig. 2. Prevalence of somatic symptoms in different age groups according to PHQ-15[1].
[1]Proportion of participants in each age group bothered "a little" or "a lot", Abbreviations: PHQ-15: Patient Health Questionnaire-15.

3.4. Fatigue

FSS mean score was 3.2 (95% CI 3.1–3.2), and 29.8% had FSS score above the cut-off value for fatigue (i.e. FSS score ≥ 4). Table 4 shows FSS mean scores in our population and Norwegian normative data in relation to gender and age groups. Women reported more fatigue than men (FSS mean score 3.3 (95% 3.2–3.4) versus 3.0 (95% CI 2.9–3.1)). Recruitment when visiting general practitioner's center was associated with more fatigue than recruitment by letter/phone (FSS mean score 3.4 (95% 3.3–3.5) versus 3.0 (95% CI 2.9–3.1)). Cronbach's α for FSS was 0.94.

3.5. Modern health worries

Mean MHW-score (n = 2891) was 2.11 (95% CI 2.07–2.15) for women and 1.86 (95% CI 1.82–1.90) for men. In a study from the general working population in Norway (applying a modified version of the MHW-questionnaire), mean MHW-score (n = 569) was 2.16 (95% CI 2.12–2.21) for women and 1.84 (95% CI 1.81–1.88) for men (Indregard et al., 2013).

Table 3
Multivariable linear regression with PHQ-15 sum score as dependent variable (n = 2850).

Independent variable		B	Standardized Beta	p-value
Anxiety and depression[1]		0.284	0.373	< 0.001
Number of diseases[2]		1.049	0.273	< 0.001
Male gender		−1.707	−0.185	< 0.001
Age (years)		−0.044	−0.120	< 0.001
Recruitment GP[3]		0.851	0.091	< 0.001
Education after primary school	≤3 years			0.275
	> 6 years	−0.737	−0.066	< 0.001
	Unknown			0.744
Tick-bite earlier in life		0.683	0.052	0.001
Erythema migrans earlier in life		0.395	0.037	0.016
Physical activity[4]		−0.192	−0.035	0.017
Modern health worries[5]		0.006	0.031	0.046
Net household income[6]				0.263
Living alone				0.772

[1] Hospital Anxiety and Depression scale sum score, [2]Number of diseases reported by the participant, [3]Recruited when visiting the GP center, [4]Mean hours physical activity/week (< 1 / ≥ 1 - < 3/ ≥ 3 - < 6 / ≥ 6), [5]Modern Health Worries questionnaire sum score, [6]Net household income/month (NOK < 10 000 / 10 000–20 000 / > 20 000), Abbreviations: PHQ-15: Patent Health Questionnaire-15, GP: General Practitioner.

Table 4
FSS mean score according to gender and age.

		Søgne		Norwegian normative data	
Gender	**Age (years)**	**n**	**FSS mean score (95 % CI)**	**n**	**FSS mean score (95 % CI)**
Male	18 - 29	108	2.7 (2.5 - 3.0)	151	3.8 (3.6 - 4.0)
	30 - 39	197	3.1 (2.8 - 3.3)	202	3.9 (3.7 - 4.1)
	40 - 49	324	3.0 (2.8 - 3.1)	180	3.7 (3.5 - 3.9)
	50 - 59	338	3.1 (2.9 - 3.3)	162	3.8 (3.6 - 4.0)
	≥ 60[1]	353	3.0 (2.8 - 3.1)	196	4.1 (3.9 - 4.3)
Female	18 - 29	164	3.4 (3.1 - 3.6)	201	3.8 (3.6 - 4.0)
	30 - 39	285	3.3 (3.1 - 3.5)	223	4.1 (3.9 - 4.3)
	40 - 49	407	3.5 (3.3 - 3.7)	204	4.0 (3.8 - 4.2)
	50 - 59	359	3.2 (3.0 - 3.3)	166	4.2 (4.0 - 4.4)
	≥ 60[1]	374	3.1 (2.9 - 3.2)	174	4.2 (4.0 - 4.4)

[1] Age 60–69 years in data from Søgne and 60–81 years in Norwegian normative data, Abbreviations: FSS: Fatigue Severity Scale, CI: Confidence Interval.

3.6. Anxiety and depression

HAD mean sum score (n = 2905) was 4.52 (95% CI 4.39–4.65) for anxiety and 3.04 (95% CI 2.92–3.15) for depression. In a Norwegian large-scale population based study from Nord-Trøndelag county HAD mean sum score was 4.02 (95% CI 3.98–4.05) for anxiety (n = 39277) and 3.33 (95% CI 3.30–3.35) for depression (n = 39573) (Leiknes et al., 2016).

4. Discussion

This study is the first to chart somatic symptom load and fatigue in an adult general population living in a high endemic area for tick-borne infections. Out of 2950 responders, as many as 85.1% reported exposure to tick-bite. This confirms a high exposure to ticks in our study population.

The mean burden of somatic symptoms in our population as measured by the PHQ-15 mean sum score was 5.3, a value within the range (5–9) defined as mild symptom load. A proportion of 16.5% had a moderate to severe somatic symptom load, as defined by a PHQ-15 sum score ≥ 10. Compared to Swedish normative PHQ-15 data, our population reported less or equal level of somatic symptom load in different age groups of males and females (Nordin et al., 2013). The mean level of fatigue as measured by FSS was also lower in our population than in Norwegian normative data adjusted for age and gender (Lerdal et al., 2005). The mean FSS score was 3.2, a value that is lower than the cut-off value for fatigue (≥ 4). These results do not support the hypothesis of a major causal connection between tick-borne infections and subjective health complaints.

Somatic symptom load obviously depends on a variety of factors. A multivariable regression analysis showed that anxiety and depression, number of other diseases, female gender, younger age, recruitment when visiting general practitioner's office, ≤ 6 years education after primary school, less physical activity and modern health worries were associated with higher somatic symptom load. We also found a weak association between exposure to tick-bite and erythema migrans earlier in life and somatic symptom load. This is opposed to another study of blood donors in a Norwegian area with lower prevalence of tick-borne infections where no association was found between subjective health complaints and exposure to tick-bite (Hjetland et al., 2015). The weak association in our study may be related to a greater tendency to attribute somatic symptoms to tick-bite in high endemic areas, and a possible over-representation of people with this assumption in our sample of the population.

The strength of our study is the large number of participants. The overall recruitment rate for answering the questionnaire was 40.0%. This is comparable to other Norwegian and Swedish studies with focus on somatic symptom load (Ihlebaek et al., 2002; Nordin et al., 2013). Applying a web-based questionnaire ensured a low proportion of missing data among the responders; 2.6% (2.0% after imputation) for PHQ-15 and 2.1% for FFS. However, some selection biases cannot be ruled out. There was a low recruitment rate among individuals aged 18–34 years (19.6%), and to a lesser extent also among men (35.5%). In the youngest age group there might be an over-recruitment among individuals with high somatic symptom load. Furthermore, recruitment among visitors to general practitioner's center probably results in finding of more health complaints than if all participants had been recruited by invitation letter/phone. As expected, the group recruited when visiting general practitioner's center, reported more somatic symptoms and more fatigue than the group recruited by invitation letter/phone. However, all these potential biases probably overestimate rather than underestimate the burden of health complaints in our population.

Further, we are aware that application of normative data as basis for comparison are subjected to some uncertainty in general, and in our study especial as the exposure to ticks and tick-borne infections is unknown in the normative samples for PHQ-15 and FSS. For PHQ-15 the normative sample is from the Västerbotten region in Northern Sweden, and for FSS from a nationwide Norwegian sample. It is therefore reasonable to expect a lower exposure to ticks and tick-borne infections in these normative samples than in our study population living in a high endemic area (Jore et al., 2011; Ljostad et al., 2003) for tick-borne infections. Differences in demographic factors and prevalence of other diseases are also potential confounders.

In conclusion, our study population reported high exposure to tick-bites, but less or equal level of somatic symptoms and less fatigue than found in normative data. The study provides no evidence that subjective health complaints are more common in a population with high exposure to ticks compared to the population as a whole. Further studies are needed to confirm this, although our study would suggest that any impact of tick-bite exposure on the prevalence of subjective health complaints would be at the most small.

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Declarations of interest

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[1]Søgne medical center, PO box 1082, 4683, Søgne, Norway

[2]Department of Neurology, Sørlandet Hospital Trust, PO Box 416, 4604, Kristiansand, Norway.

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