Quality of Life Research (2022) 31:2423–2434
https://doi.org/10.1007/s11136-022-03094-2

Coping strategies and quality of life in patients with chronic symptoms visiting a Lyme Center in a Dutch teaching hospital

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Accepted: 17 January 2022 / Published online: 5 February 2022

Abstract

Introduction Little is known on coping strategies in patients with chronic symptoms suspected of Lyme borreliosis (LB). Different coping strategies might influence quality of life (QoL). We assessed coping strategies and QoL in patients with chronic symptoms suspected of LB.

Methods Adult patients referred to the Lyme Center Apeldoorn were included (November 2019–April 2021). Participants completed the RAND-36 to assess QoL and the Utrecht Coping List to assess coping strategies. Patient data were extracted from medical records. Patients were categorized based on clinical LB and serology. Linear regression analyses were conducted to examine an association between coping strategies and QoL subscales.

Results Included were 201 patients. Patients suspected of LB had a different coping profile and lower QoL compared to the reference population. Patients with negative serology and no clinical LB scored lowest on all QoL subscales. In multivariate analyses, correcting for age, gender, comorbidity, and patient category, a negative association was found between passive coping and the QoL subscales physical functioning (β(SE) = − 1.1(0.5)), social functioning (β(SE) = − 3.3(0.5)), role limitations (emotional) (β(SE) = − 5.5(0.8)), mental health (β(SE) = − 3.7(0.3)), vitality (β(SE) = − 2.3(0.3)), pain (β(SE) = − 2.3(0.5)), and general health (β(SE) = − 2.7(0.3)). A negative association was also found between palliative coping and the QoL subscale role limitations (physical) (β(SE) = − 1.8(0.6)) and between expressing emotions and mental health (β(SE) = − 1.3(0.6)). A positive association was found between active coping and the QoL subscales mental health (β(SE) = 1.0(0.3)) and role limitations (emotional) (β(SE) = 1.9(0.8)).

Conclusion In patients suspected of LB, dysfunctional coping strategies were associated with worse quality of life. There is a need for interventions that can guide patients with chronic symptoms suspected of LB towards more active coping and increase QoL.

Keywords Lyme borreliosis · Lyme disease · Borrelia burgdorferi · Coping · Quality of life · UCL · RAND-36

Introduction

Lyme borreliosis (LB) is an infectious disease transmitted by ticks infected with spirochetes belonging to the species *Borrelia burgdorferi* sensu lato. An expanding skin rash occurring around the site of the tick bite, called an erythema migrans (EM), is the most frequently reported manifestation of localized infection. In the Netherlands, the incidence of EM increased substantially from 39 per 100,000 inhabitants in 1994 to 140 per 100,000 inhabitants in 2014 [1]. Other less common, but typical manifestations of disseminated LB are Lyme arthritis, Lyme carditis, Lyme neuroborreliosis, and acrodermatitis chronica atrophicans (ACA) [2].

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Not all patients develop or notice an EM, and complementary to the clinical signs and a history of a tick bite, serology is used to confirm infection in patients suspected of disseminated LB. Immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against *Borrelia burgdorferi* are measured in serum by a two-tiered approach using an immunoassay and immunoblot [3]. However, positive serological result does not discriminate between previous and active infection, since IgG or IgM antibodies can remain positive for up to 20 years after infection and treatment [4]. The considerable background rate of Borrelial seropositivity in several populations further complicates the interpretation of serological tests for LB [4].

Although specific manifestations of LB resolve during or after antibiotic treatment [5], there is controversy in the literature to what extent a Borrelia infection can cause chronic non-specific symptoms. Chronic non-specific symptoms can consist of musculoskeletal pain, neurocognitive difficulties, and most frequently fatigue [6]. To date, a pathophysiological explanation for non-specific symptoms following LB is lacking. Previous research showed that the prevalence of chronic non-specific symptoms did not differ between patients with versus without signs of infection, i.e. positive serology or a history of clinical LB [6]. Persistent non-specific symptoms may greatly impact quality of life (QoL) [7, 8]. QoL is a broad concept, including physical functioning, social functioning, and mental health. Prolonged antibiotic treatment was not found to be beneficial [9]. Although research is being done concerning the role of genetic factors and the immune system [10], there remains an unmet need for personalized treatment recommendations that take into account individual characteristics.

Coping refers to the strategies used in handling stressful situations and include behavioral and psychological responses [11]. While there is general agreement that coping matters in the way people deal with stressful life events, there are various models for coping in patients with chronic illnesses. Previous studies, in patients with other illnesses than LB, included coping of the patient, but also family coping and dyadic adjustment, as well as depression and anxiety levels in patients and partners [12, 13]. In addition, the definition of coping differs among studies and different standardized questionnaires are used to asses coping [14–16].

In other patient populations, studies have been performed concerning a relation between coping strategies and QoL [11, 17, 18]. Despite the aim of escaping distress temporarily, both passive and palliative coping strategies are considered generally ineffective in reducing distress over the long term, as they can interfere with the ability of patients to effectively deal with their impairments [19, 20]. Active coping on the other hand, is considered generally effective in dealing with impairments and thereby reducing distress generated by these impairments [19, 21].

Little is known on which coping strategies are used by patients with chronic symptoms suspected of LB and whether these differ between patients with and without signs of LB infection. Unique in this study was that patients were categorized according to Lyme serology results and clinical LB. We hypothesized that patients with negative Lyme serology and no clinical LB use different coping strategies than patients who do have signs of LB infection (i.e. positive serology and/or clinical LB). Different coping strategies might be associated with QoL in patients with chronic symptoms suspected of LB. Possibly coping strategies and QoL can be targeted in interventions. The main objective of this study was to assess coping strategies and QoL in patients with chronic symptoms suspected of LB.

Methods

Subjects

This observational cross-sectional study was performed at the Lyme Center Apeldoorn (LCA), which is part of Gelre hospitals. The LCA is located in a Lyme endemic region in the Netherlands and serves as a secondary and tertiary referral center. Patients are diagnosed and treated according to Dutch guidelines for LB [22]. The LCA is a multidisciplinary center to which patients are referred by general practitioners, occupational physicians, and medical specialists from all over the Netherlands. Referred patients often experience long-lasting or chronic symptoms after antibiotic treatment for LB, or are experiencing symptoms suspected of LB without having observed a tick bite or EM. In the Netherlands, patients with an EM are generally diagnosed and treated by their general practitioner and not referred to a Lyme center. Patients eligible for inclusion were: ≥ 18 years of age; referred to the LCA; had both an immunoassay and an immunoblot test performed by the LCA prior to medical consultation; and visited the LCA for medical consultation between November 2019 and April 2021. Eligible patients received information concerning the study and a link for an online questionnaire via email. In the first question of the questionnaire patients were asked for consent. Questionnaires were completed before their medical consultation at the LCA, to prevent possible bias from information given during medical consultation.

Patient medical records

Data concerning the medical consultation and laboratory diagnostics for LB were extracted retrospectively from the patient medical records and recorded using Castor Electronic Data Capture (EDC). Variables included gender, age, medical referrer, comorbidities, current or past LB

manifestations (i.e. EM, multiple EM, Lyme arthritis, Lyme neuroborreliosis, ACA, Lyme carditis, borrelial lymphocytoma, Lyme uveitis), non-specific symptoms (i.e. fatigue, sleep disturbances, musculoskeletal pain), EM and tick bites in the previous 5 years, antibiotic treatment for LB in the previous 5 years, activities with exposure to ticks, and IgM and IgG immunoassay and immunoblot results. Comorbidities were categorized according to the International Classification of Diseases 11th revision [23]. Per patient it was recorded in how many of these categories they had at least one comorbidity.

Patients were categorized based on serological and clinical data into four categories: (1) positive IgG serology and clinical LB, (2) positive IgG serology and no clinical LB, (3) negative IgG serology and clinical LB, and (4) negative IgG serology and no clinical LB [24]. Positive serology was defined as an equivocal or positive immunoassay in combination with a positive immunoblot. Negative serology was defined as a negative or indeterminate immunoblot irrespective of the immunoassay outcome. Serological testing was performed at the laboratory of Medical Microbiology and Infection Prevention of Gelre hospitals. An IgM LIAISON chemiluminescent immunoassay (CLIA) (Enzygnost Borreliosis IgM; Siemens, Erlangen, Germany) and IgG CLIA (Enzygnost Lyme link VlsE/IgG; Siemens, Erlangen, Germany) were followed by an immunoblot (recomLine Borrelia IgM and IgG; Mikrogen, Neuried, Germany). Clinical LB was defined as having an EM, multiple EM, Lyme arthritis, Lyme neuroborreliosis, ACA, Lyme carditis, borrelial lymphocytoma, or Lyme uveitis at time of medical consultation or in the past. Having solely atypical symptoms was not considered clinical LB.

Standardized questionnaires

Utrecht Coping List

The Utrecht Coping List (UCL) was used to measure coping strategies of the participants, i.e. how they deal with stressful situations in general. This Dutch questionnaire consists of 47 items to assess seven different coping strategies [15]. All items are answered on a 4-point scale: 'never' (1 point), 'sometimes' (2 points), 'often' (3 points), and 'very often' (4 points). Scores of items concerning the same coping strategy were summed to form a total score, with high scores indicating an increased tendency towards using that specific coping strategy. The seven coping strategies are considered not mutually exclusive and may be found in various combinations. Active approach (7 items, range 7–28) refers to a person's ability to oversee a situation, be focussed on the problem and confidently intend to solve it. Palliative reaction (8 items, range 8–32) refers to distracting oneself with other activities, such as smoking or drinking to not have to deal with the problem. Avoidance (8 items, range 8–32) entails not facing the problem and waiting what will happen. Seeking social support (6 items, range 6–24) consists of a person's tendency towards discussing the problem with someone and asking for help or comfort. Passive reaction (7 items, range 7–28) refers to being overwhelmed by the problem, being incapable of activity, and worrying about the past. Expressing emotions (3 items, range 3–12) assesses a person's tendency to show emotions like anger, fear, or annoyance. Reassuring thoughts (5 items, range 5–20) covers being capable of holding on to a positive mindset, believing there are worse things in life. Three items were not included in these strategies, but are included in the questionnaire [15, 25]. These three items were excluded from data analysis. The UCL can be considered to be reliable and valid [26]. Dutch reference data were available from a random male ($n = 1493$) and female ($n = 712$) sample [15].

RAND-36

Health-related QoL was assessed using the Dutch version of the RAND-36 survey. The RAND-36 is a valid, reliable and internationally used questionnaire measuring QoL that consists of 36 items on eight different scales (minimum 0, maximum 100): physical functioning (10 items), role limitations because of physical health problems (4 items), role limitations caused by emotional problems (3 items), vitality (4 items), mental health (5 items), social functioning (2 items), pain (2 items), and general health (5 items) [27–30]. The single item assessing health change included in the questionnaire, was excluded from data analysis. Questions reflect the previous four weeks. On all subscales, lower scores indicate worse QoL. Dutch reference data were available concerning 1063 respondents from the general population [28].

Statistical analysis

Statistical analyses were performed in R version 4.0.4. Anonymised clinical, laboratory and questionnaire data were exported from Castor EDC and imported and merged in R. Questionnaire data were analyzed based on the specific instructions accompanying the questionnaires [15, 28]. Data distributions were explored by calculating means, medians, and using histograms. Mean with standard deviation (SD) and median with range were used to describe continuous variables. Frequencies were used to describe categorical variables. Subgroup analyses concerning gender, age (dichotomous variable split by median), and patient categories were performed using independent sample t-test or ANOVA when comparing respectively two or more than two groups. Study data were compared to reference data using summary statistics (i.e. mean, SD, and sample size) as input for independent sample t-test. Patients scored high on UCL

subscales if they scored ≥ 80th percentile of the reference data [15]. Correlations between UCL scales and RAND-36 scales were calculated using Spearman's rank correlation coefficients. In linear regression analyses, patient characteristics (i.e. age, gender, comorbidities, and patient category) and coping strategies that correlated significantly ($p < 0.05$) and meaningfully ($\rho > 0.30$) with RAND-36 subscales were included. Variables with a p value < 0.20 were included in multivariate analyses, with QoL subscales as dependent outcome variable to study independent effects of patient characteristics and coping strategies. Stepwise backward selection was performed ($p < 0.05$).

The study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). A non-WMO declaration (nr. 201202) was received from the Medical Ethics Committee of Isala hospital, Zwolle, the Netherlands.

Results

A total of 235 patients suspected of LB were referred to the LCA (Fig. 1). Twelve patients were excluded because of age < 18 years ($n = 9$), having no email address ($n = 2$) or a language barrier ($n = 1$). Of the 223 patients asked for participation, eleven were excluded as they did not complete the questionnaire ($n = 6$) or canceled their visit to the LCA ($n = 5$). Another eleven of the 212 eligible patients were excluded for not giving informed consent ($n = 8$) or completing the questionnaire after instead of prior to the medical consultation ($n = 3$). A total of 201 patients were included in the analysis.

Demographics, exposure, and disease characteristics of the included patients are presented in Table 1. The median age was 50 years (range 18–85 years) and slightly more females (110, 54.7%) than males (91, 45.3%) were included. The median time between completing the questionnaire and medical consultation was 21 days (range 0–81 days). Of 201 patients, 24 (11.9%) had positive serology and clinical LB, 26 (12.9%) had positive serology and no clinical LB, 73 (36.3%) had negative serology and clinical LB, and 78 (38.8%) had negative serology and no clinical LB. Of 50 patients with positive IgG serology, 5 (10.0%) were also IgM positive. Of 151 patients with negative IgG serology, 19 (12.6%) were IgM positive. Of 97 patients with clinical LB, 91 experienced LB manifestations in the past, including EM ($n = 82$), Lyme neuroborreliosis ($n = 4$), multiple EM ($n = 3$), ACA ($n = 3$), Lyme carditis ($n = 2$), and Lyme arthritis ($n = 1$), with a median time between the manifestation and medical consultation of 15.5 months (range 1–285 months).

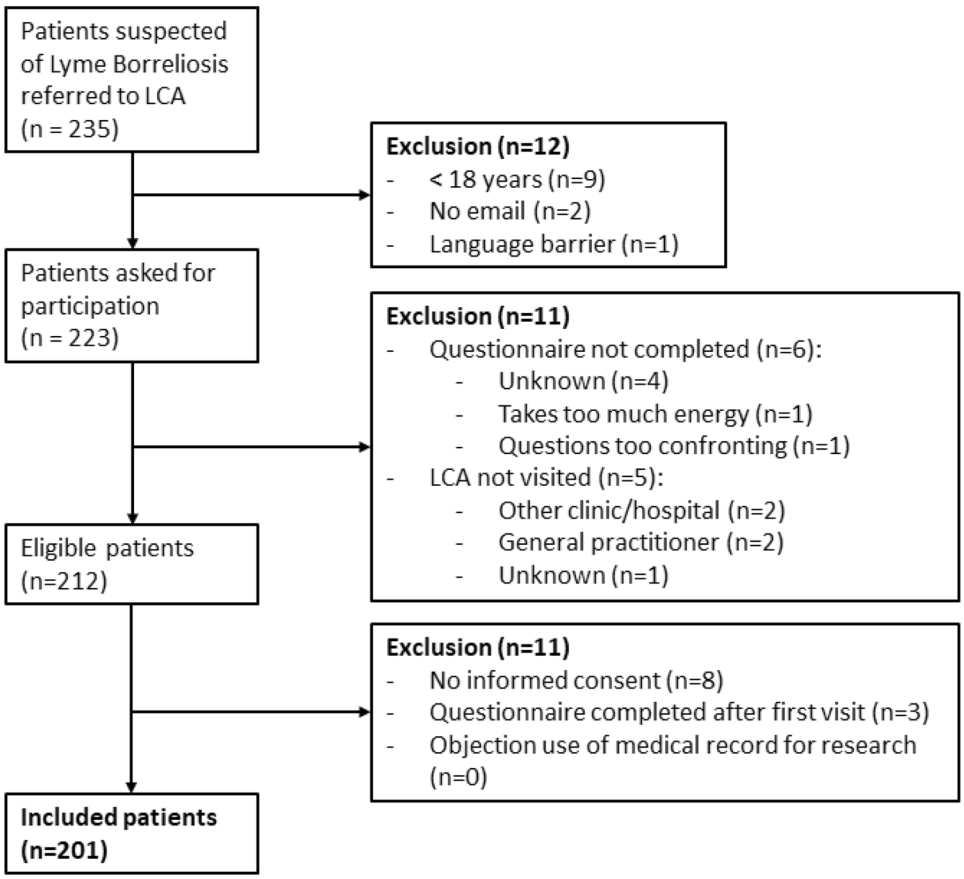

Fig. 1 Flowchart of patient inclusion

Table 1 Demographics, exposure and disease characteristics in patients referred to a Lyme Center in a Dutch teaching hospital

Demographics	Patients ($n=201$)
Gender (% female)	110 (54.7)
Median age in years (range)	50 (18–85)
Comorbidities (%)	
0	103 (51.2)
1	64 (31.8)
2	16 (8.0)
3	11 (5.5)
4	4 (2.0)
Unknown	3 (1.5)
Medical referrer	
General practitioner (%)	185 (92.0)
Medical specialist (%)	13 (6.5)
Occupational physician (%)	3 (1.5)
Exposure characteristics	
Exposure risk*	
Low (%)	104 (51.7)
Low/moderate (%)	1 (0.5)
Moderate (%)	17 (8.5)
Moderate/high (%)	4 (2.0)
High (%)	16 (8.0)
Unknown	59 (29.4)
Exposure activities	
Leisure (%)	145 (72.1)
Leisure and professional (%)	13 (6.5)
Professional (%)	18 (9.0)
None (%)	16 (8.0)
Unknown	9 (4.5)
Number of patients with tick bite in past 5 years (%)	90 (44.8)
Median number of tick bites per patient in past 5 years (range)	4 (1–150)
Disease characteristics	
LB manifestations in the past (%)**	91 (45.5)
EM	82
Neuroborreliosis	4
Multiple EM	3
ACA	3
Lyme carditis	2
Lyme arthritis	1
LB manifestations during medical consultation (%)	6 (3.0)
ACA	2
Neuroborreliosis	2
Lyme arthritis	1
Lyme carditis	1
Non-specific symptoms during medical consultation** (%)	197 (98.0)
Fatigue (%)	164 (81.6)
Musculoskeletal pain (%)	148 (73.6)
Sleep disturbances (%)	100 (49.8)
IgM serology during medical consultation (% positive)	24 (11.9)
IgG serology during medical consultation (% positive)	50 (24.9)
Antibiotic treatment for LB in the past 5 years (%)	111 (55.2)
Median duration of antibiotic treatment in days (range)***	28 (2–365)

LB lyme borreliosis, *EM* erythema migrans, *ACA* acrodermatitis chronica atrophicans

*Risk for acquiring Lyme borreliosis, determined by a medical specialist based on a combination of exposure activities and number of tick bites

**Values cannot be added together as multiple persons had more than one manifestation

***Median duration in those 111 patients that received antibiotic treatment for LB in the past 5 years

The other six patients with clinical LB presented with LB manifestations at medical consultation (i.e. ACA ($n=2$), Lyme neuroborreliosis ($n=2$), Lyme arthritis ($n=1$), and Lyme carditis ($n=1$)). Almost half of the patients (47.3%) had one or more comorbidities. Non-specific symptoms were reported by 197 patients (98.0%), with fatigue being reported most frequently (81.6%). In total, 55.2% ($n=111$) of the patients received antibiotic treatment for LB in the previous 5 years with a median duration of 28 days.

Coping

Means of the study population on the UCL subscales can be found in Table 2. In subgroup analysis, males scored significantly lower than females on the scales palliative reaction (16.8 vs 19.2, $p<0.001$), seeking social support (13.0 vs 14.1, $p=0.023$), and reassuring thoughts (11.5 vs 13.4, $p<0.001$). Patients below the age of 50 scored significantly higher on passive reaction compared to those aged 50 or above (13.1 vs 11.7, $p=0.005$). Means of the coping strategies of the four patient categories were not significantly different.

Our study population showed a different coping profile compared to reference data for both males and females. Both male and female patients scored significantly higher on palliative reaction (male: 16.8 vs 15.5, $p=0.001$; female: 19.2 vs 17.3, $p=0.001$) as well as passive reaction (male: 12.3 vs 10.7, $p<0.001$; female: 12.5 vs 10.9, $p=0.003$) compared to the reference population. Additionally, male patients scored higher on seeking social support compared to the male reference population (13.0 vs 11.3, $p<0.001$), while females scored lower on expressing emotions (5.9 vs 6.4, $p=0.030$) and higher on reassuring thoughts (13.4 vs 12.1, $p<0.001$) compared to the female reference population.

Percentages of the study population classified as high on UCL subscales were larger on palliative reaction (45.5%) and passive reaction (48.3%) compared to other subscales (active approach: 34.3%; avoidance: 32.3%; seeking social support: 32.3%; expressing emotions: 32.8%; reassuring thoughts: 33.8%). Patients with negative serology and no clinical LB had the largest proportion of patients scoring high on palliative reaction (51.3% vs 41.7% vs 40.0% vs 42.5%, $p=0.621$) (Fig. 2).

Quality of life

Means of the study population on the QoL subscales are presented in Table 2. No significant differences were found between males and females on any of the subscales. Younger patients (≤ 50 years) had a lower QoL on all subscales compared to older patients (> 50 years), of which differences on all but the pain subscale were significant ($p<0.05$). The four patient categories significantly differed on physical functioning (69.6 vs 71.0 vs 69.5 vs 56.4; $p=0.004$), social functioning (61.5 vs 55.3 vs 52.7 vs 40.1; $p=0.001$), pain (62.7 vs 62.2 vs 55.8 vs 43.5; $p<0.001$), and general health (48.8 vs 48.3 vs 43.0 vs 36.2; $p=0.007$). Patients with negative serology and no clinical LB had lowest QoL on all subscales. The study population scored lower on all QoL scales compared to the reference population, i.e. physical functioning (64.6 vs 81.9, $p<0.001$), social functioning (49.2 vs 86.9, $p<0.001$), physical role limitations (18.2 vs 79.4, $p<0.001$), emotional role limitations (56.1 vs 84.1, $p<0.001$), mental health (63.8 vs 76.8, $p<0.001$), vitality (38.2 vs 67.4, $p<0.001$), pain (52.7 vs 79.5, $p<0.001$), and general health (41.7 vs 72.7, $p<0.001$).

Patient and disease characteristics, coping, and quality of life

More use of palliative reaction, passive reaction, and expressing emotions was correlated with worse QoL on various QoL subscales (Table 3). The strongest correlation was observed between passive reaction and mental health ($\rho=-0.72$). Active approach was the only coping strategy positively correlated with QoL subscales. Avoidance, seeking social support, and reassuring thoughts did not show meaningful or significant correlations with QoL subscales and were therefore not included in regression analyses.

In univariate analysis, age and passive reaction were related to all QoL subscales ($p<0.20$) (Table 4). Passive reaction explained between 3 and 55% of the variance of the different QoL subscales, while explained variance by palliative reaction, expressing emotions, and active approach ranged between 0 and 12%. In multivariate analysis, passive reaction remained significant in all QoL subscales, except for role limitations due to physical problems (Table 4). Moreover, palliative reaction only remained significant on role limitations due to physical problems, expressing emotions remained significant on mental health, and active approach remained significant on mental health and role limitations due to emotional problems. Variance explained by the multivariate models ranged between 4% of role limitations due to physical problems and 60% of mental health.

Discussion

The study objective was to assess coping strategies and QoL in patients with chronic symptoms suspected of LB. We hypothesized that patients with negative Lyme serology and no clinical LB use different coping strategies than patients who do have signs of LB infection, defined as positive serology and/or clinical LB. Although QoL was lowest in patients who did not have signs of LB infection, coping strategies in these patients did not differ from coping strategies of patients who did have positive serology and/or clinical LB. Coping

Table 2 Mean scores on coping and QoL subscales in patients with chronic symptoms suspected of LB, by gender, age group and patient category

	Study population ($n=201$)	Gender		p^a	Age		p^a	Patient category				p^b
		Male ($n=91$)	Female ($n=110$)		≤50 years ($n=101$)	>50 years ($n=100$)		Pos sero + clinical LB ($n=24$)	Pos sero + no clinical LB ($n=26$)	Neg sero + clinical LB ($n=73$)	Neg sero + no clinical LB ($n=78$)	
		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Coping subscale (range)												
Active approach (7–28)	19.0 (3.4)	18.8 (3.4)	19.1 (3.5)	0.533	18.9 (3.4)	19.0 (3.5)	0.839	18.4 (4.4)	18.6 (3.1)	19.3 (3.4)	19.0 (3.3)	0.666
Palliative reaction (8–32)	18.1 (3.9)	16.8 (3.9)	19.2 (3.6)	<0.001***	18.6 (4.0)	17.6 (3.7)	0.054	17.5 (3.6)	17.2 (5.1)	18.2 (4.0)	18.5 (3.4)	0.390
Avoidance (8–32)	15.8 (3.0)	15.4 (2.9)	16.2 (3.1)	0.076	16.1 (2.7)	15.6 (3.3)	0.175	16.5 (3.7)	15.0 (3.4)	15.9 (2.7)	15.8 (2.9)	0.315
Seeking social support (6–24)	13.6 (3.4)	13.0 (3.6)	14.1 (3.2)	0.023*	13.9 (3.5)	13.3 (3.3)	0.197	13.6 (3.0)	14.2 (3.7)	13.9 (3.6)	13.1 (3.3)	0.366
Passive reaction (7–28)	12.4 (3.6)	12.3 (3.5)	12.5 (3.6)	0.683	13.1 (3.7)	11.7 (3.4)	0.005**	12.4 (3.7)	11.4 (3.7)	12.2 (3.4)	12.9 (3.6)	0.310
Expressing emotions (3–12)	6.0 (1.6)	6.2 (1.8)	5.9 (1.5)	0.278	6.2 (1.7)	5.8 (1.6)	0.092	5.9 (2.2)	6.1 (1.5)	5.9 (1.5)	6.1 (1.6)	0.910
Reassuring thoughts (5–20)	12.5 (2.7)	11.5 (2.6)	13.4 (2.4)	<0.001***	12.7 (2.5)	12.3 (2.8)	0.239	12.3 (2.0)	12.3 (3.2)	12.6 (2.7)	12.6 (2.6)	0.893
Quality of life subscale (0–100)												
Physical functioning	64.6 (25.7)	67.3 (26.6)	62.4 (24.9)	0.179	60.5 (26.6)	68.7 (24.3)	0.024*	69.6 (28.7)	71.0 (23.9)	69.5 (23.1)	56.4 (26.1)	0.004**
Social functioning	49.2 (27.6)	53.3 (25.9)	45.8 (28.5)	0.053	42.3 (28.3)	56.1 (25.1)	<0.001***	61.5 (32.1)	55.3 (21.8)	52.7 (26.0)	40.1 (27.0)	0.001**
Role limitations (physical)	18.2 (32.5)	21.6 (34.1)	15.5 (31.0)	0.186	13.2 (28.9)	23.3 (35.2)	0.027*	28.1 (39.2)	25.0 (36.7)	19.3 (34.3)	12.0 (25.8)	0.096
Role limitations (emotional)	56.1 (44.8)	52.0 (44.8)	59.5 (44.7)	0.241	46.7 (45.0)	65.7 (42.7)	0.003**	62.3 (48.5)	59.0 (44.5)	62.3 (42.7)	47.4 (45.1)	0.181
Mental health	63.8 (20.2)	63.6 (21.6)	63.9 (19.1)	0.934	59.8 (20.5)	67.8 (19.2)	0.005**	72.0 (19.3)	64.6 (21.0)	63.8 (20.4)	60.9 (19.7)	0.134
Vitality	38.2 (19.4)	39.5 (20.0)	37.2 (18.9)	0.423	34.0 (17.6)	42.5 (20.3)	0.002**	41.0 (22.2)	41.3 (23.7)	38.6 (16.7)	36.0 (19.4)	0.534
Pain	52.7 (25.4)	55.8 (25.0)	50.1 (25.5)	0.114	49.6 (26.5)	55.8 (23.9)	0.084	62.7 (24.8)	62.2 (18.4)	55.8 (23.1)	43.5 (26.9)	<0.001***
General health	41.7 (20.1)	43.8 (21.0)	40.0 (19.3)	0.176	38.3 (20.5)	45.2 (19.2)	0.016*	48.8 (22.2)	48.3 (20.3)	43.0 (18.6)	36.2 (19.5)	0.007**

QoL quality of life, *LB* lyme borreliosis, *pos* positive, *neg* negative, *sero* serology, *SD* standard deviation

Significance: *$p<0.05$, **$p<0.01$, ***$p<0.001$

[a]t-test comparing two groups

[b]ANOVA comparing four groups

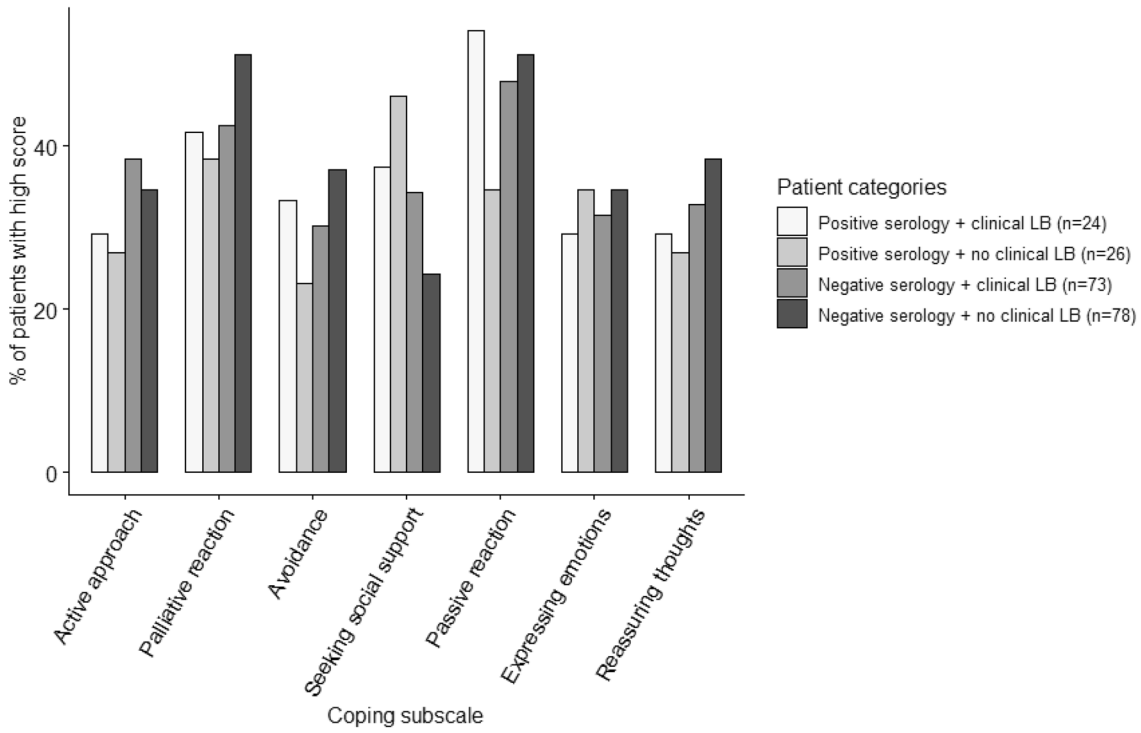

Fig. 2 Percentage of patients that scored high on the coping subscales

Table 3 Correlations between coping and QoL subscales scores of patients with chronic symptoms suspected of LB

Quality of life subscale	Coping subscale						
	Active approach	Palliative reaction	Avoidance	Seeking social support	Passive reaction	Expressing emotions	Reassuring thoughts
Physical functioning	0.00	− 0.07	0.04	0.04	− 0.18**	− 0.00	0.02
Social functioning	− 0.01	− 0.27***	− 0.07	− 0.09	− 0.49***	− 0.22**	− 0.19**
Role limitations (physical)	− 0.03	− 0.24***	− 0.06	− 0.13	− 0.24***	− 0.12	− 0.08
Role limitations (emotional)	0.26***	− 0.21**	− 0.17*	0.11	− 0.51***	− 0.10	0.00
Mental health	0.32***	− 0.33***	− 0.20**	− 0.02	− 0.72***	− 0.34***	− 0.00
Vitality	0.18*	− 0.22**	− 0.07	− 0.09	− 0.48***	− 0.18*	− 0.04
Pain	− 0.07	− 0.16*	− 0.05	0.02	− 0.33***	− 0.12	− 0.10
General health	0.03	− 0.27***	− 0.09	0.03	− 0.51***	− 0.19**	− 0.04

QoL quality of life, *LB* lyme borreliosis

Significance: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Spearman's rank correlation rho between coping and QoL subscales

strategies in all four patient categories were similar. Hence, in this specific patient population, LB was not associated with a specific coping strategy. Nevertheless, patients suspected of LB referred to a Lyme center appear to have a different coping profile compared to the Dutch reference population, which is associated with worse QoL. More use of passive reaction, palliative reaction, and expressing emotions is significantly correlated with worse QoL. Active approach is positively correlated, i.e. more active approach correlated with better QoL. In multivariate analyses, correcting for age, gender, comorbidity and patient category, an association between QoL and passive reaction remained significant.

Table 4 Univariate and multivariate linear regression analysis of an association between coping, patient characteristics, and QoL

	Physical functioning		Social functioning		Role limitations (physical)		Role limitations (emotional)	
	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)
Age								
≤ 50 years	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)
> 50 years	8.2 (3.6)*	–	13.8 (3.8)***	8.5 (3.4)*	10.1 (4.5)*	–	19.0 (6.2)**	11.0 (5.5)*
Gender								
Male	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Female	− 4.9 (3.6)†	–	− 7.5 (3.9)†	–	− 6.2 (4.6)†	–	7.5 (6.4)	–
Comorbidity								
No	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	
Yes	− 6.1 (3.6)†	–	− 13.4 (3.8)***	− 8.1 (3.4)*	− 9.3 (4.5)*	–	− 6.9 (6.4)	–
Patient categories								
Pos sero + clinical LB	13.2 (5.9)*	12.6 (5.8)*	21.4 (6.2)***	16.5 (5.4)**	16.2 (7.5)*	–	14.9 (10.6)	–
Pos sero + no clinical LB	14.6 (5.7)*	12.8 (5.7)*	15.2 (6.0)*	7.2 (5.2)	13.0 (7.3)†	–	11.5 (10.1)	–
Neg sero + clinical LB	13.0 (4.1)**	12.3 (4.1)**	12.7 (4.3)**	8.2 (3.8)*	7.3 (5.3)†	–	14.9 (7.3)*	–
Neg sero + no clinical LB	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	
Passive reaction	− 1.3 (0.5)**	− 1.1 (0.5)*	− 3.9 (0.5)***	− 3.3 (0.5)***	− 2.0 (0.6)**		− 6.3 (0.8)***	− 5.5 (0.8)***
Palliative reaction	− 0.4 (0.5)	–	− 2.0 (0.5)***	–	− 1.8 (0.6)**	− 1.8 (0.6)**	− 2.5 (0.8)**	–
Expressing emotions	− 0.5 (1.1)	–	− 3.9 (1.2)**	–	− 2.8 (1.4)*	–	− 2.8 (1.9)†	–
Active approach	0.1 (0.5)	–	0.3 (0.6)	–	− 0.0 (0.7)	–	3.5 (0.9)***	1.9 (0.8)*
Adjusted R^2		0.07		0.32		0.04		0.28

	Mental health		Vitality		Pain		General health	
	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)
Age								
≤ 50 years	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	
> 50 years	7.9 (2.8)**	–	8.5 (2.7)**	6.2 (2.4)*	6.2 (3.6)†	–	6.8 (2.8)*	–
Gender								
Male	1.0 (Ref)		1.0 (Ref)		1.0 (Ref)		1.0 (Ref)	
Female	0.2 (2.9)	–	− 2.2 (2.8)	–	− 5.7 (3.6)†	–	− 3.9 (2.8)†	–
Comorbidity								
No	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)
Yes	− 9.7 (2.8)***	–	− 9.0 (2.7)***	− 6.4 (2.4)**	− 6.1 (3.5)†	–	− 14.6 (2.7)***	− 10.5 (2.4)***
Patient categories								
Pos sero + clinical LB	11.1 (4.7)*	9.5 (3.0)**	5.0 (4.5)	–	19.2 (5.7)***	18.1 (5.4)***	12.6 (4.6)**	–
Pos sero + no clinical LB	3.7 (4.5)	-1.5 (2.9)	5.3 (4.4)	–	18.7 (5.5)***	15.3 (5.3)**	12.1 (4.4)**	–

Table 4 (continued)

	Mental health		Vitality		Pain		General health	
	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)	Univariate β (SE)	Multivariate β (SE)
Neg sero + clinical LB	2.9 (3.3)	0.0 (2.1)	2.5 (3.2)	–	12.3 (4.0)**	10.9 (3.8)**	6.9 (3.2)*	–
Neg sero + no clinical LB	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	–
Passive reaction	− 4.2 (0.3)***	− 3.7 (0.3)***	− 2.7 (0.3)***	− 2.3 (0.3)***	− 2.5 (0.5)***	− 2.3 (0.5)***	− 3.0 (0.3)***	− 2.7 (0.3)***
Palliative reaction	− 1.8 (0.3)***	–	− 1.3 (0.3)***	–	− 1.1 (0.5)*	–	− 1.5 (0.4)***	–
Expressing emotions	− 4.3 (0.8)***	− 1.3 (0.6)*	− 2.6 (0.8)**	–	− 2.2 (1.1)†	–	− 2.8 (0.9)**	–
Active approach	2.1 (0.4)***	1.0 (0.3)***	1.2 (0.4)**	–	0.1 (0.5)	–	0.5 (0.4)	–
Adjusted R^2		0.60		0.27		0.18		0.35

QoL quality of life, *pos* positive, *neg* negative, *sero* serology, *LB* lyme borreliosis, *SE* standard error, β unstandardized beta coefficient
Significance: †$p < 0.20$; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Coping scores were lower among males than females on most subscales, but few differences were found between age groups. Females often had lower QoL scores than males, but no significant differences were found. Similar trends were found in reference data [15, 28]. The reference study on QoL reported lower QoL in older respondents, whereas older patients in our study population had a higher QoL on all subscales. Similar results have been found in studies among other patient populations, in which it is explained by the change in expectations about what constitutes good QoL [31, 32]. Older individuals expect their physical and social functioning to decline as they age and are able to put this into perspective by comparing themselves to others who they consider to be in worse shape.

Although QoL and coping strategies have been investigated before among LB patients, comparison of study results is hampered due to differences in study population and use of different questionnaires. Two studies performed in the USA, including individuals experiencing symptoms lasting for six months or longer after LB, reported impaired QoL using the RAND-36 ($n = 82$) [16] and CDC 9-item metric ($n = 3{,}000$) [33]. A large study performed in the Netherlands ($n = 1135$) reported a low QoL on the pain subscale of the RAND-36 in patients reporting persistent atypical symptoms after antibiotic treatment for LB [7]. Concerning coping, a study performed in the USA found that behavioral disengagement and coping with substance use were associated with decreased emotional health in patients who had a confirmed diagnosis of Lyme disease with symptoms lasting for six months or more [16]. In our study population, QoL was lowest in patients with no signs of infection. A previous study of the LCA reported that the prevalence of depressive symptoms was highest among patients with no signs of infection [24]. A possible explanation is the large impact of medically unexplained symptoms on QoL [34]. It should be further assessed whether these specific patients might have different needs.

Coping strategies and QoL are also studied in populations with other illnesses than LB. When we compare our results to those of studies that assessed QoL in different patient populations using the RAND-36, we find a lower QoL in our study population compared to rheumatoid arthritis patients [35], a similar QoL compared to patients with Q fever reporting persistent symptoms [36], and a higher QoL compared to patients with chronic fatigue syndrome[37]. A study among individuals experiencing symptoms lasting for six months or longer after LB was diagnosed, reported significant impaired QoL compared to patients with other chronic diseases, including diabetes, arthritis, and asthma [33]. Similar to our results, a Dutch study using the UCL in 105 epilepsy patients reported a different coping profile compared to the reference population [11]. Also, the results of our study concerning the association between use of passive reaction and worse mental health have been reported before in different patient populations [11, 16–18, 20, 21].

A strength of this study is that patients were seen by both a neurologist and internist at the same time, which reinforces clinical data. Moreover, all patients underwent serological testing for Lyme borreliosis, the response rate was high, standardized questionnaires were used, and part of the data obtained from the electronic medical records was double checked to minimize bias.

A limitation of the study is that patients referred to the LCA often experience chronic symptoms, which might predispose them to a worse QoL and/or usage of more dysfunctional coping strategies. Possibly patients using more functional coping strategies, also experience less chronic complaints and are thus not referred to the LCA and not included in this study. Another limitation is possible type I error (null hypothesis rejected when it should not be) because of multiple comparisons. However, correcting for this could increase type II errors (failing to reject the null hypothesis when it should be) [38], and therefore we did not adjust the significance threshold. Another limitation is the cross-sectional design of this study, which does not allow to determine the causal nature and direction, if causal, of the associations found. It is possible that coping strategy and QoL are causally related, but it is also possible that the two merely share a common cause or effect. Also, if they are causally related, it is not yet clear if a certain coping strategy predisposes for reduced QoL or if reduced QoL can lead to changes in coping strategies.

Although causal nature and direction of the association between QoL and coping remain unknown, coping strategies are a possible target for interventions. Coping skill training is a cognitive-behavioral intervention that focusses on improving coping strategies from dysfunctional into more functional coping strategies. Coping skills training has shown to increase QoL in patients with chronic diseases, such as diabetes mellitus [39], pulmonary disease [40], and heart failure [41]. However, coping skill training has not yet been studied in patients with non-specific chronic symptoms suspected of LB. More research is necessary to determine the effectiveness in this particular patient population, preferably in a randomized clinical trial.

To date, little is known on coping and QoL in patients suspected of LB visiting a Lyme centre. This is the first study that investigated differences in coping and QoL by comparing patients suspected of LB with and without signs of infection. QoL was lower in patients with negative serology and no clinical LB compared to patients with positive serology and/or clinical LB. However, coping strategies did not differ between these patient groups. Nevertheless, the entire population of patients referred to a Lyme center suspected of LB use what appear to be dysfunctional coping strategies and have an overall low QoL. As there is an association between coping and QoL in these patients, there is a need for interventions that can guide them towards a more active coping strategy and increase QoL.

Acknowledgements We thank Kay van Wijk (Gelre hospital) for help with data collection.

Author contributions TZ and YV designed the study. Data collection and analyses were performed by AH. Data interpretation were performed by AH, TZ, YV, TB, RW, and CJ. The first draft of the manuscript was written by AH. TZ, CJ, YV, TB, and RW critically reviewed the manuscript and approved the final manuscript for submission.

Funding No external funding for this study was received.

Data availability Data and code will be made available upon reasonable request.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Ethical approval The study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). A non-WMO declaration (nr. 201202) was received from the Medical Ethics Committee of Isala hospital, Zwolle, the Netherlands.

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