Journal of Psychosomatic Research xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

journal homepage: www.elsevier.com/locate/jpsychores

Explaining the long-term impact of chronic Q fever and Q fever fatigue syndrome on psychosocial functioning: A comparison with diabetes and the general population

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ARTICLE INFO

Keywords:
Chronic Q fever
Q fever fatigue syndrome
QFS
Long term impact
Psychosocial functioning
Quality of life

ABSTRACT

Objective: After Q fever infection, 1–5% of patients develop chronic Q fever, while about 20% develops Q fever fatigue syndrome (QFS). This study examines whether these two conditions have a long-term impact on psychosocial functioning compared to the general population and patients with type 2 diabetes (DM) and investigate which mediating factors influence outcomes.

Methods: Cross-sectional study was performed, measuring psychosocial functioning including quality of life (depression and satisfaction with life), anxiety, social functioning and relationship satisfaction in patients with proven or probable chronic Q fever or QFS, 5–9 years after acute Q fever infection. Multivariate linear regression was used to analyse differences between groups, correct for confounders and identify relevant mediators (fatigue, physical or cognitive functioning, illness perception).

Results: Quality of life and social functioning of chronic Q-fever and QFS patients was significantly lower and anxiety significantly higher compared to DM patients and the general population. The impact was completely mediated by fatigue in both Q fever groups. Physical and cognitive functioning and illness perception partially mediated the impact.

Conclusions: Health care workers need to be aware of the long-term impact of chronic Q fever and QFS on psychosocial functioning of patients in order to provide proper guidance.

1. Background

Following acute Q fever infection, two prominent long-term sequelae have been described. First, 1–5% of the patients develop chronic Q fever, primarily in those with pre-existing cardiac valvulopathies, aneurysms, vascular prosthesis or immunosuppression [1]. The most common manifestations of chronic Q fever are endocarditis and infection of an aneurysm or vascular prosthesis [2]. Chronic Q-fever is more prevalent in males, most likely because aneurysms and vascular prostheses occur more often in this group [3]. Second, approximately 20% of patients with symptomatic acute Q fever develop Q fever fatigue syndrome (QFS) [4]. This condition is characterized by debilitating fatigue, persisting for > 6 months, often with additional complaints, such as muscle and joint aches, night sweats and loss of concentration [4,5].

Previous research examined the health status of Q fever patients two to four years after acute infection and found higher levels of fatigue and an impaired quality of life compared to a healthy reference group [6,7]. However, these studies did not distinguish whether patients suffered from chronic Q fever, QFS or neither. Research examining the long-term impact of chronic Q fever or QFS focused primarily on clinical outcomes and treatment effects [8–11]. The long-term impact of chronic Q fever and QFS on psychosocial functioning has received little attention in scientific research, even though patients anecdotally reported feelings

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https://doi.org/10.1016/j.jpsychores.2019.03.185
Received 13 April 2018; Received in revised form 25 March 2019; Accepted 30 March 2019

of depression and anxiety, and problems in social functioning [12].

Therefore, the main objective of this study was to examine psychosocial functioning including quality of life (as defined by depression and satisfaction with life), anxiety, social functioning and relationship satisfaction in chronic Q fever and QFS patients five to nine years after their acute Q fever infection compared to a reference group from the general population. Additionally, the Q fever groups were compared to a reference group of patients with type 2 diabetes mellitus (DM), to assess whether the long-term impact of another chronic illness is comparable to that of chronic Q fever or QFS. In order to gain understanding in possible mechanisms underlying this association, this study examined the mediating role of health-related concepts (fatigue, physical functioning, cognitive functioning and illness perception) on the impact of QFS or chronic Q fever on psychosocial functioning. We assumed these health-related concepts are a direct result of the illness and may influence psychosocial outcomes.

2. Methods

In this cross-sectional study, psychosocial functioning was measured using validated questionnaires in patients diagnosed with QFS or chronic Q fever and compared to DM patients and persons from the general population.

2.1. Study population

2.1.1. Chronic Q fever and QFS patients

This study included two Q fever patient groups. Patients meeting the criteria of proven or probable chronic Q fever, according to the Dutch consensus guideline on chronic Q fever diagnostics (Table 1) [13], or diagnosed with QFS, according to the criteria as defined in the Dutch multidisciplinary guideline concerning fatigue after Q fever infection (Table 1) [5,14], were eligible for this study. The QFS guideline was partly based on the diagnosis and treatment of patients with chronic fatigue syndrome (CFS) with the addition that the fatigue must be related to the acute Q-fever infection. In QFS patients, the fatigue was not present before acute Q fever infection or has significantly increased since acute Q fever infection. Patients with CFS triggered by other events were not included, as this study focused on the long term impact of sequelae of Q fever. Patients were invited for participation independent of their disease status, i.e. whether they had been declared cured or were still under treatment at the time of inclusion. Physicians from four Dutch hospitals, with the highest number of chronic Q fever patients according to a national database [15] (Radboud university medical center, Nijmegen; Jeroen Bosch Hospital, 's-Hertogenbosch; Bernhoven Hospital, Uden; St. Elisabeth Hospital, Tilburg), were asked to send an information letter and informed consent form for participation in this study to patients with chronic Q fever in their clinic. QFS patients were invited through physicians from the Radboud university medical center (QFS expert centre in the Netherlands), as the majority of diagnosed QFS patients in the Netherlands are referred to this hospital [8].

2.1.2. Reference groups from the general population and patients with diabetes

Persons from the general population were eligible for participation in the first reference group. As we did not aim to compile a healthy control group, persons with morbidity were not excluded. A second reference group consisted of patients with a different chronic illness that has clear diagnostic criteria, is prevalent in the general population with a similar distribution in gender and age as the Q fever groups and has an impact on quality of life. DM patients met all these criteria and were chosen as a reference group. DM patients with a disease duration similar to the chronic Q fever and QFS patients, namely 5–9 years at the time of participation in the study, were eligible for participation. References were excluded if they had been diagnosed with Q fever by a medical professional at any time in their life, by definition excluding a diagnosis of chronic Q fever or QFS. Persons from the general population were recruited with two advertisements in a local newspaper with a call for participation in this study. Snowball sampling through participants with consent was used to include more participants in this reference group. Included persons forwarded a request for participation to friends or family who were also interested in this study. During inclusion, the age and gender distribution was assessed. As the first

Table 1
Diagnostic criteria for QFS and chronic Q fever.

QFS (14)	Chronic Q fever (13)		
	Proven	Probable	Possible
Persisting fatigue longer than six months AND Laboratory-confirmed acute Q fever, but no chronic Q fever AND No existing somatic or psychiatric co-morbidity, which could explain the fatigue AND Fatigue causes significant limitations in daily functioning AND Complaints of fatigue were not present prior to the acute Q fever infection or the complaints have since then clearly increased in severity.	1. Positive *C. Burnetii* PCR in blood or tissue in absence of acute infection OR 2. IFA ≥ 1:1024 for *C. Burnetii* phase I IgG AND - definite endocarditis according - to the modified Duke criteria [45] - OR - - proven large vessel or prosthetic infection by imaging studies (FDG-PET, CT, MRI)	IFA ≥ 1:1024 for *C. Burnetii* phase I IgG AND One or more of the following criteria: - Valvulopathy not meeting the major - criteria of the modified Duke criteria [45] - Known aneurysm and/or vascular or - cardiac valve prosthesis without signs of - infection by means of TEE/TTE, FDG-PET, CT, MRI or abdominal doppler ultrasound - Suspected osteomyelitis or hepatitis as - manifestation of chronic Q fever - Pregnancy - Symptoms and signs of chronic infection, - such as fever, weight loss and night - sweats, hepatosplenomegaly, persistent raised ESR and CRP - Granulomatous tissue inflammation, - proven by histological examination - Immunocompromised state	IFA ≥ 1:1024 for *C. Burnetii* phase I IgG without manifestations meeting the criteria for proven or probable chronic Q fever

PCR: polymerase chain reaction, IFA: immunofluorescence assay, FDG-PET: (fluorodeoxyglucose) positron emission tomography, CT: computed tomography, MRI: magnetic resonance imaging, TEE: transesophageal echocardiography, TTE: transthoracic echocardiography, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

advertisements did not yield sufficient male participants of 30 years or older, an additional advertisement was put in the same local newspaper, specifically targeting this group. DM patients were identified based on electronic patient records (ICPC-code T90.02) [16] from seven practices located in both rural and urban areas from the Academic General Practices Network of the Radboud university medical center [17]. General practitioners (GPs) from these practices were asked to send an information letter and informed consent form for participation in our study to all eligible patients. GPs were asked not to invite patients who they deemed not fit to participate according to their professional opinion, e.g. patients with severe multi-morbidity, language barrier, mental disability or patients who relocated to a different area.

2.2. Data collection

After returning the written informed consent form, participants were sent an online or paper questionnaire, depending on their preference stated on the consent form. Two reminders by telephone or e-mail were sent to persons who did not return the questionnaire after four and eight weeks of receiving the questionnaire. When incomplete questionnaires were returned, participants were called by a member of the research team to complete the missing questions. Participants from the reference group who filled out a questionnaire received a gift card of 10 Euros.

2.2.1. Questionnaire

Psychosocial functioning was measured with four domains using validated questionnaires, as presented in Table 2: [1] Quality of Life, as defined by the Nijmegen Clinical Screening Instrument (NCSI) [18] by combining the standardized z-scores of two instruments measuring depression and satisfaction with life [19,20], [2] Anxiety [21], [3] Social functioning [22,23] and [4] Relationship satisfaction [24]. In addition, the following domains were used to measure the mediating role on long-term psychosocial functioning (Table 2): [1] Fatigue [25,26]. [2] Physical functioning [27,28], [3] Cognitive functioning [29] and [4] Illness perception [30], the latter was only measured in the patient groups. Socio-demographic and general health questions were included, namely age, gender, educational level, (co-)morbidity, and onset of acute Q fever infection (as estimated by the patient) or diagnosis DM (as received from the Network database) for the patient groups. Educational level was divided into low (no education to lower secondary education), moderate (moderate secondary and vocational education and higher secondary education) and high education (higher vocational education and university degree). Participants were classified as having one or more (co-)morbidities if they received treatment or regular check-ups from their medical doctor for any condition or disorder other than the condition for which they participated in this study. Conditions causing an increased risk of disease, but not being debilitating by themselves, such as hypertension, obesity, high cholesterol and allergies (hay fever or lactose intolerance), were not considered (co-)morbidities.

2.3. Statistical analysis

All questionnaires were entered online, either directly by the participants or indirectly by the research team. Subsequently, all data were analysed with SPSS, version 22. For a variable to be a mediator, the following criteria had to be met: 1) significant effect of independent variable (group) on the outcome measure (quality of life, anxiety, social functioning or relationship satisfaction), 2) significant effect of independent variable (group) on mediator variable (fatigue, physical or cognitive functioning, illness perception), 3) significant association of mediator with outcome measure [31]. ANOVA and Chi Square tests were used to analyse the differences in demographics, psychosocial functioning and mediating factors between study groups (criteria 1 and 2). Bonferroni post hoc testing was performed to analyse the pair wise difference in more detail and to correct for multiple testing. For criteria 3, correlation coefficients were used to analyse the association between mediators and outcome measures.

Furthermore, two multivariate linear regression models with correction for confounders (age, gender, education level and co-morbidity) were created to identify which domain has the greatest mediating effect. The first model analysed the mediating role of fatigue, physical and cognitive functioning on psychosocial functioning in QFS and chronic Q fever patients compared to the general population. The second model analysed the mediating role of each illness perception domain on psychosocial functioning in QFS and chronic Q fever patients compared to the DM patients. As a measure of mediation, the proportion of the effect that was mediated was calculated to determine whether or not there was complete mediation of the effect, up to a maximum of 100% [32]. If the regression coefficient for the association of QFS or chronic Q fever with a psychosocial outcome parameter decreased with 80% or more or was no longer statistically significant after adding one of the mediating factors to the corrected linear regression model, this was considered complete mediation. A decrease between 50% and 79% was considered partial mediation and < 50% was considered no mediation.

2.4. Ethics

The Medical Ethical Review Board of the region Arnhem-Nijmegen reviewed and approved the study protocol (NL55961.091.15). All participants gave written informed consent before participation in this study.

3. Results

3.1. Inclusion of study groups

In total, 142 chronic Q fever patients and 251 QFS patients were eligible to participate and therefore received a letter from their attending physician. Of these eligible participants, 80 chronic Q fever patients (56%) and 155 QFS patients (62%) completed the questionnaires. All general practices combined had 900 DM patients who matched the required disease duration. Among them, 130 were considered not eligible by their attending general practitioner. Of the 770 remaining DM patients, 157 (20%) completed the questionnaire. In total, 331 persons from the general population responded to the advertisements or snowball sampling and 279 (84%) completed the questionnaire. No statistically significant differences in age and gender distributions were found between responders and non-responders in all groups separately (data not shown).

3.2. Demographic characteristics

As shown in Table 3, chronic Q fever patients are on average older (mean age 70.1 years) and more often male (86.3%) compared to QFS patients, DM patients and the general population and they are on average lower educated (47.5%) compared to QFS patients and the general population. QFS patients are significantly younger (mean age 47.9 years) and more often female (56.8%) compared to chronic Q fever patients, DM patients and the general population. There are no significant differences in time interval since acute Q fever infection or DM diagnosis between the three patient groups.

3.3. Differences in psychosocial functioning between study groups

Table 4 shows that both groups of Q fever patients had a lower quality of life (more depression and lower satisfaction with life), higher levels of anxiety and lower levels of social functioning compared to DM patients and the general population. QFS patients had significantly higher levels of anxiety and lower levels of social functioning and

Table 2
Domains and sub domains of the psychosocial outcome measures and mediating factors in the administered questionnaire.

Domain	Instrument	Items	Range			Cut-off value [1]	Higher score means …	Ref.
Sub domain								
Psychosocial outcome measures								
Quality of life	Nijmegen Clinical Screening Instrument (NCSI)	12	0	–	100	86.67	Higher quality of life	[18]
Depression	Beck Depression Inventory Fast Screen (BDI)	7	0	–	21	4	Higher level of depressive symptoms	[19]
Satisfaction with life	Satisfaction with Life (SWL)	5	0	–	35		Higher level of satisfaction with life	[20]
Anxiety	Generalized Anxiety Disorder-7 (GAD7)	7	0	–	21	10	Higher level of anxiety	[21]
Social functioning	Short Form-36 (SF-36)	2	0	–	100		Higher social functioning	[22,23]
Relationship satisfaction	Maudsley Marital Questionnaire (MMQ)	10	0	–	80		Lower level of satisfaction	[24]
Mediating factors								
Fatigue	Checklist Individual Strength (CIS-Fatigue)	8	8	–	56	35	Higher level of fatigue	[25,26]
Physical functioning	Sickness Impact Profile (SIP)	22	0	–	151	17.38	Lower physical functioning	[27,28]
Home management		10	0	–	67			
Mobility		12	0	–	84			
Cognitive functioning	Cognitive Failure Questionnaire (CFQ)	25	0	–	100		Lower cognitive functioning	[29]
Illness perception	Illness Perception Questionnaire (IPQ)							[30]
Timeline		6	6	–	30		More beliefs on chronic progression of illness	
Consequences		6	6	–	30		More beliefs on negative consequences of illness: illness has large influence on patient's life	
Personal control		6	6	–	30		Higher level of personal controllability: illness can be influenced by the patient	
Treatment control		5	5	–	25		Higher level of treatment controllability: illness can be influenced by others	
Illness coherence		5	5	–	25		Higher level of personal understanding of illness	
Timeline cyclical		4	4	–	20		Higher cyclical nature of illness: illness has an unpredictable and fluctuating course	
Emotional representations		6	6	–	30		Higher level of negative emotions about illness: illness causes fears, anger and worries	

[1] Participants with a score higher or lower (depending on the questionnaire) than the cut-off value were classified as 'impaired' in that specific domain.

Table 3
Demographic characteristics, (co-)morbidity and illness duration per study group.

		QFS	Chronic Q fever	Type II diabetes	General population
Variable		(n = 155)	(n = 80)	(n = 157)	(n = 279)
Gender (male)	%	43.2[a]	86.3[b]	59.2[c]	51.3[a, c]
Age in years[1]	mean (sd)	47.9 (12.1)[a]	70.1 (10.1)[b]	65.6 (9.3)[c]	52.9 (15.3)[d]
Education level	%				
	Low	24.5[a]	47.5[b]	57.3[b]	17.6[a]
	Moderate	43.9[a]	30.0[a.b]	22.9[b]	31.9[a.b]
	High	31.6[a]	22.5[a]	19.7[a]	50.5[b]
(Co-)morbidity (one or more)[2]	%	38.1[a, b]	80.0[c]	47.1[b]	33.3[a]
Illness duration[3]	mean (sd)	6.7 (1.5)[a]	6.7 (1.9)[a]	6.6 (1.7)[a]	–

The same superscript letter in each row denotes which proportions/means do not differ significantly from each other at the 0.05 level with correction for multiple testing with Bonferroni post-hoc testing. Consequently, different letters represent statistically significant differences.

[1] Age on the day of filling in the questionnaire.

[2] (Co-)morbidities include, but are not limited to, heart and vascular disease, chronic disease (of lung, liver, kidney, etc.), cancer, chronic neck and back complaints.

[3] Time since acute Q fever infection or diagnosis diabetes in years. There are 5 missing values for QFS patients and 25 missing values for chronic Q fever patients.

relationship satisfaction compared to chronic Q fever patients. Furthermore, the proportion of chronic Q fever and QFS patients with an impaired quality of life, depression and anxiety level was higher compared to those in DM patients and the general population. There were no significant differences in psychosocial functioning between DM patients and the general population.

As shown in Tables 5 and 6, differences between the Q fever groups and the reference groups in psychosocial functioning remained statistically significant after correction for gender, age, education level and (co-)morbidity. This was not the case for relationship satisfaction, which showed no significant differences between study groups after correction for confounders (data not shown). In Table 5, for example, the unstandardized B coefficient for quality of life shows that after correction, QFS patients scored on average 11.1 points lower than the general population ($p < .001$) and chronic Q fever patients scored 8.5 points lower ($p < .001$) on a scale of 0 to 100.

3.4. Mediating effect of health-related concepts

Table 4 shows the differences in scores between the study groups for the various health-related concepts. The mean scores on all health-related mediating factors (fatigue, physical and cognitive functioning) were significantly worse for the two Q fever groups as compared to the DM patients and the general population. The proportion of chronic Q fever and QFS patients with an impaired level of fatigue and physical functioning was higher compared to DM patients and the general population. Fatigue, physical and cognitive functioning were significantly

Table 4
Mean scores on all psychosocial outcome measures and health-related concepts for the four study groups.

	QFS			Chronic Q fever			Type II Diabetes			General population		
	(n = 155)			(n = 80)			(n = 157)			(n = 279)		
Psychosocial outcome measures	Mean	(sd)	n	Mean	(sd)	n	Mean	(sd)	n	Mean	(sd)	n
Quality of life	74.8[a]	(14.5)	153	78.6[a]	(17.1)	79	87.0[b]	(12.2)	153	86.9[b]	(12.4)	279
Depression	2.8[a]	(9.4)	153	2.4[a]	(10.1)	79	1.1[b]	(6.7)	153	1.2[b]	(7.1)	279
Satisfaction with life	20.1[a]	(7.2)	153	22.8[a]	(8.8)	79	26.6[b]	(7.1)	157	27.0[b]	(7.2)	279
Anxiety	6.5[a]	(4.8)	153	4.5[b]	(5.0)	79	2.9[c]	(3.9)	157	2.6[c]	(3.6)	279
Social functioning	51.2[a]	(25.6)	153	63.0[b]	(29.2)	79	81.5[c]	(22.3)	157	84.3[c]	(21.6)	279
Relationship satisfaction	11.7[a]	(10.2)	115	7.0[b]	(8.5)	57	10.7[a.b]	(12.1)	113	10.4[a.b]	(10.9)	219
Impairment[1]	% impaired (n)			% impaired (n)			% impaired (n)			% impaired (n)		
Quality of life	77% (118)[a]			58% (46)[b]			39% (59)[c]			38% (105)[c]		
Depression	22% (33)[a]			19% (15)[a]			4% (6)[b]			7% (19)[b]		
Anxiety	19% (29)[a]			17% (13)[a]			5% (7)[b]			4% (10)[b]		
Mediating factors	mean	(sd)	n	mean	(sd)	n	mean	(sd)	n	mean	(sd)	n
Fatigue	44.6[a]	(10.8)	155	38.2[b]	(13.2)	79	26.5[c]	(13.4)	156	22.6[d]	(12.4)	279
Physical functioning	17.0[a]	(13.8)	152	18.9[a]	(20.0)	79	8.7[b]	(13.2)	157	4.9[c]	(10.3)	279
Cognitive functioning	39.9[a]	(16.4)	152	28.1[b]	(15.2)	78	24.7[b.c]	(13.1)	157	23.3[c]	(12.6)	279
Illness perception												
Timeline	22.5[a]	(5.6)	153	22.8[a]	(6.0)	80	21.3[a]	(5.4)	157	–	–	–
Consequences	21.5[a]	(5.7)	153	19.6[b]	(5.5)	79	14.7[c]	(4.4)	157	–	–	–
Personal control	17.4[a]	(5.2)	153	15.0[b]	(4.6)	79	21.2[c]	(4.9)	157	–	–	–
Treatment control	13.5[a]	(3.5)	153	14.6[a]	(3.9)	79	18.0[b]	(3.8)	155	–	–	–
Illness coherence	15.4[a]	(4.5)	153	14.0[a]	(4.8)	79	16.7[b]	(4.6)	155	–	–	–
Timeline cyclical	13.0[a]	(3.9)	153	11.4[b]	(4.3)	79	9.0[c]	(3.4)	156	–	–	–
Emotional representations	15.8[a]	(4.9)	153	16.3[a]	(5.1)	79	12.1[b]	(3.9)	157	–	–	–
Impairment[1]	% impaired (n)			% impaired (n)			% impaired (n)			% impaired (n)		
Fatigue	85% (130)[a]			56% (44)[b]			26% (40)[c]			18% (50)[c]		
Physical functioning	38% (52)[a]			43% (34)[a]			18% (28)[b]			9% (24)[c]		

[a, b, c, d] The same superscript letter in each row denotes which proportions/means do not differ significantly from each other at the 0.05 level with correction for multiple testing with Bonferroni post-hoc testing. Consequently, different letters represent statistically significant differences.

[1] Quality of Life, Depression, Anxiety, Fatigue and Physical functioning had a continuous outcome, as well as a cut-off value to indicate impairment. These outcomes were measured with the same instrument as stated in Table 2.

Table 5
Differences between study groups in psychosocial outcome measures, with and without correction for confounders, and the mediating effect of health-related concepts.

Psychosocial outcome measures	Uncorrected model	Corrected model[1]	Corrected models including one of the following mediating factors:					
			Fatigue		Physical functioning		Cognitive functioning	
	B (95% CI)	B (95% CI)	B (95% CI)	%[2]	B (95% CI)	%[2]	B (95% CI)	%[2]
Quality of life								
QFS	−12.1 (−14.9; −9.4)	−11.1 (−13.9; −8.3)	1.5 (−1.5; 4.5)	100%	−5.9 (−8.7; −3.1)	47%	−4.2 (−7.1; −1.5)	62%
Chronic Q fever	−8.4 (−11.8; −4.9)	- 8.5 (−12.5; −4.5)	0.97 (−2.7; 4.6)	100%	−4.3 (−8.1; −0.54)	49%	−6.2 (−9.8; −2.6)	28%
General population	Ref	Ref	Ref		Ref		Ref	
Depression								
QFS	1.6 (1.1; 2.1)	1.4 (0.91; 1.9)	−0.49 (−1.1; 0.08)	100%	0.58 (0.06; 1.1)	60%	0.25 (−0.27; 0.76)	83%
Chronic Q fever	1.2 (0.62; 1.9)	1.4 (0.67; 2.1)	−0.04 (−0.74; 0.65)	100%	0.71 (0.02; 1.4)	49%	0.99 (0.33; 1.6)	29%
General population	Ref	Ref	Ref		Ref		Ref	
Satisfaction with life								
QFS	−6.8 (−8.3; −5.3)	−6.4 (−7.9; −4.8)	−0.12 (−1.8; 1.5)	98%	−4.0 (−5.5; −2.4)	38%	−3.4 (−5.0; −1.9)	46%
Chronic Q fever	−4.2 (− 6.1; −2.3)	−3.9 (−6.0; −1.7)	0.82 (−1.2; 2.9)	100%	−1.9 (−4.0; 0.16)	50%	−2.8 (−4.9; −0.81)	26%
General population	Ref	Ref	Ref		Ref		Ref	
Anxiety								
QFS	3.8 (3.0; 4.6)	3.3 (2.4; 4.1)	−0.23 (−1.2; 0.69)	100%	2.2 (1.3; 3.0)	34%	1.0 (0.21; 1.9)	68%
Chronic Q fever	1.9 (0.82; 2.9)	2.1 (0.94; 3.3)	−0.50 (−1.6; 0.63)	100%	1.2 (0.06; 2.4)	42%	1.4 (0.30; 2.4)	36%
General population	Ref	Ref	Ref		Ref		Ref	
Social functioning								
QFS	−33.1 (−37.9; −28.3)	−31.5 (−36.4; −26.7)	- 4.7 (−9.4; −0.06)	85%	−19.2 (−23.7; −14.7)	39%	−21.6 (−26.7; −16.5)	32%
Chronic Q fever	−21.3 (−27.4; −15.3)	−20.6 (−27.5; −13.7)	−0.37 (−8.7; 5.4)	98%	−10.8 (−16.8; −4.8)	48%	−17.1 (−23.7; −10.6)	16%
General population	Ref	Ref	Ref		Ref		Ref	

[1] Corrected for age, gender, (co-)morbidity and education level.
[2] Percentage change in B coefficient between corrected model and corrected model including one specific mediating factor.

correlated with every outcome measure (data not shown). Table 5 shows that fatigue completely mediated the association of patient groups with quality of life and anxiety (100%) and social functioning (85% for QFS patients and 98% for chronic Q fever patients). Physical functioning only partly mediated the effect of QFS on depression (60%). Cognitive functioning completely mediated the effect of QFS on depression (83%), and partly mediated the effect of QFS on quality of life (62%) and anxiety (68%). Physical and cognitive functioning did not mediate any effects of chronic Q fever.

3.5. Mediating effect of various illness perception domains

Table 4 shows the difference in scores on the various domains of illness perception between the three patient groups. Timeline and illness coherence were excluded as mediators, as they did not meet criteria 2 and 3, respectively. Table 6 shows the influence of relevant mediating illness perception factors. The domain consequences induced complete mediation after entering the corrected model of quality of life, depression and anxiety in QFS patients only (84%, 95% and 91%, respectively) and partial mediation in satisfaction with life and social functioning (73% and 55%). Consequences caused partial mediation in all outcomes in chronic Q fever patients (between 57% and 75%). The domain emotional representations showed complete mediation in chronic Q fever patients for anxiety (100%) and partial in all other outcomes (between 51% and 63%), while in QFS patients it only showed partial mediation in anxiety (67%) and depression (51%). Other illness perception domains had no mediating effects.

4. Discussion

This is the first study that presents the impact of chronic Q fever or QFS, five to nine years after acute infection, on psychosocial functioning in a large group of patients. Both chronic Q fever and QFS patients experienced a significantly reduced psychosocial functioning compared to DM patients and the general population, with the exception of relationship satisfaction, which was not significantly reduced in any of the groups after correction for confounders. The impact of chronic Q fever or QFS on quality of life, anxiety and social functioning was completely mediated by the level of fatigue. Although physical and cognitive functioning and some illness perception domains partially mediated the impact on psychosocial functioning, these were less pronounced than the effect of fatigue. Only in QFS patients, the mediating effect of the illness perception domain consequences was complete. Overall, fatigue was found to be the most important mediating factor for both the chronic Q fever as well as the QFS group.

In our study, QFS patients as well as chronic Q fever patients reported lower levels of quality of life, social functioning and higher levels of anxiety compared to the reference groups. This is not surprising, since chronic Q fever patients suffer from a range of physical symptoms and have a high risk on mortality [15]. While QFS causes no mortality, it does have major health-related consequences and patients frequently report many additional complaints besides fatigue [4]. There is a lack of literature on the long-term psychosocial impact of chronic Q fever and QFS, however our results complement previous studies performed on the shorter term in Q fever patients. Strauss et al. showed that Q fever patients with severe fatigue two years after infection showed higher psychosocial complaints compared to matched controls [7]. Van Loenhout et al. demonstrated an impact on quality of life in Dutch Q fever patients four years after infection [6]. Moreover, studies in other infectious diseases, such as Legionnaires' disease, dengue fever or viral meningitis, demonstrated psychosocial impact within one year after acute infection as well [33,34].

Results also showed that DM patients did not experience a reduced psychosocial functioning compared to the general population, while other studies have shown that these patients can suffer from a reduced quality of life or be affected with depression and anxiety compared to a healthy control group [35,36]. The reference group from our study was not a healthy control group, which might partly explain why no large

Table 6
Differences between patient groups in psychosocial outcome measures, with and without correction for confounders, and the mediating effect of various illness perception domains.

Psychosocial outcome measures	Uncorrected model	Corrected model[1]	Influence of mediating factor on corrected model:									
			Consequences		Personal control		Treatment control		Timeline cyclical		Emotional representations	
	B (95% CI)	B (95% CI)	B (95% CI)	%[2]	B (95% CI)	%[2]	B (95% CI)	%[2]	B (95% CI)	%[2]	B (95% CI)	%[2]
Quality of life												
QFS	−12.2 (−15.4; −9.0)	−8.8 (−12.8; −4.8)	−1.4 (−5.5; 2.6)	84%	−5.6 (−9.8; −1.4)	37%	−4.7 (−9.0; −0.29)	47%	−7.0 (−11.3; −2.8)	20%	−5.0 (−8.8; −1.2)	43%
Chronic Q fever	−8.4 (−12.3; −4.5)	−9.0 (−13.1; −4.9)	−3.7 (−7.6; 0.27)	59%	−5.2 (−9.6; −0.83)	42%	−6.1 (−10.4; −1.9)	32%	−7.7 (−11.9; −3.5)	14%	−3.4 (−7.4; 0.66)	63%
Type II diabetes	Ref	Ref	Ref		Ref		Ref		Ref		Ref	
Depression												
QFS	1.7 (1.1; 2.3)	1.3 (0.54; 2.0)	0.06 (−0.68; 0.80)	95%	0.71 (−0.05; 1.5)	44%	0.58 (−0.21; 1.4)	54%	1.0 (0.29; 1.8)	17%	0.62 (−0.08; 1.3)	51%
Chronic Q fever	1.4 (0.68; 2.1)	1.5 (0.79; 2.3)	0.65 (−0.07; 1.4)	57%	0.86 (0.08; 1.7)	43%	1.0 (0.28; 1.8)	31%	1.4 (0.61; 2.1)	10%	0.56 (−0.17; 1.3)	63%
Type II diabetes	Ref	Ref	Ref		Ref		Ref		Ref		Ref	
Satisfaction with life												
QFS	−6.5 (−8.2; −4.8)	−4.6 (−6.7; −2.5)	−1.2 (−3.4; 0.95)	73%	−3.3 (−5.5; −1.1)	29%	−2.9 (−5.2; −0.61)	37%	−3.6 (−5.8; −1.4)	23%	−3.0 (−5.0; −0.92)	36%
Chronic Q fever	−3.9 (−5.9; −1.8)	−4.0 (−6.2; −1.9)	−1.6 (−3.7; 0.58)	61%	−2.5 (−4.8; −0.14)	39%	−2.9 (−5.1; −0.66)	29%	−3.2 (−5.5; −1.0)	19%	−1.6 (−3.8; 0.58)	60%
Type II diabetes	Ref	Ref	Ref		Ref		Ref		Ref		Ref	
Anxiety												
QFS	3.5 (2.5; 4.5)	1.9 (0.77; 3.2)	0.19 (−1.1; 1.5)	91%	1.4 (0.13; 2.7)	28%	1.4 (0.01; 2.72)	31%	1.4 (0.072; 2.6)	32%	0.67 (−0.47; 1.8)	67%
Chronic Q fever	1.6 (0.36; 2.8)	1.8 (0.52; 3.0)	0.44 (−0.81; 1.7)	75%	1.1 (−0.26; 2.4)	38%	1.3 (0.02; 2.6)	25%	1.3 (0.013; 2.6)	27%	−0.18 (−1.4; 1.0)	100%
Type II diabetes	Ref	Ref	Ref		Ref		Ref		Ref		Ref	
Social functioning												
QFS	−30.2 (−35.8; −24.6)	−27.1 (−34.1; −20.0)	−12.2 (−19.1; −5.3)	55%	−22.3 (−29.7; −14.9)	17%	−22.0 (−29.7; −14.2)	19%	−23.3 (−30.7; −16.0)	14%	−20.8 (−27.6; −14.1)	23%
Chronic Q fever	−18.5 (−25.3; −11.7)	−17.9 (−25.1; −10.8)	−7.0 (−13.8; −0.29)	61%	−12.3 (−19.9; −4.6)	32%	−14.4 (−21.9; −6.9)	20%	−15.1 (−22.4; −7.6)	16%	−8.7 (−15.9; −1.6)	51%
Type II diabetes	Ref	Ref	Ref		Ref		Ref		Ref		Ref	

[1] Corrected for age, gender, co morbidity and education level.
[2] Percentage change in B coefficient between corrected model and corrected model including one specific mediating factor.

differences in psychosocial functioning between the general population and DM patients were observed. DM patients might have benefited from systematic follow-up by their GP which is standard in Dutch diabetes care [37]. Furthermore, we gave GPs the possibility of excluding DM patients who they deemed not fit to participate. This has likely resulted in the exclusion of patients with either more severe DM or multi-morbidity, thus a rather healthy DM population was recruited.

We identified only few studies that investigated the role of mediators on the psychosocial impact of an infectious disease. Chandra et al. measured factors potentially influencing perceived health related quality of life in patients with post-treatment Lyme disease syndrome (PTLDS), which includes symptoms such as chronic subjective pain, severe fatigue and cognitive impairment. This study concluded that fatigue is the most important factor contributing to an impaired health related quality of life in PTLDS patients [38]. The study by Chandra et al., as well as our study, demonstrated the importance of fatigue in mediating or attributing to psychosocial problems in these patient groups.

Our study focused on the long term impact of sequelae of Q fever and only included QFS patients and no patients with CFS triggered by other events. As there are differences in diagnostic criteria between QFS and CFS patients, we believe it is better to distinguish between QFS and CFS. Furthermore, a study by Keijmel et al. also showed several differences between CFS and QFS, taking into account the discrepancy in diagnostic criteria and illness duration [39]. QFS patients were less often female and had a higher BMI compared to CFS patients. QFS patients reported less additional symptoms than CFS patients, however there were no differences in fatigue severity and psychological distress [39].

To our knowledge, this is the first study measuring illness perception in Q fever patients. Chronic Q fever and QFS patients reported more negative beliefs about their illness than DM patients, such as more negative consequences and emotions, a lower level of control and personal understanding of their illness and a higher cyclical nature of the illness. As mortality remains high in chronic Q fever [40,41] and QFS patients mostly received treatment in an experimental setting [8,42], this might explain the differences in negative illness beliefs compared to DM patients. Negative illness perceptions can negatively affect the prognosis in patients with chronic fatigue syndrome [43]. Cognitive behavioural therapy (CBT) aims to change dysfunctional beliefs and behaviours with respect to fatigue and has been shown to reduce symptoms in QFS patients [42].

Our study had some limitations. First, this study only focused on the impact on psychosocial functioning, but the impact of a disease is much broader. Especially looking at chronic Q fever, which is a serious illness with a significant mortality rate (15.8%, 5 years after the outbreak) [15]. Only taking into account the impact on psychosocial functioning may have lead to an underestimation of the overall impact of chronic Q fever. Second, there is an uncertainty on whether our reference group was a good representation of the general population. Participants were recruited through a local newspaper and this might have lead to a selected group who read this newspaper and included only participants who had the time to participate. Also certain groups may be over-represented as some participants from the general population were recruited by snowball sampling. However, we did correct for socio-demographic characteristics and these had no major consequences on the outcomes. Third, seronegativity for Q fever was not tested in participants from the general population and the DM patients. During the epidemic, acute Q fever was highly prevalent in the province of Noord-Brabant, but was also present in every other province of the Netherlands. Although we did not recruit references from the general population in the province of Noord-Brabant, it is possible that participants had an asymptomatic or subclinical Q fever infection [44]. Fourth, since onset of illness of patients varied between five to nine years, there might have been variation in outcome measures between patients due to this fact. However, due to inclusion of the general population in our models, illness duration could not be included as a factor in our study. Lastly, the mediation analysis presumes causality, but causality cannot be inferred using cross-sectional data. However, assuming health-related concepts as mediators is most plausible as these concepts, rather than psychosocial outcomes, are more likely to be a direct result of the illness.

In conclusion, this study demonstrated that patients with chronic Q fever and QFS experienced a high long-term impact on quality of life (depression and satisfaction with life), anxiety and social functioning compared to the general population and patients with DM, with fatigue being the most important factor that explains the low functioning. Health care workers need to be aware of the long-term impact of chronic Q fever and QFS on psychosocial functioning in order to provide proper guidance.

Funding

This work was supported by Q-support [grant number AMPHI150114-00].

Competing interest

The authors have no competing interests to report.

Acknowledgement

We like to thank E. de Vries for her assistance in the data collection and all participants in this study for participation. We wish to acknowledge the assistance and collaboration from M. van den Berg (patient organisation Q-uestion), S. Keijmel and R. Raijmakers (Radboud university medical center), P. Wever and S. Shamelian (Jeroen Bosch Hospital), M. Leclerq (Bernhoven Hospital), M. van Kasteren (Elisabeth Hospital), J. Vercoulen (Radboud university medical center) and the general practitioners from the Radboud university medical center Academic General Practices Network.

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