1 **Long-term health outcomes of Q-fever fatigue syndrome patients**

2 Inge Spronk[1*], Iris M. Brus[1], Annemieke de Groot[2], Peter Tieleman[2], Alfons G. M. Olde Loohuis[2], Juanita

3 A. Haagsma[1], Suzanne Polinder[1]

4

5 [1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, P.O. Box 2040,

6 3000CA, Rotterdam, the Netherlands

7 [2]Q-support, Goudsbloemvallei 1, 5237 MH 's Hertogenbosch, the Netherlands

8

9 *Corresponding author:

10 I. Spronk

11 Erasmus MC, University Medical Center Rotterdam, Department of Public Health

12 P.O. Box 2040, 3000 CA Rotterdam

13 The Netherlands

14 Tel. 0031 1070 38914

15 Email: i.spronk@erasmusmc.nl

16

17

Summary

This study determined long-term health outcomes (≥10 years) of Q-fever fatigue syndrome (QFS). Long-term health complaints, health-related quality of life (HRQL), health status, energy level, fatigue, post exertional malaise, anxiety and depression were assessed. Outcomes and determinants were studied for the total sample and compared among age subgroups: young (<40y), middle-aged (≥40-<65y), and older (≥65y) patients.

368 QFS patients were included. Participants reported a median number of 12.0 long-term health complaints. Their HRQL (median EQ-5D-5L index: 0.63) and health status (median EQ VAS: 50.0) were low, their level of fatigue was high, and many experienced post-exertional malaise complaints (98.9%). Young and middle-aged patients reported worse health outcomes compared to older patients, with both groups reporting a significantly worse health status, higher fatigue levels and anxiety, and more post-exertional malaise complaints; and middle-aged patients having a lower HRQL and a higher risk of depression. Multivariate regression analyses confirmed that older age is associated with better outcomes, except for the number of health complaints. QFS has thus a considerable impact on patients' health more than 10 years after infection. Young and middle-aged patients experience more long-term health consequences compared to older patients. Tailored healthcare is recommended to provide optimal care for each QFS patient.

1. Introduction

The largest Q-fever epidemic worldwide happened in the Netherlands between 2007 and 2010 [1]. Q-fever is a zoonotic disease caused by the bacterium *Coxiella burnetii* [2]. About 40% of the infected individuals experience short-term complaints ranging from mild flu-like symptoms, such as fatigue and headache, to severe symptoms like high fever, pneumonia and hepatitis [3].

Acute Q-fever usually resolves within a few weeks, however, about 20% of the patients remain chronically fatigued and develop Q-fever Fatigue Syndrome (QFS) [4]. QFS patients experience persisting fatigue over six months causing an impaired health status and significant limitations in daily functioning [4-7]. In addition to fatigue, QFS symptoms include a wide range of health symptoms, like headache, blurring of vision, impaired memory, sleeping problems, exacerbation of symptoms after exercise (post exertional malaise: PEM), and musculoskeletal pain [4-7].

Early works, that studied the impact of Q-fever on health outcomes up to 10 years after the acute Q-fever infection, showed that Q-fever, and especially QFS, has a prolonged negative impact on patients' health status, health-related quality of life (HRQL) and well-being [4, 6, 8-10]. Besides QFS has a negative economic impact for both patients and society [3]. Compared to the general population, QFS patients have a substantially worse HRQL, and experience more health complaints and increased levels of fatigue [6, 8, 10]. In addition, QFS is associated with reduced social function and labor participation, and increased sick leave [3, 8, 10, 11].

The vast majority of previous studies included QFS patients as a subgroup; not specifically focusing on this important patient group which has to deal with substantially more long-term effects compared to Q-fever patients not having QFS. Besides, the impact of Q-fever and QFS on patients' lives have been studied up to 10 years post infection [4, 6, 8-10]. As patients continue to suffer from the prolonged consequences, it is important to get insights into the impact longer periods of time after the infection in this patient group. Focusing on QFS patients provides the opportunity to study subgroups as well as

3

determinants of health and long-term consequences. An earlier study found some differences in HRQL among age subgroups, with younger Q-fever patients having a worse HRQL compared to older patients [8]. However, this study did not investigate this specifically for QFS patients nor studied age specific differences for other long-term outcomes. Therefore, the aim of the present study was to determine long-term health outcome (≥10 years) of QFS, both for the total QFS patient population as well as separately for three different age-groups of patients: <40 years old; ≥40-<65 years old; and ≥65 years old.

2. Materials and methods

2.1. Study design and participants

This study was performed in collaboration with Q-support, the Q-fever expertise and support center for patients and healthcare professionals in the Netherlands [12]. This study describes the baseline measurement of a large longitudinal study aiming at improving insights into the long-term impact of QFS on patient's health, wellbeing, social participation and healthcare use. In September 2021, adult QFS patients registered at Q-support received an e-mail invitation to fill out an online questionnaire about the impact of QFS on their lives. The questionnaire was developed in collaboration with healthcare providers and QFS patients (Appendix A). Patients could request a paper version of the questionnaire. If patients did not respond within two weeks, an e-mail reminder was sent. A second reminder was sent if patients did not respond within two weeks on the first reminder; a third reminder was sent if patients did not respond within two weeks on the second reminder.

Study participation was voluntary, and all participants provided online informed consent before filling out the questionnaire. The study was approved by the Medical Ethics Review Board of Erasmus MC (MEC-2021-1606), conducted in line with the principles of the Declaration of Helsinki and followed the STROBE guidelines. For this manuscript, patients ≥10-year post Q-fever infection were selected. In case

4

year of Q-fever infection was unknown, the year of QFS diagnoses was used as substitute. In case year of QFS diagnoses was also unknown, patients were excluded.

2.2. Measures

2.2.1. Sociodemographic and medical characteristics

Questions on sociodemographic and medical characteristics were included in the questionnaire. Sociodemographic characteristics included age, gender, educational level, and living situation. Age was categorized into young (<40 years old), middle-aged (≥40-<65 years old), and older (≥65 years old). These age subgroups are conform the age distribution used by Statistics Netherlands [13]. Educational level was categorized into low, middle and high according to the International Standard Classification of Education [14]. Living situation was dichotomized as living alone and not living alone for regression analyses.

Medical characteristics were self-reported and included year of Q-fever infection, year of QFS diagnosis, use of antibiotics and hospitalization during the acute infection, as well as the number of hospitalizations since infection. Furthermore, patients indicated whether they had coexisting chronic diseases from a list of fourteen chronic diseases, or supplemented the list with any other chronic via an open answer option.

2.2.2. Long-term health complaints

The questionnaire included a list of 30 health complaints related to Q-fever and/or QFS which was composed based on available literature and experts in the field. Patients were asked to indicate which of these 30 complaints they had experienced since the acute Q-fever infection.

5

2.2.3. Health-related quality of life

Generic HRQL at day of filling out the questionnaire was measured with the EQ-5D-5L+cognitition (EQ-5D-5L+C) [15]. This instrument consists of the original five EQ-5D dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and includes an extra cognition dimension. For each dimension, patients indicated if they experienced no problems, slight problems, moderate problems, severe problems or extreme problems on the day of completing the questionnaire. Based on the five original dimensions and using the Dutch value set the EQ-5D index was calculated, ranging from 0 (for a health state considered as bad as being dead) to 1 (full health) [16]. In addition, participants scored their overall health status on a visual analogue scale (EQ VAS), which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

2.2.4. Energy, fatigue and post exertional malaise

Patients were asked to estimate their current energy level compared to before their Q-fever infection. Fatigue in the previous days was measured with the Multidimensional Fatigue Inventory (MFI) [17]. This instrument includes 20 items on five different scales: general fatigue, physical fatigue, reduction in activity, reduction in motivation, and mental fatigue. Items are scored on a 5-point Likert scale ranging from 1 ('yes, that is true') to 5 ('no, that is not true'). Item scores are summed into scale scores ranging from 4 to 20; higher scores indicate more fatigue [17]. The MFI-20 total score was calculated as the sum of all MFI items, ranging from 20 to 100.

Post exertional malaise (PEM) in the previous days was assessed using the five items for post exertional neuroimmune exhaustion [18]. Patients scored items on a 5-point Likert scale ranging from 1 ('yes, that is true') to 5 ('no, that is not true').

6

2.2.5. Mental health

Depression in the previous two weeks was measured with the two-item version of the Patient Health Questionnaire-9 (PHQ-2) [19]. Anxiety in the previous two weeks was measured with the two-item version of the Generalized Anxiety Disorder-7-NL-4 (GAD-2) [20]. Items of the PHQ-2 and GAD-2 were scored on a 4-point Likert scale, ranging from 0 ('do not suffer from these problems at all') to 3 ('suffer almost every day'). Total scores for the PHQ-2 and GAD-2 ranged from 0 to 6. A score of ≥3 indicates that anxiety or depression is likely [19, 20]. Depression (PHQ-2) and anxiety (GAD-2) outcomes were dichotomized based on the cut-off point.

2.3. Statistical analysis

Descriptive statistics were used to describe the sociodemographic and medical characteristics, and outcomes of the total study sample and of age subgroups [13]. Continuous data were reported as mean (SD) if normally distributed, and as median (IQR) if not-normally distributed. Categorical data were reported as numbers (percentage).

Depending on the normality of the distribution, ANOVA or Kruskall Wallis H tests, were used to test differences in scores of continuous variables between the three age subgroups. Chi-square test were used to compare the distribution of categorical variables, except for small numbers (n<5), then the Fisher's exact test was used. If appropriate; when the test result was significant for the comparison among the three age subgroups, Bonferroni tests were used for multiple comparisons.

To study determinants associated with the number of long-term health complaints, HRQL, health status, fatigue univariate linear regression was applied. EQ-5D index scores (HRQL) and total MFI-20 scores (fatigue) outcomes were transformed to a 0-100 scale to make outcomes comparable and easier to interpret: 0 represents the worst outcome and 100 the best outcome. Determinants associated with PEM, anxiety and depression were studied using logistic regression. For PEM, item 1 ('Marked, rapid

7

physical and/or cognitive fatigability in response to exertion') was used, which was dichotomized into 'no PEM' (score 4-5) and 'any PEM problems' (score 1-3). Sociodemographic and medical characteristics were included as independent variables. The collinearity (>0.8 or <-0.8) of all determinants with a p-value <0.10 in univariate analyses was checked. The remaining determinants were used in multivariate analyses. Regression coefficients and standard errors were presented. A p-value of <0.05 was considered statistically significant. We used IBM SPSS Statistics 28 for all analyses.

3. Results

3.1. Patient characteristics

A total of 842 patients were invited to participate, of whom 457 completed the questionnaire (response rate: 54.3%) (Appendix B). Eighty-nine patients were excluded because they did not meet the inclusion criteria, resulting in the inclusion of 368 patients. The main reason for exclusion was a Q-fever infection less than 10 years ago.

The median age of patients was 57 years old (IQR: 49.0 – 64.0) and 54.1% was female (Table 1). The majority of patients lived together (74.4%) and many of them had comorbidity (66.3%). The median time since Q-fever infection was 12 years (IQR: 12.0 – 13.0). During the acute phase of the Q-fever infection, 63.6% of the patients received antibiotics and 16.0% was hospitalized. The three age subgroups differed statistically significantly on gender, level of education, household composition, comorbidity and use of antibiotics during the acute phase of the infection (Table 1). In particular, the youngest age group had a larger proportion of females (79.1%), and the lowest proportion of patients with a coexisting chronic disease (37.2%).

[Table 1 here]

3.2. Long-term health complaints

For the total study sample, the median number of long-term health complaints was 12.0 (IQR: 8.0 – 16.0) out of a predefined list of thirty complaints (Table 2). All patients reported one or more health complaints, with few patients (10.1%) reporting ≤5 complaints. The most reported health complaint was fatigue (93.8%), followed by concentration problems (83.2%) and physical exhaustion (76.9%) (Figure 1a). Many patients (64.1%) reported all these three complaints.

Younger patients (<40 years old) reported a median of 13.0 (IQR: 9.0 – 18.0) health complaints; middle-aged patients (40 – <65 years old) a median of 12.0 (IQR: 8.0 – 16.0) health complaints; and older patients (≥65 years old) a median of 11.0 (IQR: 7.0 – 14.0) health complaints. The top-three of complaints was identical for all three age subgroups studied. The prevalence of nine out of thirty complaints was statistically significantly different among the groups (Figure 1b). The prevalence of headache, painful glands and food intolerance was higher in younger patients compared to middle aged and older patients (p<0.001 – p=0.006). Muscle soreness and irritability were more often reported by young compared to old patients (p=0.004 – 0.005), and digestive problems by young versus middle-aged patients (p=0.009). Both young and middle-aged patients experienced more physical exhaustion than older patients (p=0.008 – 0.016), and sadness was more often reported by middle-aged patients compared to older patients (p=0.037). Voice complaints were more prevalent among older patients compared to young patients (p=0.007).

[Table 2 here]

3.3. Health-related quality of life

The median EQ-5D-5L index for the total study sample was 0.63 (IQR: 0.38 – 0.75; mean: 0.56 (SD: 0.25)), and the median EQ VAS was 50.0 (IQR: 34.3 – 61.8; mean: 49.3 (SD: 19.4)) (Table 2). Many patients reported any problems on the dimensions pain/discomfort (95.7%) and usual activities (91.0%) (Figure 2). HRQL (EQ-5D-5L index score) was lowest for the middle-aged group (median: 0.61; IQR: 0.33 – 0.74) and

9

statistically significant worse compared to the oldest age group (median: 0.67; IQR: 0.50 – 0.79; p=0.018). Health status (EQ VAS score) was lowest for the youngest age group (median: 40.0; IQR 30.0 – 60.0) and highest for individuals of ≥65 years old (median: 60.0; IQR: 41.5 – 70.0). The health status was statistically significantly better for the oldest age group compared to both the young and middle-aged subgroups (p<0.001). All dimensions, except for pain/discomfort and usual activities were scored significantly different among the age subgroups (Figure 3). Especially the proportion of patients experiencing problems with cognition was considerably higher for younger patients (93.0%) versus middle-aged (83.5%) and old patients (70.5%) (p<0.001).

3.4. Energy, fatigue and post exertional malaise

Compared to before the Q-fever infection, as reported via recall in the questionnaire, patients had a median energy level of 45.0% (IQR: 30.0-60.0%). This percentage was not statistically significantly different among the subgroups (p=0.179). The median level of fatigue (MFI-20 score) was high (median: 77.0; IQR: 65.0 – 84.0), with patients scoring worst on the domain "general fatigue" (median: 18.0; IQR: 15.0 – 20.0) and relatively best on the domain "reduction in motivation" (median: 12.0; IQR: 9.3 – 15.0) (Table 2). Older patients had a statistically significant lower MFI-20 fatigue score and lower scores for all domains compared to young and middle-aged patients (p<0.001), indicating relatively less fatigue problems in the oldest age group (Table 2).

Post exertional malaise complaints were common in QFS patients; all (98.9%) except four patients reported at least mild complaints at one of the five post exertional malaise domains. Almost all patients reported at least mild complaints (95.6 – 97.8%) on four of the post exertional malaise domains, and many also reported at least mild post exertional symptom exacerbation (88.6%) (Figure 4). Older patients reported statistically significant less post exertional malaise complaints (Figure 5; p<0.001 – p=0.032), except for the domain 'low threshold of physical and mental fatigability'; for which patients in all

10

subgroups reported many problems (96.7 – 100%). No significant differences were found between the younger and middle-aged patient groups.

3.5. Mental health

The median depression score for all patients was 2.0 (IQR: 1.0 – 3.0) (Table 2). In total, 27.4% of all QFS patients had a score that is indicative of having a depression. Over half those patients (n=56; 55.4%) also had a score that is indicative of having anxiety. The proportion of patients with a likely depression was statistically significantly higher in middle-aged patients (33.8%) compared to oldest patients (14.8%; p<0.001); no statistically significant differences were found for the other age group comparisons (Table 2).

QFS patients had a median anxiety score of 1.0 (IQR: 0.0 – 2.0), and 21.5% of the patients had a score that is indicative of having anxiety (Table 2). The young age group had the highest proportion of patients likely having anxiety (25.6%). The proportion of patients likely having anxiety was statistically significant higher in the middle-aged group (24.1%) compared to the oldest age group (12.5%; p=0.006).

3.6. Determinants of long-term health outcomes

Univariate and multivariate predictive determinants of long-term health outcomes are presented in Appendix C and Table 3. Older age (≥65 years old) was universally significantly associated with better outcomes in univariate analyses. In multivariate analyses, older age remained associated with better outcomes for all health outcomes studied, except for the number of long-term health complaints (Table 3a, Table 3b). Other determinants in the univariate analyses were less universal and differed per outcome studied. In multivariate analyses, living alone was associated with an increased number of long-term health complaints; not having a coexisting chronic disease with a better HRQL and a better health status;

11

males had a higher risk of depression; and having a low education was associated with an increased risk of having anxiety.

[Table 3a, 3b here]

4. Discussion

The present study determined long-term health outcomes of patients living with QFS and determinants associated with health outcomes. In general, QFS patients experience a wide range of health complaints, high levels of fatigue and PEM, have a low HRQL and an increased risk of depression and anxiety. Almost all patients reported to experience at least slight pain, and the usual activities of nine out of ten patients were limited to some extent. Patients' median level of energy was less than half compared to before the Q-fever infection. Generally, young and middle-aged patients seemed to experience more long-term consequences compared to older patients, they reported a significantly worse health status, higher fatigue levels and anxiety, and more post-exertional malaise complaints; and middle-aged patients have a lower HRQL, and a higher risk of depression. Multivariate regression analyses confirmed that older age was associated with better health outcomes, except for the number of long-term health complaints.

The HRQL of QFS patients in our sample was low, which is in line with earlier studies that reported a diminished HRQL of QFS patients up to 10 years post-infection [8, 10]. The HRQL of QFS patients was considerably lower than the HRQL of the Dutch population (mean EQ-5D index: 0.56 versus 0.89) indicating the large impact of QFS on patients' HRQL [21]. Patients' health status was also severely impacted and much lower compared to the norm score for the Netherlands (mean EQ VAS: 49.3 vs 82.0) [21]. The largest discrepancies in reported problems between the QFS patients and the Dutch general population were on the dimensions usual activities and pain/discomfort [21]. However, these norm scores are only available for the EQ-5D-3L which impacts the comparability as research showed that the 3L version of the instrument is less sensitive, especially for mild problems [22]. When comparing results to a

12

large study in the general Dutch population with the EQ-5D-5L (mean EQ index: 0.83), the QFS patients have still a substantially worse HRQL, also in comparison to patients with a chronic health condition (mean EQ index: 0.73) corroborating the large impact of QFS on patients' HRQL [23, 24].

The high number and large diversity of health complaints, and the more than fifty percent energy reduction compared to pre-infection may explain the diminished HRQL. Patients experienced, on average, twelve different health complaints, and the proportion of patients experiencing fatigue was considerably higher than in the Dutch general population [23]. In line with earlier studies, it was found that fatigue was the most frequent and most severe health complaint for QFS patients [6, 8, 9, 25]. Being fatigued has been shown to be associated with lower HRQL in other patient populations [26]. Concentration problems and physical exhaustion were also amongst the three most prevalent health complaints. Strikingly, more than half of the patients (64.1%) experienced all three complaints. An earlier study reported the identical top-three most prevalent complaints up to 10 years post-infection [8]. These long-lasting complaints thus seem to remain and can be considered chronic health complaints. The median number of total health complaints was somewhat higher in the previous study (median 13 out of 27 vs. 12 out of 30 complaints in our study); possibly indicating that the number of total complaints slightly decrease over time. However, this should be confirmed in a longitudinal study. It might also be caused by the different study sample, or the slightly different list of complaints.

In addition to these health complaints, the majority of patients experienced severe PEM problems. This is line with recent studies that showed that PEM is an important and severe health complaint in QFS patients as well as in other patient populations that experience long-term sequelae of infectious diseases [27]. Also, patients who provided input for our study indicated that PEM is a relevant but underexposed theme for them. The impact and importance of PEM for QFS patients was underlined by our study results.

13

Mental health problems were less prevalent. Over a quarter of QFS patients had scores indicative of depression, which is more than twice the prevalence in the Dutch general population (27.4% vs 12.6%). Also, the percentage of patients likely having anxiety was almost two times higher (21.5% vs 11.0%) [28]. It is somewhat questionable whether these anxiety and depression rates were fully representable as they were measured during the COVID-19 pandemic; COVID-19 has a proven negative effect on anxiety and depression rates [29, 30]. However, the comparison rates used were also assessed during the COVID-19 pandemic, though one year earlier (April-May 2020) [28]. Similar to other patient populations, depression and anxiety frequently co-occurred in QFS patients; over half of the patients in our study who had a score indicative of depression also had a scores indicative of anxiety [31].

Our results suggest large differences in health outcomes between subgroups of patients based on age. In general, young and middle-aged QFS patients seem to have worse health outcomes than older patients. However, all patients, including the older patients, have a substantial worse HRQL, health status, level of fatigue, and increased risk of anxiety and depression compared to their counterparts without QFS [21, 28]. Our results might be somewhat surprising, as generally, older age is associated with more comorbidity, higher levels of fatigue and a lower HRQL [21]. However, our results might be explained by the fact that people have different social roles in different stages of life. Young and middle-aged patients have more clearly defined social roles, such as education, work and/or parenting, and particularly younger patients (aged <40 years old) have to perform an extensive range of social roles. Younger and middle-aged patients might experience more problems as they have, in general, a busier life and less time to recover than older, retired, people with less specified roles and more time to rest and a slower pace of life. Multivariate regression analyses confirmed that an older age was associated with better health outcomes, except for the number of long-term health complaints. However, these findings should be interpreted with some caution as the number of patients was not evenly divided among the three subgroups studied. Patients 40-65 years old represented a large part of our study sample, as they do in the total Q-support

14

QFS population. Also, differences in characteristics in the three age subgroups might have influenced the differences in outcomes. The youngest age group had a larger proportion of females, many patients with a high level of education, and the lowest proportion of patients with a coexisting chronic disease. Literature shows that, in general, females tent to experience more health complaints, or are more willing or open to report health complaints which may have led to an overrepresentation of long-term complaints [32]. In contrast, earlier studies indicate that low education is associated with impaired health outcomes and HRQL [33, 34]; this might have led to underrepresentation of long-term complaints in the youngest age group. The oldest age group had, as expected, the highest proportion of patients with comorbidity, which is generally associated with more long-term complaints [21].

In our study, not having a coexisting chronic disease was associated with a better HRQL and health status, which is in line with the existing literature that describes a strong relation between multimorbidity and a diminished HRQL [35]. Hospitalization and antibiotic treatment during the acute phase of the Q-fever infection were not associated with less severe long-term health outcomes in QFS patients in our study. This is in line with previous research that concluded that long-term doxycycline use did not reduce the severity of health outcomes [36]. Furthermore, our results showed an association between being male and a higher likelihood of depression. This is in contrast with findings of large meta-analyses on depression in representative national samples from over 90 countries that reported that there are roughly twice as many females with depression as males with depression [37]. The relation found in our study might be provoked by the fact that many QFS patients are severely limited in their daily activities, including their work activities, which might have a stronger impact on males' mental health as males are traditionally considered the main wage-earner in a household.

This study had several strengths, including a large cohort of QFS patients and information on various determinants and health outcomes, enabling us to study a variety of health outcomes in specific subgroups of patients. Also, the long-term aspect of our study was unique, and, considering the impaired

15

health and functioning of patients, which may have hampered participation in this study, the response rate (54.3%) was high. However, also some limitations were present, like the enrollment of solely patients registered at Q-support in this study. Even though Q-support is the Q-fever expertise and support center for patients in the Netherlands, the patients registered at Q-support may not be representative of all QFS patients in the Netherlands. Besides, we were unable to perform a non-response analysis as information on time since infection was not available. We were therefore not able to study whether responder's characteristics differed from non-responders. Due to the long-follow up period, there is a risk of recall bias in our results regarding the situation before and during acute Q-fever infection [38]. Another limitation is the cross-sectional study design which hampered the insight into the course of health complaints and health outcomes over time and determinants for worse health outcomes. Furthermore, it is possible that patients with severe health problems have not completed the full questionnaire which may have led to underestimating the severity of the problems. However, this may have been countered partly by QFS patients without or with few complaints who did not participate in the questionnaire, for example, because they have less time or less interest to complete a questionnaire on a disease that is barely impacting their lives. Also, the uneven distribution of patients in the age categories might be considered a limitation, as well as the statistically significant differences in characteristics among the three age subgroups, which might have impacted our results. Besides, in our regression analyses for the EQ-5D index, not all assumptions for linear regression were met, therefore these results have been presented with somewhat more caution but still provide a good insight into the relation with associated determinants. Lastly, the questionnaires used for fatigue and PEM might have been suboptimal for our population, as a recently published study showed that the MFI-20 has a questionable factor structure in the general Dutch population [39], and the PEM questions based on diagnostic criteria [18], whereas a brief questionnaire for PEM has been recently developed and might be a better option to use for future studies [40].

16

5. Conclusions

QFS has a considerable impact on patients' health more than 10 years after the Q-fever infection. Patients have to live and cope with a wide range of health complaints, high levels of fatigue and a diminished HRQL. This emphasizes the long-term negative impact for patients, but also the complexity of treatment of health complaints by healthcare providers. Young and middle-aged QFS patients experience more long-term consequences compared to older patients. Besides, males tend to have an increased risk of depression. Tailored healthcare is recommended to provide optimal care and support for each QFS patient, keeping these age specific health consequences in mind.

17

List of abbreviations

HRQL   Health-related quality of life

PEM   Post exertional malaise

QFS   Q-fever fatigue syndrome

Declarations

18

REFERENCES

1.   **Kluthcovsky ACGC***, et al.* (2012) Fatigue after treatment in breast cancer survivors: prevalence, determinants and impact on health-related quality of life*. Supportive Care in Cancer*; **20**: 1901-1909.

2.   **Raoult D, Marrie TJ, Mege JL**. (2005) Natural history and pathophysiology of Q fever*. The Lancet Infectious Diseases*; **5**: 219-226.

3.   **Morroy G***, et al.* (2012) Self-reported sick leave and long-term health symptoms of Q-fever patients*. European Journal of Public Health*; **22**: 814-819.

4.   **Morroy G***, et al.* (2016) Fatigue following Acute Q-Fever: A Systematic Literature Review*. Plos One*; **11**.

5.   **van Loenhout JAF***, et al.* (2014) Serious long-term health consequences of Q-fever and Legionnaires' disease*. Journal of Infection*; **68**: 527-533.

6.   **Wildman MJ***, et al.* (2002) Chronic fatigue following infection by Coxiella burnetii (Q fever): ten-year follow-up of the 1989 UK outbreak cohort*. QJM: An International Journal of Medicine*; **95**: 527–538.

7.   **Hickie I***, et al.* (2006) Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study*. British Medical Journal*; **333**: 575-578.

8.   **Bronner MB***, et al.* (2020) Long-term impact of a Q-fever outbreak: An evaluation of health symptoms, health-related quality of life, participation and health care satisfaction after ten years*. Journal of Psychosomatic Research*; **139**: 110258.

9.   **Limonard GJM***, et al.* (2016) Persistence of impaired health status of Q fever patients 4 years after the first Dutch outbreak *Epidemiology & Infection*; **144**: 1142-1147.

10. **Reukers DFM***, et al.* (2019) 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*. Journal of Psychosomatic Research*; **121**: 37-45.

11. **Van Loenhout JAF***, et al.* (2015) Work participation in Q-fever patients and patients with Legionnaires' disease: A 12-month cohort study*. Scandinavian Journal of Public Health*; **43**: 294-301.

12. **Q-support**. We support Q-fever patients. 2022; Available from: https://www.q-support.nu/.

13. **CBS**. Leeftijdsverdeling. 2022 [cited 2022 28-03]; Available from: https://www.cbs.nl/nl-nl/visualisaties/dashboard-bevolking/leeftijd/bevolking.

14. UNESCO Institute for Statistics, *International Standard Classification of Education ISCED 2011*, UIS, Editor. 2011, UIS: Montreal, Canada.

15. **Herdman M***, et al.* (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)*. Quality of Life Research*; **20**: 1727-1736.

16. **Versteegh M***, et al.* (2016) Dutch tariff for the five-level version of EQ-5D*. Value Health*; **19**: 343-352.

17. **Smets EMA***, et al.* (1995) The multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue*. Journal of Psychosomatic Research*; **39**: 315-325.

18. **Carruthers BM***, et al.* (2011) Myalgic encephalomyelitis: International Consensus Criteria*. Journal of Internal Medicine*; **270**: 327-338.

19. **Kroenke K, Spitzer RL, Williams JBW**. (2003) The Patient Health Questionnaire-2: Validity of a Two-Item Depression Screener. *Medical Care*; **43**: 1284-1292.

20. **Kroenke K***, et al.* (2007) Anxiety Disorders in Primary Care: Prevalence, Impairment, Comorbidity, and Detection*. Annals of Internal Medicine*; **146**: 317-325.

21. **Szende A, Janssen B, Cabses J**, Self-Reported Population Health: An International Perspective based on EQ-5D. 2014: Springer Open.

22. **Janssen M***, et al.* (2013) Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Quality of Life Research*; **22**: 1717-1727.

23. **Spronk I***, et al.* (2021) The relation between EQ-5D and fatigue in a Dutch general population sample: an explorative study. *Health and Quality of Life Outcomess*; **19**: 135.

24. **Spronk I***, et al.* (2022) Adding a fatigue item to the EQ-5D-5L improves its psychometric performance in the general population. *Journal of Patient-Reported Outcomes*; **6**: 1.

25. **van Loenhout JAF***, et al.* (2015) Q-fever patients suffer from impaired health status long after the acute phase of the illness: Results from a 24-month cohort study. *Journal of Infection*; **70**: 237-246.

26. **Rupp I***, et al.* (2004) Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis & Rheumatology*; **51**: 578-585.

27. **Choutka J***, et al.* (2022) Unexplained post-acute infection syndromes. *Nature Medicine*; **28**: 911-923.

28. **Long D***, et al.* (2022) Anxiety, depression, and social connectedness among the general population of eight countries during the COVID-19 pandemic. *Archives of Public Health*; **80**: 1-16.

29. **Robinson E***, et al.* (2022) A systematic review and meta-analysis of longitudinal cohort studies comparing mental health before versus during the COVID-19 pandemic in 2020. *Journal of Affective Disorders*; **296**: 567-576.

30. **Santomauro DF***, et al.* (2021) Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *The Lancet*; **398**: 1700-1712.

31. **Strand EB*, et al.*** (2020) Pain and depression are associated with more anxiety in ME/CFS: A cross-sectional cohort study between Norway and Spain*. Clinical Medicine Insights: Psychiatry*; **11**: 1-8.

32. **Bartley EJ, Fillingim RB**. (2013) Sex differences in pain: a brief review of clinical and experimental findings*. British Journal of Anaesthesia*; **111**: 52-58.

33. **van der Vlegel M*, et al.*** (2021) Health care utilization and health-related quality of life of injury patients: comparison of educational groups*. BMC Health Services Research*; **21**: 1-12.

34. **Spronk I*, et al.*** (2021) Health Inequality Analysis in Europe: Exploring the Potential of the EQ-5D as Outcome*. Frontiers in Public Health*; **9**: 744405.

35. **Makovski TT*, et al.*** (2019) Multimorbidity and quality of life: Systematic literature review and meta-analysis*. Ageing Research Reviews*; **53**: 100903.

36. **Keijmel SP*, et al.*** (2017) Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial*. Clinical Infectious Diseases*; **64**: 998-1005.

37. **Salk RH, Hyde JS, Abramson LY**. (2017) Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms*. Psychological Bulletin*; **143**: 783.

38. **Spronk I*, et al.*** (2019) Correspondence of directly reported and recalled health-related quality of life in a large heterogeneous sample of trauma patients*. Quality of Life Research*.

39. **Kieffer JM*, et al.*** (2021) A questionable factor structure of the multidimensional fatigue inventory in the general Dutch population*. Journal of Clinical Epidemiology*; **137**: 266-276.

40. **Cotler J*, et al.*** (2018) A brief questionnaire to assess post-exertional malaise*. Diagnostics*; **8**: 66.

Figure legends

Figure 1. Percentage of Q-fever fatigue syndrome patients that reported a specific health complaint, for total sample and for subgroups of patients based on their age.

*Indicating statistically significant differences (p<0.05) among the three age subgroups.
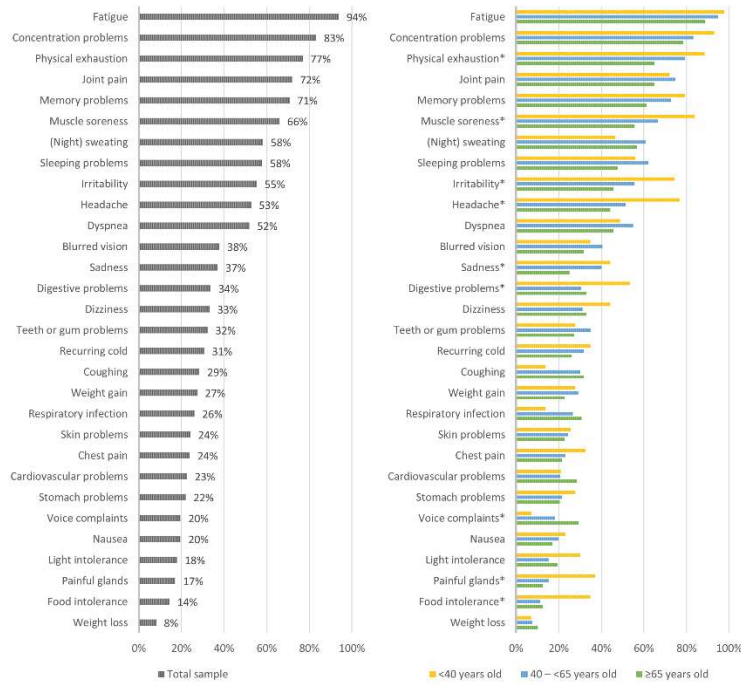
Figure 2. Frequency of responses to the EQ-5D-5L+C dimensions for total sample of patients.
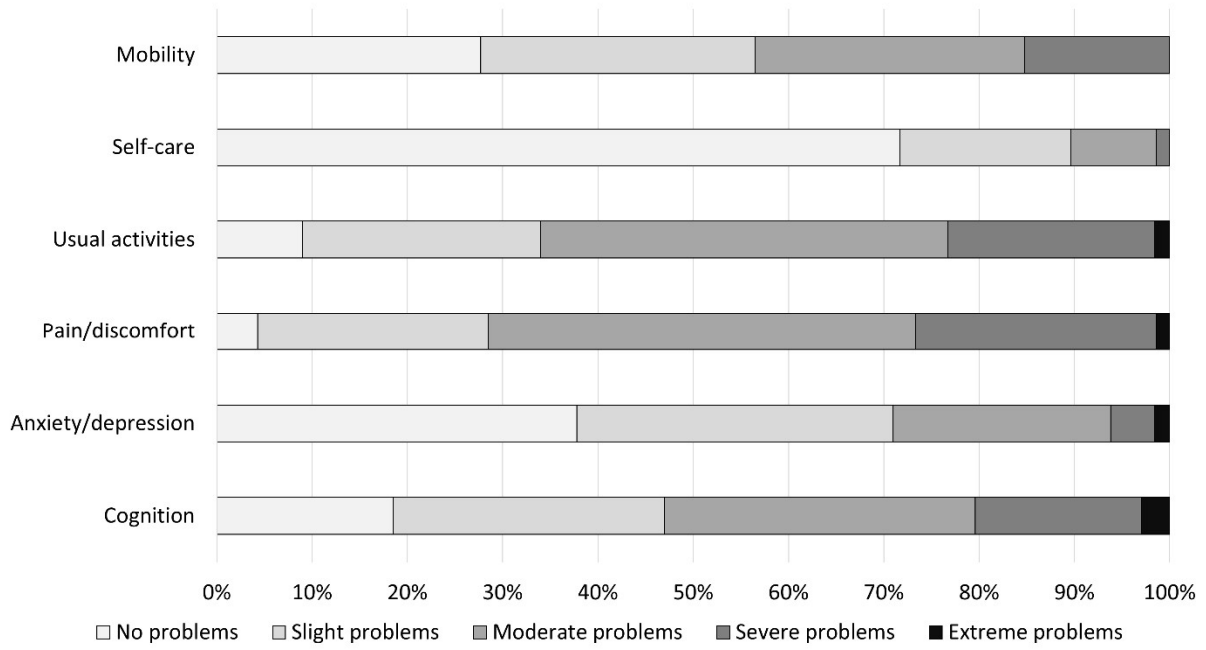
Figure 3. Frequency of responses to the EQ-5D-5L+C dimensions for subgroups of patients based on age.

MO=mobility, SC=self-care, UA=usual activities, PD=pain/discomfort, AD=anxiety/depression, CO=cognition.

*Indicating statistically significant differences (p<0.05) among the three age subgroups.
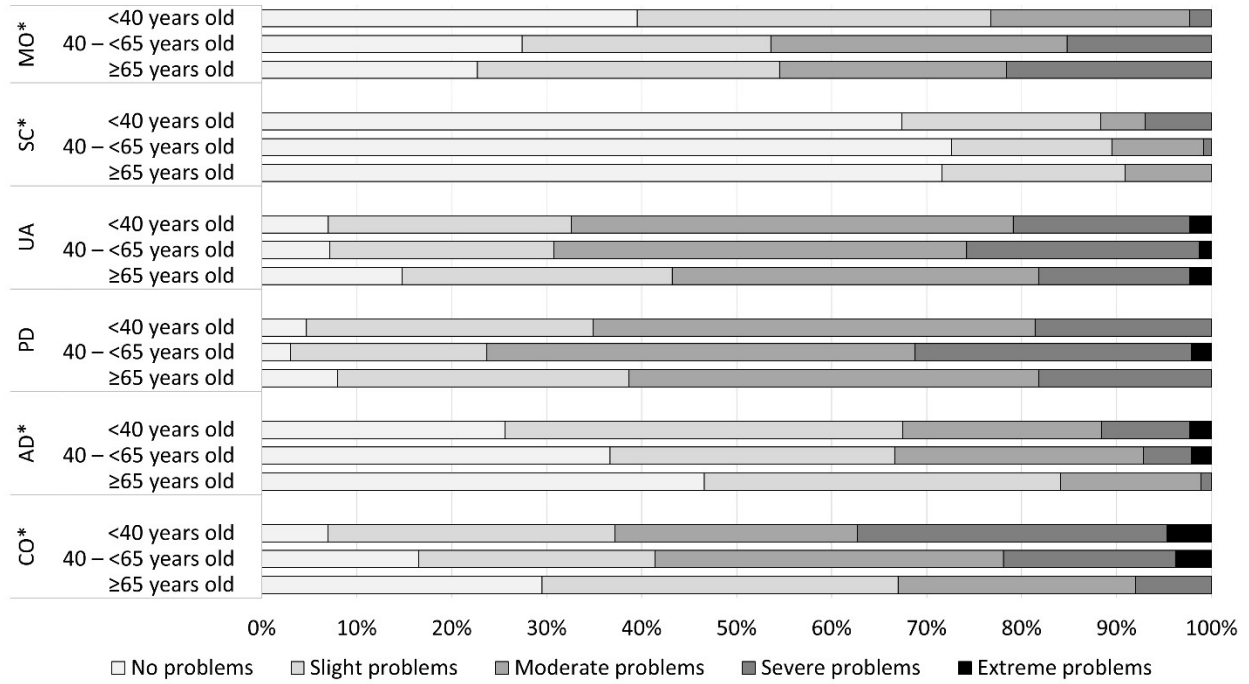
Figure 4. Frequency of responses to the Post exertional malaise (PEM) dimensions for total sample of patients.
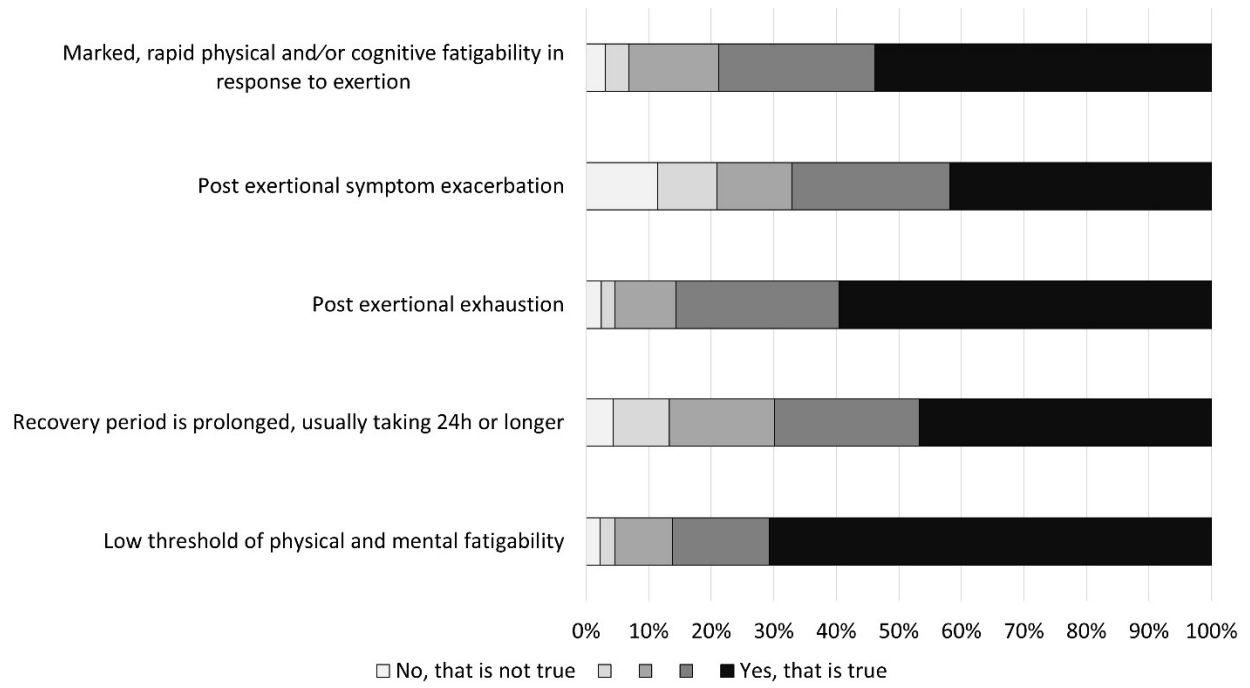
Figure 5. Frequency of responses to the post exertional malaise (PEM) dimensions for subgroups of patients based on age.

*Indicating statistically significant differences (p<0.05) among the three age subgroups.

RF=Marked, rapid physical and/or cognitive fatigability in response to exertion

PS=Post exertional symptom exacerbation

PE=Post exertional exhaustion

RP=Recovery period is prolonged, usually taking 24h or longer

LF=Low threshold of physical and mental fatigability

Tables

Table 1. Sociodemographic and medical characteristics of chronically fatigued and develop Q-fever

Fatigue Syndrome assisted at Q-support Netherland, 2021

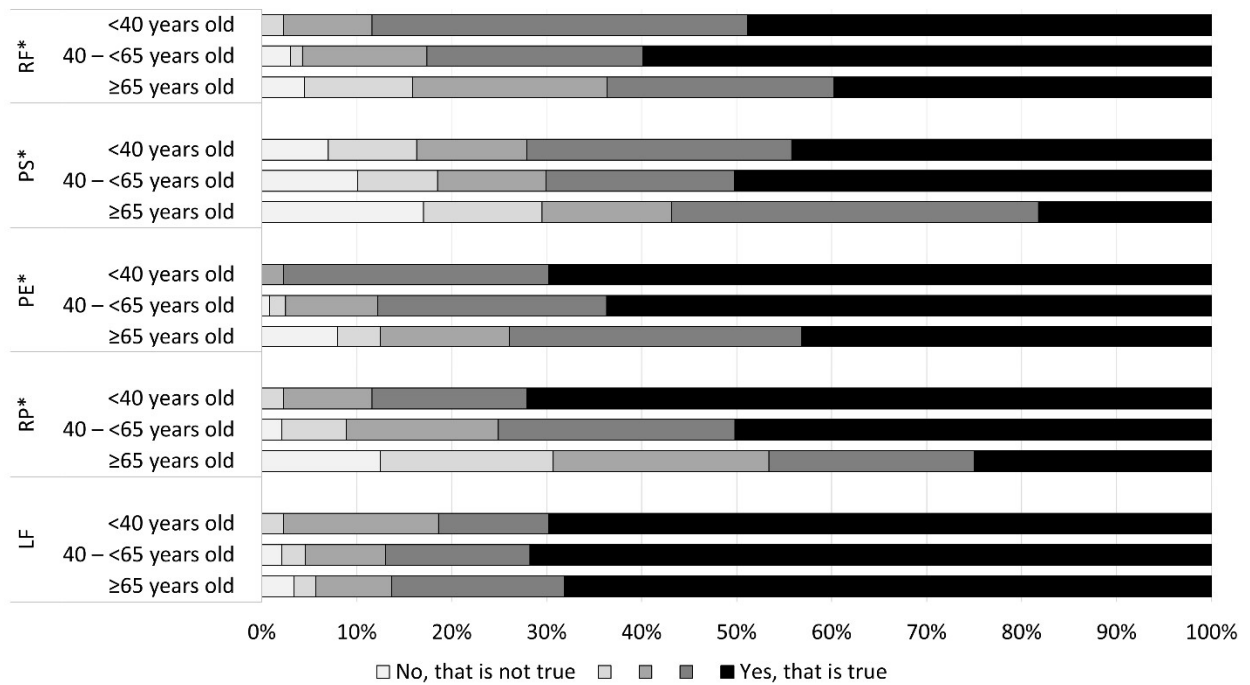|	Total sample (n=368)	Patients <40 years old (n=43)	Patients 40 – <65 years old (n=237)	Patients ≥65 years old (n=88)	P-value for difference
Age at time of study, median (IQR)	57.0 (49.0 – 64.0)	32.0 (29.0 – 35.0)	54.0 (49.5 – 60.0)	69.0 (66.0 – 72.0)	
Age at time of infection, median (IQR)	44.0 (36.0 – 51.0)	20.0 (17.0 – 23.0)	42.0 (37.0 – 48.0)	57.0 (54.0 – 60.0)	
Gender					<0.001
Male	169 (45.9%)	9 (20.9%)	110 (46.4%)	50 (56.8%)	
Female	199 (54.1%)	34 (79.1%)	127 (53.6%)	38 (43.2%)	
Level of education					<0.001
Low	102 (27.7%)	3 (7.0%)	69 (29.1%)	30 (34.1%)	
Middle	149 (40.5%)	22 (51.2%)	106 (44.7%)	21 (23.9%)	
High	117 (31.8%)	18 (41.9%)	62 (26.2%)	37 (42.0%)	
Household composition					<0.001
Married or living together without children living at home	159 (43.2%)	7 (16.3%)	76 (32.1%)	76 (86.4%)	
Married or living together with children living at home	111 (30.2%)	19 (44.2%)	88 (37.1%)	4 (4.5%)	
One-parent household without children living at home	6 (1.6%)	0 (0.0%)	5 (2.1%)	1 (1.1%)	
One-parent household with children living at home	14 (3.8%)	1 (2.3%)	12 (5.1%)	1 (1.1%)	
Living alone	61 (16.6%)	10 (23.3%)	46 (19.4%)	5 (5.7%)	
Other	17 (4.6%)	6 (14.0%)	10 (4.2%)	1 (1.1%)	
Comorbidity					<0.001
No coexisting chronic disease	124 (33.7%)	27 (62.8%)	77 (32.5%)	20 (22.7%)	
≥1 coexisting chronic disease	244 (66.3%)	16 (37.2%)	160 (67.5%)	68 (77.3%)	

28

Years since Q-fever infection, median (IQR)	12.0 (12.0 – 13.0)	12.0 (11.0 – 12.0)	12.0 (12.0 – 13.0)	12.0 (12.0 – 13.0)	0.883
Before 2007	19 (5.2%)	1 (2.3%)	14 (5.9%)	4 (4.5%)	
Between 2007-2011	349 (94.8%)	42 (97.7%)	223 (94.1%)	84 (95.5%)	
Antibiotics during the acute phase of the infection					0.04
Yes	234 (63.6%)	19 (44.2%)	158 (66.7%)	57 (64.8%)	
No	111 (30.2%)	18 (41.9%)	66 (27.8%)	27 (30.7%)	
Not sure	23 (6.3%)	6 (14.0%)	13 (5.5%)	4 (4.5%)	
Hospitalization during the acute phase of the infection					0.127
Yes	59 (16.0%)	3 (7.0%)	44 (18.6%)	12 (13.6%)	
No	309 (84.0%)	40 (93.0%)	193 (81.4%)	76 (86.4%)	

29

Table 2. Long-term health outcomes for Q-fever fatigue syndrome patients assisted at Q-support Netherland, 2021

	Total (n=368)	Patients <40 years old (n=43)	Patients 40 – <65 years old (n=237)	Patients ≥65 years old (n=88)	P-value for difference
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	
Number of long-term complaints	12.0 (8.0 – 16.0)	13.0 (9.0 – 18.0)	12.0 (8.0 – 16.0)	11.0 (7.0 – 14.0)	0.043
Health-related quality of life					
EQ-5D-5L index	0.63 (0.38 – 0.75)	0.67 (0.41 – 0.74)	0.61 (0.33 – 0.74)	0.68 (0.50 – 0.78)	0.018
EQ VAS	50.0 (34.3 – 61.8)	40.0 (30.0 – 60.0)	46.0 (30.0 – 60.0)	60.0 (41.5 – 70.0)	<0.001
Fatigue					
MFI-20 total score	74.0 (65.0 – 84.0)	77.0 (66.0 – 83.0)	76.0 (67.0 – 85.0)	69.0 (61.3 – 76.0)	<0.001
General fatigue	18.0 (15.0 – 20.0)	19.0 (18.0 – 20.0)	18.0 (15.0 – 20.0)	16.0 (14.0 – 19.0)	<0.001
Physical fatigue	16.0 (14.0 – 19.0)	17.0 (15.0 – 19.0)	16.0 (14.0 – 19.0)	15.0 (13.0 – 17.0)	0.001
Reduction in activity	14.0 (12.0 – 17.0)	14.0 (10.0 – 17.0)	15.0 (12.0 – 17.0)	14.0 (10.0 – 16.0)	0.029
Reduction in motivation	12.0 (9.3 – 15.0)	11.0 (9.0 – 14.0)	12.0 (10.0 – 15.0)	12.0 (8.3 – 13.0)	0.013
Cognitive fatigue	14.0 (12.0 – 17.0)	15.0 (12.0 – 18.0)	15.0 (12.0 – 17.5)	13.0 (11.0 – 16.0)	<0.001
Depression					0.018
PHQ-2 score	2.0 (1.0 – 3.0)	2.0 (1.0 – 2.0)	2.0 (1.0 – 3.0)	1.0 (0.0 – 2.0)	

30

Depression likely (score ≥3), n(%)	101 (27.4%)	8 (18.6%)	80 (33.8%)	13 (14.8%)	
Anxiety					0.025
GAD-2 score	1.0 (0.0 – 2.0)	1.0 (0.0 – 3.0)	1.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)	
Anxiety likely (score ≥3), n(%)	79 (21.5%)	11 (25.6%)	57 (24.1%)	11 (12.5%)	

31

Table 3a. Multivariate linear regression analyses for long-term health complaints, health-related quality of life and fatigue.

	Health complaints		Health-related quality of life				Fatigue	
	Number of long-term complaints		Transformed EQ-5D-5L index		EQ VAS		Transformed MFI-20 score	
	Coef.	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
Age at time of study								
<40 years old								
40 - <65 years old (reference)								
≥65 years old			9.645	**0.001**	11.798	**<0.001**	7.305	**<0.001**
Gender								
Male								
Female (reference)								
Education								
Low								
Middle (reference)								
High								
Living situation								
Not living alone (reference)								
Living alone	1.868	**0.009**						
Comorbidity								
No coexisting chronic disease			10.578	**<0.001**	5.674	**0.007**		
≥1 coexisting chronic disease (reference)								
Antibiotics								
Yes (reference)								
No								
Not sure								
Hospitalization during the acute phase of infection								
Yes								

32

No (reference)

Note. EQ VAS = EQ visual analogue scale; MFI-20 = Multidimensional Fatigue Inventory 20-item version

p-values printed in bold indicate statistically significant values (p<0.05).

Table 3b. Multivariate logistic regression analyses for post exertional malaise, depression and anxiety.

	Post exertional malaise		Depression		Anxiety	
	Item 1		PHQ-2		GAD-2	
	OR	p-value	OR	p-value	OR	p-value
Age at time of study						
<40 years old						
40 - <65 years old (reference)						
≥65 years old	0.216	**<0.001**	0.323	**<0.001**	0.409	**0.012**
Gender						
Male			2.412	**<0.001**		
Female (reference)						
Education						
Low					2.137	**0.005**
Middle (reference)						
High						
Living situation						
Not living alone (reference)						
Living alone						
Comorbidity						
No coexisting chronic disease						
≥1 coexisting chronic disease (reference)						
Antibiotics						
Yes (reference)						
No						
Not sure						
Hospitalization during the acute phase of infection						
Yes						
No (reference)						

34

Note. PEM item 1 = Marked, rapid physical and/or cognitive fatigability in response to exertion. PHQ-2 = Patient Health Questionnaire 2-item version, Generalized Anxiety Disorder 2-item version.

p-values printed in bold indicate statistically significant values (p<0.05).