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The health status of a village population, 7 years after a major Q fever outbreak

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SUMMARY

From 2007 to 2010, The Netherlands experienced a major Q fever outbreak with more than 4000 notifications. Previous studies suggested that Q fever patients could suffer long-term post-infection health impairments, especially fatigue. Our objective was to assess the *Coxiella burnetii* antibody prevalence and health status including fatigue, and assess their interrelationship in Herpen, a high-incidence village, 7 years after the outbreak began. In 2014, we invited all 2161 adult inhabitants for a questionnaire and a *C. burnetii* indirect fluorescence antibody assay (IFA). The health status was measured with the Nijmegen Clinical Screening Instrument (NCSI), consisting of eight subdomains including fatigue. Of the 70·1% (1517/2161) participants, 33·8% (513/1517) were IFA positive. Of 147 participants who were IFA positive in 2007, 25 (17%) seroreverted and were now IFA negative. Not positive IFA status, but age <50 years, smoking and co-morbidity, were independent risk factors for fatigue. Notified participants reported significantly more often fatigue (31/49, 63%) than non-notified IFA-positive participants (150/451, 33%). Although fatigue is a common sequel after acute Q fever, in this community-based survey we found no difference in fatigue levels between participants with and without *C. burnetii* antibodies.

Key words: *Coxiella burnetii*, IFA, NCSI, post-infection fatigue, Q fever.

INTRODUCTION

Q fever is a zoonosis caused by the bacterium *Coxiella burnetii*. In 2007, Herpen, a small village in the south of The Netherlands was heavily affected by a Q fever outbreak [1]. This outbreak was followed by larger outbreaks in 2008 and 2009, in a larger geographical

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area and culminated in 4107 notifications nationwide by 2010 [2].

A common sequel of acute Q fever is protracted incapacitating fatigue [3–5], often denoted as Q fever fatigue syndrome (QFS) that may continue for ⩾10 years [6, 7]. Patients with QFS may experience severe sweating, breathlessness, blurred vision, reduced exertion, myalgia, arthralgia, sleeping disorders and mood swings [7, 8], symptoms that resemble chronic fatigue syndrome (CFS). The aetiology of QFS is not entirely understood. Dysregulation of cytokines due to persisting antigens of *C. burnetii* are described as causing chronic stimulation of the immune system [9, 10]. A post-infection fatigue syndrome (PIFS) [11] may also occur after other infections [12], such as *Borrelia burgdorferi* [13], *Legionella pneumophila* [14], Epstein–Barr virus and Ross River virus infections [12]. According to several studies, Q fever patients have an impaired health status, pulmonary disorders and an increased risk of problems in general and social functioning [3–8, 12, 14].

General practitioners (GPs) and the population in the Q fever affected area, and the national Q fever patient organization, speculated that the number of infections and long-term consequences such as fatigue were underestimated. The local municipal health service (MHS) therefore initiated the 'Q-Herpen-II' study in – this small rural village with a stable Caucasian population – in order to investigate the presence of antibodies against *C. burnetii* in relation to the health status with an emphasis on fatigue.

METHODS

Study design and study population

The Municipal Health Service (MHS) 'GGD Hart voor Brabant' executed this study as part of the larger Q-Herpen-II study. The Medical Ethics Review Committee of Utrecht University Medical Centre, approved the study (protocol 13-367/D Q-Herpen II). For this cross-sectional population study all adult inhabitants (aged ⩾18 years) in the village of Herpen (postal code 5373) were invited to participate. The municipal administration provided demographic data for the 2161 inhabitants. In January 2014, all were sent a letter by mail containing information on the study with a participation request, a questionnaire and an informed consent form. The questionnaire included questions on demographics, smoking, the participant's knowledge or perception of their Q fever status, risk factors associated with chronic Q fever, Q fever vaccination status, chronic medical conditions and medication use.

The current health status was assessed with the Nijmegen Clinical Screening Instrument (NCSI), which is a validated method originally developed to measure the health status of COPD patients in a clinical setting [15]. The instrument consists of the main domains: symptoms, functional impairment, and quality of life. These are divided into eight subdomains (Table 1). Patients' scores are subdivided into 'normal', 'mild problems' and 'clinically relevant problems'. The only exception is the subdomain general quality of life (GQOL) that is divided into 'normal' and 'clinically relevant problems'/'severe problems'. In the univariate and multivariate analysis, the NCSI categories mild problems and clinically relevant problems were combined into one category designated 'problems'. Age, smoking behaviour, and educational level were dichotomized.

During 5 days in February and 1 day in March 2014, questionnaires were handed in by participants and checked for missing information and errors by medical staff together with the participant. This was followed by venepuncture.

Antibodies against *C. burnetii* were determined with the indirect fluorescence antibody assay (IFA). An IFA IgG phase I or II titre ⩾1:64 was considered positive. The IFA results were reported to participants and their GPs with a medical recommendation. Data on the occurrence of chronic Q fever are described in a separate publication [16].

We verified if participants had been notified previously, by using the local MHS data. In The Netherlands acute Q fever is notifiable. Any acute Q fever diagnosis must be reported to the MHS both by the clinician and the laboratory of medical microbiology. Reported cases that according to the MHS meet the predefined national case definition are notified and registered in a national surveillance system. Notification criteria used at the beginning of the outbreak in 2007 were: a laboratory confirmation and matching clinical symptoms. In July 2008 the Dutch Q fever notification criteria were changed to: the presence of fever, pneumonia or hepatitis and a laboratory diagnosis plus a report to the MHS within 90 days following the onset of illness. For notification at least one of the following laboratory criteria should be met: seroconversion or a ⩾fourfold *C. burnetii* IgG antibody titre increase in paired sera (minimally 2 weeks apart) of an IFA or a complement fixation

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Table 1. *Domains and subdomains of the Nijmegen Clinical Screening Instrument (NCSI) with their definition, the instruments on which they are based and number of question used*

Domains	Subdomain	Definition	Instruments	No. of questions
Symptoms	Subjective pulmonary symptoms	Overall burden of pulmonary symptoms	PARS-D Global Dyspnoea Activity, Global Dyspnoea Burden	2
	Dyspnoea emotions	Level of frustration and anxiety experienced when dyspnoeic	DEQ Frustration, Anxiety	6
	Fatigue	Level of experienced fatigue	CIS Subjective Fatigue	8
Functional impairment	Behavioural impairment	The extent of inability to perform specific and concrete activities as a result of the disease	SIP Home Management, Ambulation	22
	Subjective impairment	Experienced degree of impairment in general and in social functioning	QoLRiQ General Activities	4
Quality of life	General (GQOL)	Mood and the satisfaction with life as a whole	BDI Primary Care Satisfaction with Life Scale	12
	Health related (HRQOL)	Satisfaction related to physiological functioning and the future	Satisfaction Physiological Functioning, Satisfaction Future	2
	Satisfaction relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction Spouse, Satisfaction Social	2

PARS-D, Physical Activity Rating Scale – dyspnoea; DEQ, Dyspnoea Emotions Questionnaire; CIS, Checklist Individual Strength; SIP, Sickness Impact Profile; QoL-RiQ, Quality of Life for Respiratory Illness Questionnaire, BDI, Beck Depression Inventory.

test (CFT), or presence of IgM phase II antibodies or a positive *C. burnetii* PCR (unless the sample is from a patient with chronic Q fever). If any of the clinical, laboratory or time criteria were not met a Q fever case would, although reported, not be registered (notified) in the national surveillance system.

We assumed that IFA-positive (IgG phase I or II $\geqslant$1:64) participants who reported that they did not to recall an acute Q fever episode, had either previously experienced an asymptomatic or mild acute infection that had not been medically evaluated. These individuals were classified as 'no recollection of a previous infection'. Participants that were adamant that they had been infected and reported their belief as a past infection even if this was without evidence of any medical proof were classified as 'belief in a previous infection'. We conducted a stratified analysis, using the Mantel–Haenzel Summary χ^2 test, to control for the confounding effect of knowledge of/belief of a past episode of acute Q fever. It is therefore not a multivariate statistical model.

Statistical analysis

Questionnaires were digitally scanned into a SPSS database and analysed with SPSS v. 21.0 (SPSS Inc., USA) and Open Epi (http://www.openepi.com/Menu/OE_Menu.htm). Information on age and gender of non-participants was obtained from the municipal administration.

Participants that had been vaccinated against Q fever were excluded from the analysis.

Proportions were compared with the χ^2 test. Multivariate logistic regression analyses was used to compare the NCSI subdomain scores incorporating 2014 IFA status, age, gender, smoking, educational level, rheumatoid arthritis, psychiatric disorders and/or use of psychiatric medication, and other co-morbidity. A P value <0·05 was considered significant.

RESULTS

Participants and non-participants

Of the 2161 inhabitants, 70·9% (1534/2161) participated. Both a blood sample and a questionnaire were received from 70·2% (1517/2161) participants.

Participants and non-participants were comparable with respect to gender and age (data not shown).

Characteristics and IFA status of participants

Of the participants 33·8% (n = 513) were IFA positive. As the five participants vaccinated against Q fever

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were removed from our database, data were analysed for the remaining 1512 participants, including 510 IFA positives.

There were no differences in gender, age, educational level and presence of co-morbidity between IFA-positive and IFA-negative participants (Table 2). IFA-positive participants were more often current smokers than IFA-negative participants (Table 2). Of note, of the 147 participants who were IFA positive in 2007, 25 (17%) seroreverted and were IFA negative in 2014 [16].

NCSI subdomains in relation to IFA status

IFA-positive participants did not score significantly higher (worse) on NSCI subdomains compared to IFA-negative participants (Fig. 1, for data see Supplementary Table S1). By contrast, in IFA-positive participants, the odds ratios (ORs) for the three subdomains; subjective pulmonary complaints [OR 0·69, 95% confidence interval (CI) 0·55–0·88, $P < 0·01$], dyspnoea emotions (OR 0·65, 95% CI 0·49-0·85, $P < 0·01$) and subjective impairment (OR 0·77, 95% CI 0·59–0·98, $P = 0·04$) were <1.

A positive IFA status was not an independent risk factors for fatigue in the multivariate model but being aged <50 years, a current smoker, and having an underlying medical condition (co-morbidity) were (Table 3). See Table 4 for the independent risk factors for GQOL.

Regardless of IFA status 37·7% of participants reported fatigue including 22·6% with clinically relevant fatigue. Participants with chronic medical conditions such as psychiatric disorders had both a severely impaired GQOL and fatigue in 64·0% and 48·0% of cases, respectively. While 35·4% of participants with rheumatoid arthritis had a severely impaired GQOL, for fatigue this figure was 36·9%.

When using the IFA titre as a semi-quantitative measure, participants with a higher IFA titre did not report more fatigue than those with a lower IFA titre (data not shown).

Notification in relation to the subdomains fatigue and GQOL

Of the 510 IFA-positive participants, 51 had previously been notified for acute Q fever, 49 of whom completed the subdomain fatigue part of the questionnaire. These notified participants presented mild and clinically relevant fatigue (63·3%, $n = 31/49$) significantly more often (Table 5) than IFA-positive participants with a known positive Q fever status, who had not fitted the notification criteria combined with those who were first identified during this study (33·3%, $n = 150/451$, OR 3·4, 95% CI 1·9–6·5, $P < 0·01$). These notified and non-notified IFA-positive participants did not differ significantly for the subdomain GQOL.

Belief in a previous Q fever infection in relation to fatigue

The questionnaire contained several questions about perceived or medically confirmed acute Q fever. Of the 181 participants that reported a medically confirmed diagnosis or believed that they had suffered from acute Q fever, 137 (76%) were IFA positive in 2014 (Supplementary Table S2). We assumed that IFA-positive participants who did not recall an acute Q fever episode had previously experienced an asymptomatic acute infection, or mild illness that had not been medically evaluated. A stratified analysis showed no evidence of confounding by belief in a past Q fever episode in the relationship between IFA status and fatigue (Supplementary Table S2).

DISCUSSION

In this unique, large cross-sectional population study in a Q fever high-incidence village, 7 years after a large Q fever outbreak, we found a high seroprevalence (34%) of *C. burnetii* antibodies. An impaired GQOL or abnormal fatigue status, was not associated with *C. burnetii* IFA-positive serological test results. Overall, 37·7% of participants reported fatigue including 22·6% with clinically relevant fatigue. In the nearby city of Nijmegen, a study in 2009 found that more than 30% of a random population sample suffered from fatigue for >6 months [17]. A German study, also reported that 30% of participants from a general population sample reported moderate fatigue during the last 6 months while 10% of participants had substantial fatigue for the last ⩾6 months [18]. These two studies clearly indicate that fatigue levels in the general population are high. The reported 37·7% prevalence figure for fatigue in our study seems large, but compared to the above-mentioned figure of 30% it is not. As these two studies used different instruments to assess fatigue, only a rough comparison of the prevalence of fatigue is possible.

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Table 2 *Characteristics of study participants and the presence of* Coxiella burnetii *antibodies measured with the immunofluorescence assay (IFA)*

	All		IFA positive		IFA negative		
	(*N* = 1512)	(100%)	(*n* = 510)	(33·8%)	(*n* = 1002)	(66·2%)	*P* value
Mean age, years	51·9	(S.D. = 16·5)	51·5	(S.D. = 15·7)	52·1	(S.D. = 16·9)	0·54*
Gender							0·70†
Male	748	(49·6)	256	(50·2)	492	(49·1)	
Female	764	(50·4)	254	(49·8)	510	(50·9)	
Smoking							0·04†
Current	276	(18·3)	110	(21·6)	166	(16·6)	
Former	565	(37·5)	191	(37·5)	374	(37·5)	
Never	666	(44·2)	209	(41·0)	457	(45·8)	
Educational level†							0·05†‡
Low	822	(55·2)	289	(57·5)	533	(54·0)	
Average	425	(28·5)	149	(29·6)	276	(28·0)	
High	243	(16·3)	65	(12·9)	178	(18·0)	
Known or perceived previous Q fever†							
Yes, medically confirmed	147	(9·8)	122	(24·1)	25	(2·5)	<0·01†
Yes, own belief	46	(3·1)	23	(4·5)	23	(2·3)	
No	775	(51·8)	219	(42·3)	556	(56·2)	
Don't know	527	(35·3)	142	(28·1)	385	(38·9)	
Rheumatoid arthritis							
Yes	127	(8·4)	37	(7·3)	90	(9·0)	0·28†
No	1378	(91·6)	471	(92·7)	907	(91·0)	
Psychological disease or medication†							
Yes	80	(5·3)	31	(6·1)	49	(4·9)	0·33†
No	1430	(94·7)	479	(93·9)	951	(95·1)	
Other co-morbidity							
Yes	442	(29·3)	144	(28·2)	298	(29·8)	0·55†
No	1069	(70·7)	366	(71·8)	703	(70·2)	

* Analysed with the independent sample *t* test or † Pearson's χ^2 test.
‡ The actual *P* value is 0·054.

GQOL and fatigue were, in this study, severely impaired in participants with chronic medical conditions such as psychiatric disorders and rheumatoid arthritis. The influence of chronic medical conditions on fatigue has been reported previously for psychiatric disorders [19–21], rheumatoid arthritis [22], diabetes [23], and heart failure [24, 25].

Studies in The Netherlands and elsewhere clearly document persisting fatigue and an impaired quality of life after Q fever. These studies focused on proven acute Q fever episodes, i.e. patients with clinical disease and with a confirmed laboratory diagnosis that often fitted the national notification criteria (symptomatic cases) [3, 4, 11, 14, 26]. Our findings are in line with the international literature, as we also documented persisting fatigue in the small group of 49 previously notified participants. However, in this community-based study we found no increased risk for an impaired health status or fatigue in participants with *C.burnetii* antibodies. Nor could we find a relationship between the fatigue level and IFA titre. This finding was similar to data from Hussain-Yusuf *et al.* [27] who also found no detectable relationship between fatigue levels and serology 6 years after exposure.

The present study and other studies support the notion that the severity of symptoms during the acute episode predicts long-term symptoms such as fatigue [4, 12] and that QFS follows clinically overt infections, but rarely that of a subclinical infection [28]. While the severity of the infection during the acute phase (here notification) was related to the intensity of the later PIFS, psychological and microbiological factors were not.

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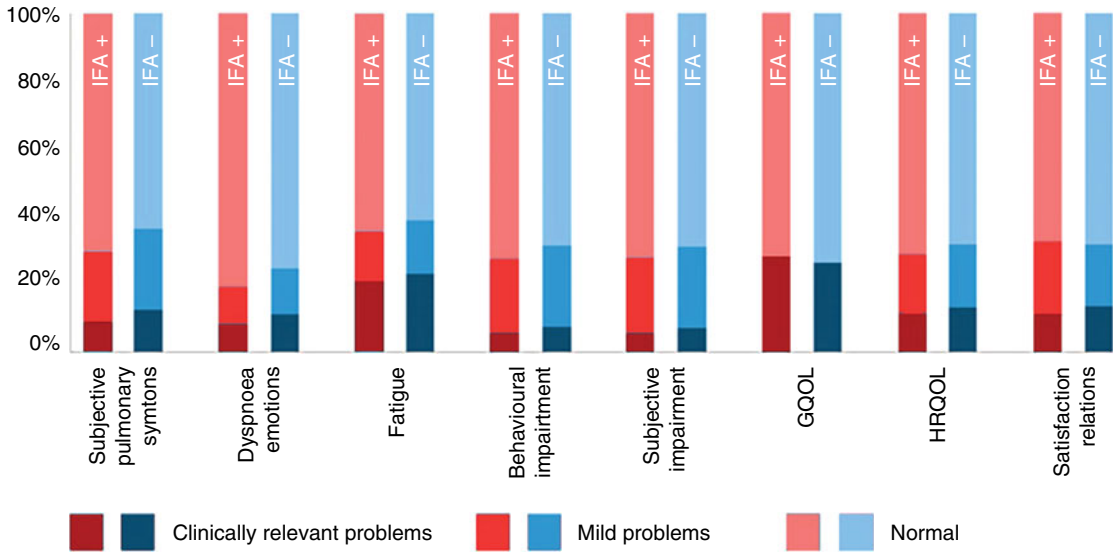

Fig. 1. NCSI subdomains in paired columns as indirect fluorescence antibody assay (IFA) positive (IFA+) ($n = 509$) and negative (IFA–) ($n = 998$) divided into: clinically relevant problems (bottom), mild problems (middle) and normal (top). GQOL, General quality of life; HRQOL, health-related quality of life.

The majority of participants with a positive IFA result had never been notified for acute Q fever, presumably because the acute infection episode had passed with only mild clinical symptoms or was entirely asymptomatic.

A previous study from The Netherlands reported no significant difference in the NCSI subdomain scores between asymptomatic cases infected with *C. burnetii* ($n = 11$) and healthy controls ($n = 23$) [5]. Although that study's sample size was small its results are in accordance with our findings.

A comparison between patients with a lower respiratory tract infection of several causes ($n = 32$) and those with Q fever ($n = 50$) showed no significant differences for most NCSI subdomains (including fatigue and GQOL approximately 15 months after the initial infection [29]. Twelve months after the onset of symptoms 50% *vs.* 42·6% of patients with a *Legionella* infection had severe fatigue and GQOL, respectively (measured with the NCSI) [14]. However, notified (and therefore symptomatic) Q fever patients scored worse for severe fatigue and GQOL with 60·2% and 50·0%, respectively, compared to those with a *Legionella* infection [14].

We were unable to verify the severity of any acute illness episode with certainty because the acute episode could have taken place years ago. We speculated that participants who believed that they had suffered from an acute Q fever episode in the past would report current fatigue more often. We also expected to find that people with fatigue in communities affected by Q fever would attribute their fatigue to a previous Q fever episode, even when acute Q fever was not medically diagnosed. However, our analysis showed that this factor was not significant and could be disregarded.

From historical data we know that 17% of participants from this population that were IFA seropositive in 2007, had become seronegative by 2014 [16]. This shows that negative Q fever serology does not rule out a previous *C. burnetii* infection which should be taken into account if high-risk populations are vaccinated against Q fever. This also shows that Q fever serology is insufficient to diagnose whether long-term fatigue might been caused by Q fever.

The major strengths of this study are the high response rate of 70·9%, a questionnaire check before venepuncture and the inclusion of participants from the same homogenous village with a high Q fever prevalence. This is the first large study to compare IFA-positive and IFA-negative cases from the same homogenous population. The whole spectrum from initially asymptomatic, mildly symptomatic and severe symptoms during an acute Q fever infection is included. Furthermore, the control groups used in many other studies were often healthier than the general population as only individuals without known co-morbidities were selected [3, 4, 14]. Our control group included participants with co-morbidities and is therefore a realistic representation of the general population. Together this results in unique and robust data.

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Table 3. *Univariate and multivariate logistic regression of factors for the outcome fatigue†*

	Fatigue†							
	Univariate analysis				Multivariate analysis			
Characteristic	Total *N*	OR	(95% CI)	*P* value	Total *N*	OR	(95% CI)	*P* value
IFA								
Positive	482	0·8	(0·7–1·1)	0·2	472	0·8	(0·6–1·03)	0·08
Negative	942	1·0‡			921	1·0‡		
Age dichotomous								
⩽50	654	1·4	(1·1–1·7)	<0·01	641	2·0	(1·5–2·5)	<0·01
>50	780	1·0‡			752	1·0‡		
Gender								
Female	730	1·3	(1·1–1·6)	0·01	705	1·2	(0·9–1·5)	0·12
Male	704	1·0‡			688	1·0‡		
Smoking								
Current	260	1·9	(1·5–2·6)	<0·01	256	1·8	(1·3–2·4)	<0·01
Former or never	1172	1·0‡			1137	1·0‡		
Education level								
Median and high	756	1·2	(0·9–1·5)	0·05*	751	1·3	(1·0–1·6)	0·05**
Low	642	1·0‡			642	1·0‡		
Rheumatoid arthritis								
Yes	122	2·1	(1·4–3·0)	<0·01	122	2·1	(1·4–3·2)	<0·01
No	1309	1·0‡			1309	1·0‡		
Psychiatric condition/medication								
Yes	75	4·6	(2·7–7·7)	<0·01	74	4·1	(2·4–6·9)	<0·01
No	1359	1·0‡			1319	1·0‡		
Other chronic diseases								
Yes	418	1·9	(1·5–2·4)	<0·01	407	2·0	(1·6–2·6)	<0·01
No	1016	1·0‡			689	1·0‡		

OR, Odds ratio; CI, confidence interval.
† Fatigue is divided into normal *vs.* the combination of mild and clinically relevant fatigue scores, here designated fatigued or abnormal fatigue score.
‡ Reference group.
The actual *P* value is * 0·053 and ** 0·054.

Another strength is that by using a validated instrument, i.e. the NCSI, we can compare our data with other studies that used this instrument.

Lower and higher [30] IFA cut-off values are internationally used for screening. Lacking an international standard we used the IFA value 1:64 that is commonly used in The Netherlands.

Another limitation of the study is that the fatigue status of participants before the outbreak is unknown, thus participants might already have been fatigued for other reasons before the outbreak took place. The use of a self-reporting questionnaire is also a limitation. Even though questionnaires were checked for missing information or errors by medical and paramedical staff, it was not possible to entirely avoid missing information. A non-quantifiable recall bias is likely to have occurred for the following two reasons: perceived acute Q fever episodes were reported with a time lag of 4–7 years [31]. Furthermore, cross-sectional study designs with retrospective components have in general a higher risk of recall bias [32]. An acute illness in the past could also have been erroneously reported by a participant as Q fever regardless of the cause.

CONCLUSIONS

Seven years after the start of the Q fever epidemic in The Netherlands, the prevalence of antibodies against *C. burnetii* in the adult population of an affected village was still 34%. A large proportion of the population reported an impaired health status with fatigue. However, there were no differences between those with and those without antibodies against *C. burnetii* for fatigue and other health status parameters.

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Table 4. *Univariate and multivariate logistic regression of factors for the outcome general quality of life (GQOL)*

	Clinically relevant abnormal GQOL*							
	Univariate analysis				Multivariate analysis			
Characteristic	Total *N*	OR	(95% CI)	*P* value	Total *N*	OR	(95% CI)	*P* value
IFA								
Positive	497	1·1	(0·9–1·4)	0·46	487	1·0	(0·8–1·3)	0·94
Negative	978	1·0†			954	1·0†		
Age dichotomous								
⩽50	665	0·9	(0·7–1·1)	0·35	651	1·4	(1·1–1·8)	0·01
>50	825	1·0†			790	1·0†		
Gender								
Female	752	0·9	(0·7–1·1)	0·27	718	1·0	(0·8–1·3)	0·88
Male	738	1·0†			723	1·0†		
Smoking								
Current	266	1·5	(1·1–2·0)	<0·01	260	1·3	(0·9–1·8)	0·09
Former or never	1222	1·0†			1368	1·0†		
Education level								
Median and high	790	1·2	(0·9–1·6)	0·08	785	1·2	(0·9–1·6)	0·14
Low	656	1·0†			656	1·0†		
Rheumatoid arthritis								
Yes	127	1·5	(>1·0–2·2)	0·38	121	1·5	(1·0–2·3)	0·06
No	1359	1·0†			132	1·0†		
Psychiatric condition/medication								
Yes	75	5·2	(3·2–8·4)	<0·01	73	4·7	(2·9–7·8)	<0·01
No	1415	1·0†			1368	1·0†		
Other chronic diseases								
Yes	441	1·5	(1·2–1·9)	<0·01	424	1·4	(1·1–1·9)	0·04
No	1049	1·0†			1017	1·0†		

* GQOL is divided into normal *vs.* clinically relevant abnormal GQOL.
† Is the reference group.

Table 5. *Notification status and characteristics of 500 IFA-positive participants in relation to fatigue status*

								Fatigue status					
	Total	Male		Mean		Age ⩽50 yr		Normal		Mild problem		Clinically relevant problem	
	N	*n*	(%)	age, yr	(S.D.)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Notified	49	29	(58·2)	52·9	(14·3)	22	(44·9)	18	36·7	8	16·3	23	46·9
Positive not notified	72	47	(65·3)	56·3	(11·7)	19	(26·4)	49	68·1	6	8·3	17	23·6
Identified in 2014	379	176	(46·4)	50·2	(16·3)	187	(49·3)	252	66·5	54	14·2	73	19·3
Total	500							319		68		113	

Participants who had been notified for clinically apparent acute Q fever, reported twice as much fatigue compared to those who had serological evidence of a past infection but who had previously not been notified because they did not fulfil the notification criteria or because they had experienced a mild or asymptomatic infection.

There are many reasons for fatigue and in some cases a Q fever episode can be an attributing or causative factor. Even though some individuals developed

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fatigue after a *C. burnetii* infection the majority of individuals became fatigued due to other and often unknown reasons.

SUPPLEMENTARY MATERIAL

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DECLARATION OF INTEREST

None.

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