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Linking health inequalities of outcomes and opportunities:

The association between socioeconomic status, health-related quality of life and health care utilisation of Q-fever patients who experience long-term health consequences

*Masterthesis Population Studies,
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ABSTRACT

Objective. More than ten years after the Dutch Q-fever epidemic (2007-2010), approximately twenty per cent of Q-fever patients still experience consequences. Understanding the long-term health-related quality of life (HRQoL) of socioeconomic status (SES) groups provides insight into health inequalities following Q-fever.

Theory. Based on patient population studies, inequalities of outcomes were expected: patients with lower SES have lower HRQoL than patients with higher SES. In line with Sen's Capability Approach, SES was seen as a resource to transform capabilities (choices between health care providers) into functionings (getting the necessary health care), and health inequalities in opportunities between SES groups were expected. Lastly, health care utilisation was expected to mediate the association between SES and HRQoL.

Methods. This study assessed the association between educational level (as a proxy for SES), HRQoL (EQ-5D-5L), and health care utilisation (number of appointments with health care providers) by performing descriptive statistics and a mediation analysis with a multicategorical independent variable.

Results. Secondary analysis of a dataset of 433 patients with long-term complaints after Q-fever showed that patients with lower educational level had a lower HRQoL than those with higher education. However, the results did not show a difference between educational level on the number of appointments with healthcare providers, nor that healthcare utilisation mediated the association between educational level and HRQoL.

Conclusion. This research increased the knowledge of the long-term consequences of Q-fever and showed the opportunities to assess mechanisms between macro determinants and long-term health outcomes for Q-fever patients. It is recommended to assess these underlying patterns and improve care for patients with chronic diseases following zoonoses based on future research.

Keywords: Health inequalities, Inequalities of outcomes, Inequalities of Opportunities, Q-fever, Zoonosis, Health-related quality of life (HRQoL), Socioeconomic Status (SES), Health care utilisation

PREFACE

I present to you my master thesis titled: *“Linking health inequalities of outcomes and opportunities: The association between health-related quality of life, socioeconomic status and health care utilisation in Q-fever patients who experience long-term health consequences”*. This thesis has been written for the graduation of the master Population Studies, Faculty of Spatial Sciences, University of Groningen. I started studying Population Studies in February 2021, in addition to completing my master's in Sociology of Health, Welfare and Care. Unexpectedly, I was offered a job at the Department of Public Health, Erasmus Medical Center (EMC) after obtaining my master's degree in Sociology. I accepted the job without knowing how busy my life would be in the academic year 2022-2023. After all, I also had a master's to complete.

From the beginning of my job as a junior scientific researcher in Rotterdam, I was amazed at how little was known about syndromes after zoonoses. Although many studies have already been set up for Post-Acute Sequelae of SARS-CoV-2 Infection (also known as Long COVID), there are still significant unknowns about the long-term health outcomes after Q fever. Apart from studies with descriptive statistics on Q Fever Fatigue Syndrome (QFS) and Chronic Q-fever (CQ), which show the substantial long-term impact on patients' lives, relatively little is known about the factors that can contribute to improving the long-term well-being of patients.

During my studies, I learned that several social determinants might impact health. However, to my knowledge, only a few studies assessed the association between the social determinants and health outcomes for Q-fever patients. This is how the idea for this thesis, which investigates the association between socioeconomic status (SES) and health-related quality of life (HRQoL), arose.

I would like to thank EMC and Q-support for making the data available. Also, I would like to thank the patients who completed the questionnaire in 2019. I hope that my research has contributed in some way to the knowledge about the long-term consequences of Q-fever and provided some clues for improving the well-being of patients. I would also like to thank Juanita A. Haagsma from the Department of Public Health, EMC, for the guidance in determining the thesis topic.

Furthermore, I would like to thank Tess Osborne from the University of Groningen for the supervision. The suggestions she gave were valuable and helped me improve the thesis.

Last but not least, I would like to thank my loved ones.

I hope you will enjoy reading my thesis.

Anna Harbers

Sintjohannesga, 30 June 2022

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iii. List of abbreviations

AQ	Acute Q-fever
CQ	Chronic Q-fever
HRQoL	Health-Related Quality of Life
SES	Socioeconomic Status
QFS	Q-fever Fatigue Syndrome

1. INTRODUCTION

From 2007 to 2010, the Netherlands experienced the most extensive known Q(uey)-fever epidemic worldwide. In this epidemic, approximately 50,000 to 100,000 people got infected (data Sanquin, Q-koorts.nl, no date) with the bacterium *Coxiella burnetii* through direct or indirect contact with infected goats (Raoult, Marrie, & Mege, 2005). Q-fever is symptomatic in 40% of the patients, who, in most of the cases, experience short-term symptoms ranging from mild flu-like symptoms to more severe symptoms, including pneumonia or hepatitis (Raoult et al., 2005) (Acute Q-fever (AQ); Figure 1). Usually, the symptoms resolve within a few weeks.

However, over ten years after the Dutch Q-fever epidemic, some patients still experience long-term health symptoms (Figure 1). Chronic Q-fever (CQ) manifests in approximately 1-5% of all infected individuals and has endocarditis and endovascular infection as the primary clinical manifestations (Fournier, Marrie, & Raoult, 1998) (Figure 1). In about 20% of the patients who experienced symptoms due to the Q-fever infection, the health symptoms persist over the years, including fatigue, concentration problems and physical exhaustion (Fournier et al., 1998; Morroy et al., 2016). This chronic syndrome following Q-fever is called Q-fever Fatigue Syndrome (QFS) (Figure 1).

Research showed that these chronic diseases not only have negative consequences on the health of patients (e.g., Bronner et al., 2020; Limonard et al., 2016; Morroy et al., 2016; Van Loenhout et al., 2015) but also impacts (social) participation (e.g., Bronner et al., 2020; Reukers et al., 2019), and lowers the well-being and health-related quality of life (e.g., Bronner et al., 2020; Morroy et al., 2016) of these patients. Health-Related Quality of Life (HRQoL) is defined as the "perceived well-being in physical, mental, and social domains of health" and functionings in daily life (Hays & Reeve, 2010, p. 195).

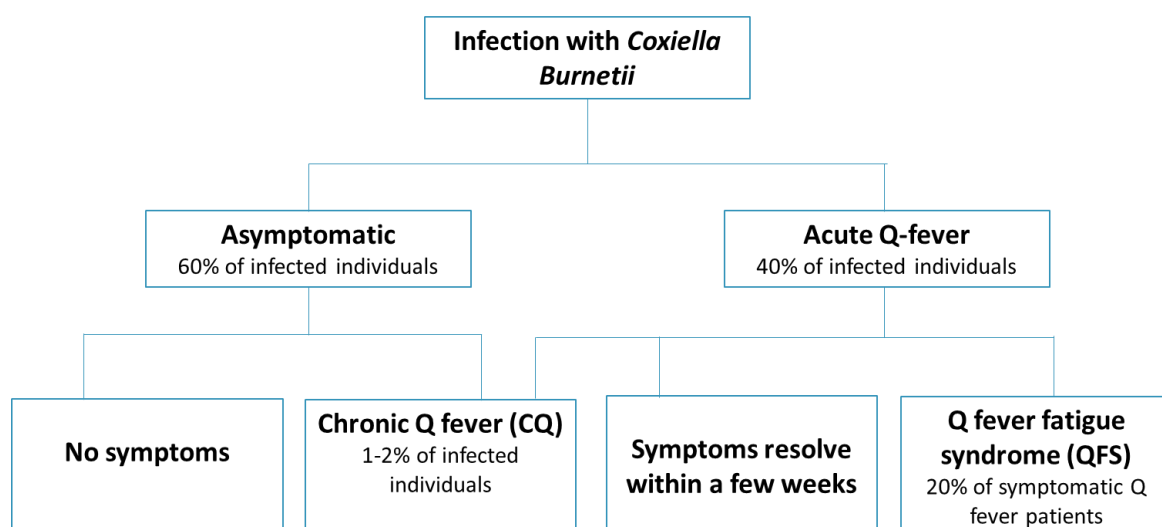


Figure 1. Chronic diseases/syndromes following Q-fever infection (Fournier et al., 1998).

Health inequalities are structural differences in health outcomes (Crammond & Carey, 2016) or "differences in health status or in the distribution of health determinants between different population groups" (World Health Organization, 2012, p. 3). These inequalities stem from various social determinants of health, usually reflected by socioeconomic status (SES): (1) level of education, (2) income, and (3) occupation. In the general population, HRQoL increases with increasing SES, while lower SES is associated with higher morbidity (Mackenbach et al., 2008; Mielck, Vogelmann, & Leidl, 2014) and lower HRQoL (Hoeymans, Van der Lindert, & Westert, 2005).

Furthermore, social determinants also influence individuals' health opportunities, such as their ability to choose the appropriate health care. Studies showed differences in health care provider appointments between individuals with lower and higher SES (Droomers & Westert, 2004; Filc, Davidovich, Novack, & Balicer, 2014). In turn, appropriate health care influences health outcomes: individuals who get adequate health care will have higher health outcomes than those who do not (Mackenbach & de Jong, 2018).

1.1. Research problem

The association between HRQoL, health care utilization and SES has not yet been assessed for Q-fever patients with long-term health symptoms. These patients are chronically ill and have had, on average, six different health care providers over the past decade (Bronner et al., 2020). If there is an association between SES and HRQoL for these patients similar to the general population, examining patients' HRQoL without considering SES would lead to an underestimation of health inequalities (Mielck et al., 2014). Consequently, policy recommendations based on HRQoL analyses could be biased (Mielck et al., 2014). Furthermore, if there are health inequalities due to SES differences in QFS, QLD and CQ patients, there may be a need to identify strategies to ensure equal access to health care services and helps to understand the healthcare needs of these patients in different SES groups.

1.2. Research objective

This study aimed to assess the differences in health care utilisation and HRQoL among different SES groups of QFS, AQ and CQ patients in the Netherlands in order to identify determinants of health inequalities in this specific patient group. Identifying possible health inequalities, their determinants and possible explaining mechanisms are needed in order to improve policy recommendations for improving HRQoL, understanding the health care needs of patients, and ensuring equal access to health care for SES groups.

The research question of this study was:

What are the associations between SES, health care utilisation and HRQoL for QFS, AQ, and CQ patients?

This research question has three sub-research questions were:

- 1) What is the association between SES and HRQoL for QFS, AQ, and CQ patients?
- 2) What is the association between SES and the health care utilisation of QFS, AQ, and CQ patients?
- 3) Does health care utilisation mediate the effect of SES on HRQoL?

1.3. Scientific relevance

There is a scientific knowledge gap in the research on the long-term consequences of Q-fever. A large proportion of the available literature on the long-term consequences of Q-fever is focused on assessing the health impact (e.g., Morroy et al., 2016; Van Loenhout et al., 2015), ways for improving the assessment of the health impact of this specific patient population (e.g., Geraerds et al., 2022), and the origins of Q-fever, CQ, and QFS (for example, abnormalities in the immune system) (e.g., Helbig et al., 2005; Raijmakers et al., 2019). With the recent focus on positive health (Huber et al., 2011), research on Q-fever also included the impact of Q-fever on quality of life, well-being and social functioning (e.g., Bronner et al., 2020; Q-support, 2022; Reukers et al., 2019). However, very few studies reported on factors that might influence the severity of long-term consequences (e.g., Breukers et al., 2019; Keijmel et al., 2013; Reukers et al., 2019).

The current study assessed if a macro determinant (SES) influences health inequalities of opportunities (HRQoL) and outcomes (health care utilization). Furthermore, this study also assessed the possible association between SES and HRQoL via health care utilization. Understanding the long-term consequences of Q-fever and assessing possible mechanisms between determinants of health and health outcomes or why treatments do (not) work is needed to improve the support and treatments for patients who experience long-term consequences of their Q-fever infection. In addition, research on determinants of health outcomes and health care may provide direction for further research on the long-term consequences of Q-fever and other zoonoses, such as Post-Acute Sequelae of SARS-CoV-2 (PASC, also referred to as Long COVID).

2. THEORETICAL FRAMEWORK

As mentioned in the Introduction (pages 1-3), there are many unknowns in understanding the long-term consequences of Q-fever. While several studies reported on the long-term consequences of Q-fever (e.g., Morroy et al., 2016; Van Loenhout et al., 2015), few studies have reported on factors that might influence the severity of the long-term consequences (e.g., Breukers et al., 2019; Keijmel et al., 2013; Reukers et al., 2019). In the following paragraphs, research on other patient populations (some who experience similar symptoms as QFS and CQ patients) is cited because knowledge about the processes and mechanisms impacting the health status of QFS and CQ is lacking. It is expected that there will be associations between SES, health care utilisation and HRQoL similar to general populations and other patient populations.

Health inequalities are reflected by SES. Research showed that people with lower SES suffer more often from disease, disability and premature death (Mackenbach, 2015). Within health inequalities, two different inequalities can be distinguished: (1) inequalities of outcomes and (2) inequalities of opportunities.

2.1. Inequalities of outcomes: Health-Related Quality of Life

Inequalities of outcomes mean that individuals do not possess the same level of specific outcomes (United Nations, 2015), for example, on HRQoL. Differences between individuals or patients can be the result of different SES levels. In the general Dutch population, HRQoL increases with increasing SES, while lower SES is associated with higher morbidity (Mackenbach et al., 2008) and lower HRQoL (Hoeymans et al., 2005; Spronk, Haagsma, et al., 2021).

Several studies of different patient populations showed significant associations between SES and HRQoL: HRQoL was lower for patients with a lower SES compared to the high SES group (Aarts et al., 2010; Klein et al., 2016; Mielck et al., 2014; van der Vlegel et al., 2021). Patients with health symptoms similar to QFS, AQ and CQ showed diminished quality of life. Survivors of endocarditis, also a symptom of CQ, had persisting symptoms and diminished quality of life one year after hospital discharge (Verhagen et al., 2009). Furthermore, a study showed that low SES was associated with lower quality of life in patients with chronic fatigue syndrome and/or fibromyalgia, which has similar health symptoms as QFS and AQ (Schoofs, Bambini, Ronning, Bielak, & Woehl, 2004).

As the association between HRQoL and SES is apparent in the general population and other patient populations, it is expected that in patients with long-term health symptoms related to Q-fever, patients with a lower SES have a lower HRQoL. Therefore, the first hypothesis is:

Hypothesis 1. QFS, AQ and CQ patients with lower SES have a lower HRQoL compared to patients with a higher SES.

2.2. Inequalities of opportunities: Health care utilisation

Inequalities of opportunities mean that individuals do not possess the same possibilities or probabilities to do or decide certain things, i.e., different individuals have different freedoms to choose between or act on different options in their life (United Nations, 2015).

The Capability Approach of economist Sen considers development as an individual's capability to do certain things and sees resources as the means to this (Robeyns, 2011; Sen, 1992). Capabilities are the possibilities or opportunities individuals have to do certain things. In this study, the capabilities are individuals' freedom to choose between different health care providers. Capabilities can be transformed into functionings, which is the individuals' realisation of the achievements based on the most valued option. In this research, getting the necessary health care is seen as a functioning for QFS, AQ and CQ patients.

Capabilities can be transformed into functionings using specific resources and conversion factors (Robeyns, 2005; Sen, 1992). Poorer health and higher comorbidity (van der Heide et al., 2015), financial restrictions, and lower health literacy (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011) may lead to difficulties in finding appropriate health care (van der Heide et al., 2015), thus impeding the ability to transform the capabilities into functionings. On the other hand, financial means, higher health literacy, and better health might help the ability to transform capabilities into functionings. In this way, SES can be seen as a resource that can be used to transform the capability into the functioning. The general understanding is that individuals with lower SES use primary care more often, while people with a higher SES use specialised care more often (Droomers & Westert, 2004; Lueckmann et al., 2021).

Studies showed that there can be an association between SES and health care utilization. In a study among older adults, SES was associated with lower access to health care services and delayed health care (Yamada et al., 2015). Other studies concluded that individuals with lower SES visited primary care providers more, while individuals with a higher SES visited more specialists (Droomers & Westert, 2004; Filc et al., 2014).

In line with the Capability Approach and previous research, the SES of Q-fever patients is expected to influence the adequacy of the individuals' resources for health care; in this study defined as the number of appointments with primary and specialised health care providers. A lower SES is expected to impede seeing the possibilities for different forms of health care due to a lack of resources to transform capabilities into functionings, thereby impeding getting the needed health care. On the

other hand, a higher SES is expected to help QFS, AQ and CQ patients choose the health care they need. Therefore, they are expected to be able to get the most effective health care. Specialised health care providers are expected to be better at treating Q-fever and its long-term consequences, as specialists have more treatment options than primary health care providers, especially for rare diseases (such as Q-fever). Therefore, the hypothesis is split up into two parts:

Hypothesis 2a. The number of primary care appointments is higher among patients with lower SES compared to patients with a high SES.

Hypothesis 2b. In contrast, utilisation of specialised care is higher for patients with higher SES compared to patients with a lower SES.

2.3. Linking Inequalities of Outcomes and Opportunities

As people with CQ, QFS and AQ often have an extensive range of health symptoms, their health care utilisation is high (Bronner et al., 2019). Health care is supposed to help people improve their life expectancy and quality of life. However, diagnosis of a disease might not necessarily lead to better health care and, therefore, might not necessarily lead to better HRQoL. In particular, this might be the case for chronic diseases compared to acute diseases (Kaplan, 2003). Chronic diseases process gradually, and treatment is sometimes unavailable. Chronic diseases are not curable, and patients must adapt their (daily) lives to their diseases. CQ, QFS and AQ are chronic diseases whose underlying causes are not entirely known. For these chronic conditions, diagnosis and treatment might not improve the quality of life (Kaplan, 2003). Several studies showed this association between higher health care utilisation and lower HRQoL (e.g., Singh et al., 2005; Traino et al., 2021).

Whether inequalities in health care utilisation generate different health outcomes for individuals with a lower SES compared to individuals with a higher SES depends on the quality and effectiveness of the health care for those who make use of the care compared to those who do not (Mackenbach & de Jong, 2018). For example, a study among older adults in Mexico showed that using preventive health care services was strongly associated with higher HRQoL (Gallegos-Carrillo et al., 2008). The relationship between HRQoL and health care use can also be directed the other way around (Miilunpalo, Vuori, Oja, Pasanen, & Urponen, 1997), in that lower HRQoL can lead to a higher rate of consultations and hospitalisations (Lam, Fong, Lauder, & Lam, 2002).

Thus, it is expected that SES directly influences HRQoL (Mielck et al., 2014) and can indirectly influence HRQoL via health care use (Mackenbach & de Jong, 2018). Socioeconomic position influences health determinants, including health behaviours and access and care utilization (Kunst,

Bos, & Mackenbach, 2001). Health care utilisation, in turn, can determine the health status, including the HRQoL (Kunst et al., 2001). Therefore, the hypothesis is:

Hypothesis 3. SES has a direct impact on HRQoL and an indirect impact on HRQoL via health care utilisation.

2.4. Conceptual model

The theoretical framework highlighted three key concepts: SES, health care utilisation, and HRQoL. Based on the hypotheses, the conceptual model for this research is shown in figure 2.

Apart from the three central concepts, sociodemographic and medical factors were considered to be associated with HRQoL. Four determinants will be included: sex, age, diagnosis, number of health symptoms related to the diagnosis, and the presence of comorbidities. Women have, on average, lower HRQoL than men (Cherepanov, Palta, Fryback, & Robert, 2010). Furthermore, older age is associated with lower HRQoL due to physical health problems and increasing limitations in daily life (Etxeberria, Urdaneta, & Galdona, 2019). Similarly, having many health symptoms and comorbidities are associated with lower HRQoL (Etxeberria et al., 2019). Lastly, diagnosis with QFS, AQ or CQ is included to assess if the associations between SES, HRQoL and health care utilisation differs between the diagnosis groups. This may be the case as CQ has different clinical manifestations than QFS and AQ (Fournier et al., 1998; RIVM, 2019) and, therefore, CQ may impact HRQoL differently than QFS or AQ.

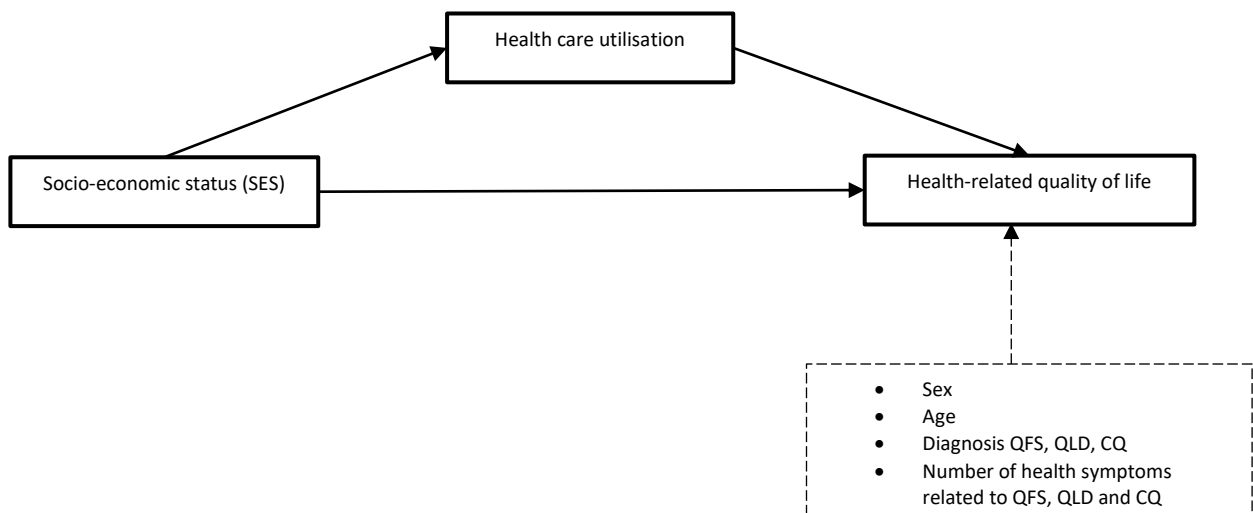


Figure 2. Conceptual model SES on HRQoL via health care utilisation of patients who experience long-term health consequences.

3. METHODS

3.1. Study design

This study involves secondary analysis of data acquired by the Erasmus Medical Center (EMC), the Dutch expertise centre for Q-fever *Q-support* and patient organisation *Q-uestion* using a questionnaire. The data was gathered to assess Q-fever patients' health status, health care utilisation, and healthcare needs up to ten years after infection (Bronner et al., 2020). Therefore, the questionnaire contained questions about sociodemographic and (Q-fever-related) medical characteristics, Q-fever-related health symptoms, well-being and HRQoL, social participation (including labour participation), health care utilisation, and health care needs.

Q-uestion and *Q-support* sent the online questionnaire to Q-fever patients in December 2018. After four weeks, a reminder to complete the questionnaire was sent out to the patients. Patients' participation in the questionnaire was voluntary, and all participants gave informed consent to use their data for scientific research.

The anonymised dataset contains data from Dutch Q-fever patients aged 18 years or older who were members of *Q-Support* and/or *Q-uestion*. For this study, the dataset was analysed using descriptive statistics and linear regression analysis, indicating that this study has a quantitative cross-sectional design.

3.2. Study population

Patients were eligible if they were a *Q-uestion* and/or *Q-support* member, aged 18 years or older, and had a good command of Dutch. A positive laboratory test result for the *Coxiella Burnetii* bacterium is needed, indicating that members experienced Q-fever infection, to become a member of *Q-uestion* or *Q-support*.

In total, 880 patients were eligible. The online questionnaire was sent to 700 patients by *Q-support* and 400 by *Q-uestion*; 20% of the patients got an invitation from both organisations. Patients were categorised into three categories based on their self-reported diagnosis in the questionnaire: CQ, QFS or acute Q-fever. Table 1 describes, based on existing literature, the percentage of patients, clinical manifestations and diagnostic criteria of these three diagnoses.

Table 1: Types of diseases/syndromes following Q-fever and their clinical manifestations and diagnostic criteria.

Types of Q-fever	Percentage of patients	Clinical manifestations	Diagnostic criteria
Acute Q-fever (AQ)	Approximately 40% of individuals infected with <i>Coxiella burnetii</i> (Raoult et al., 2005)	Flu-like symptoms to more severe symptoms like pneumonia, hepatitis	<ul style="list-style-type: none"> • Clinical presentation with fever • Pneumonia or hepatitis • Positive serology by laboratory tests (U.S. Department of Health and Human Services, 2009)
Chronic Q-fever (CQ)	Approximately 2% of individuals infected with <i>Coxiella burnetii</i> (RIVM, n.d.)	Endocarditis, endovascular infection	<ul style="list-style-type: none"> • Positive laboratory testing: antibody level in phase I of $\geq 1:1024$ for <i>Coxiella Burnettii</i> • Focus on infection (Wegdam-Blans et al., 2012)
Q-fever fatigue syndrome (QFS)	Approximately 20% of patients with acute Q-fever (RIVM, 2019)	Fatigue and a range of other physical symptoms, including but not limited to concentration problems, physical exhaustion, joint pain	<ul style="list-style-type: none"> • Persisting fatigue longer than six months AND • No comorbidity that could explain the fatigue • Fatigue significantly limits daily functioning • No fatigue before the Q fever infection, or the health symptoms increased clearly in severity (RIVM, 2019)

3.3. Operationalisation of concepts

3.2.1. Sociodemographic and medical characteristics

Age, sex and living situation were included as sociodemographic variables. Age was categorised into five groups: ≤ 39 years, 40-49 years, 50-59 years, 60-69 years and 70 years or older. Living situation was dichotomised as living alone (0) versus living together (1). Sex was a dummy variable: males (0) and females (1).

Patients were asked about several medical characteristics, including antibiotic use (yes/no/do not know) and hospitalization when infected (yes/no). Patients were classified into three diagnosis groups based on their self-reported diagnosis: Q-fever Fatigue Syndrome (QFS), Acute Q-fever (AQ), and Chronic Q-fever (CQ). Furthermore, the questionnaire included a list of 27 common health complaints - patients selected which were a problem for them since the Q-fever infection. A total score of health complaints per patient was calculated by counting the number the symptoms.

3.2.2. Educational level

In this study, the level of education was used as a proxy for SES. Although it is not ideal to use a proxy for SES, using the level of education was the only available information on SES in the dataset. Possible limitations because of the use of this proxy are addressed in the Discussion (pages 25-28).

Educational level was recoded into three categories based on the International Standard Classification of Education (ISCED) (UNESCO institute for Statistics, 2011): (1) low, (2) middle (higher

secondary education and middle vocational education), and (3) high (higher vocational education, university).

3.2.3. Health-related quality of life (HRQoL)

HRQoL was measured with the EQ-5Dimension-5Level (EQ-5D-5L), a generic, brief instrument to measure the health status of individuals (EuroQol Research Foundation, 2019). The questionnaire distinguishes five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and cognition (EuroQol Research Foundation, 2019). On each dimension, there are five answer options: (1) no problems, (2) some problems, (3) moderate problems, (4) severe problems and (5) extreme problems. For each dimension, descriptive statistics were given to indicate the percentage of patients who experience problems in the domains.

Furthermore, every individual has a health state, which is a number that consists of the severity levels of the five dimensions. Combining the five dimensions with the five answer options, the EQ-5D-5L describes $5^5=3125$ unique health states. For example, the health state 11111 refers to no problems in all domains, while the health state 55555 refers to severe problems in all domains.

These health states can be converted into one single number, a utility index, using population-specific value sets (EuroQol, 2021). A value set collects all the possible health states in a population. In this study, the value set of Versteegh et al. (2016) is used, and, therefore, the utility index reflects the health status of Q-fever patients compared to the general Dutch population. Versteegh et al. (2016) calculated the utility scores for the general Dutch population by multiplying the scores on the five dimensions with coefficients of a Tobit model for a representative sample of the Dutch population controlled by age, sex and education. In theory, the utility index can take values between 1 (perfect health, for a health state 11111) to 0 (death) (Dolan, 1997). However, the produced values are allowed to be negative, indicating a worse-than-death health state (lowest utility index=-0.446, for a health state 55555) (Versteegh et al., 2016). As value sets can assign different utilities to slightly different health states, the EQ-5D-5L utility index was regarded as a continuous variable.

3.2.4. Health care utilization

Patients were asked which health care providers they have visited since the Q-fever infection out of a list of 21 health care providers (14 primary and 7 specialised health care providers). The total number of visited healthcare providers per patient was calculated by counting all healthcare providers patients selected. Health care providers were categorised into two groups based on the Dutch health care system (Westert, Stronks, Klazinga, & Polder, 2012): (1) primary health care providers (e.g., general practitioner, social worker, occupational physician, dietician, occupational therapists), and (2)

specialised health care workers (e.g., surgeon, internist, pulmonologist). Patients also had to indicate how often they visited health care providers. If patients did not visit the health care provider, a score of 0 was given. The total numbers of appointments were calculated by adding up the total number of appointments with primary health care providers and the total number of appointments with specialised health care providers, resulting in two variables for health care utilization.

3.3. Data analysis

The software program used to analyse the data is IBM SPSS Statistics Version 25, including the macro extension PROCESS (Hayes, 2022). The data analysis consisted of (1) descriptive statistics and (2) regression analyses.

3.3.1. Descriptive statistics

First, descriptive statistics were performed to describe the sociodemographic and medical characteristics of the patients. Furthermore, proportions and descriptive statistics were described to describe the health outcome variables: the five HRQoL dimensions and the (number of appointments with) health care providers. Median and IQR were estimated for the EQ-5D-5L utility index, the number of health care providers, and the number of appointments with primary and specialised health care providers. Differences between the three educational level groups were tested with χ^2 -tests for binary and categorical variables, and Kruskal-Wallis H tests or Mann-Whitney U tests for ordinal and continuous variables. A p-value of <0.05 was considered significant for all descriptive statistics.

3.3.2. Regression analyses for hypotheses testing

Univariate and multivariate linear regression analyses were performed with the EQ-5D-5L utility index as the continuous outcome variable. Ordinary Least Squares (OLS) is the most commonly used regression technique for the EQ-5D-5L utility index and is applicable for analysing underlying mechanisms between a variable and HRQoL (Devlin, Parkin, & Janssen, 2020). However, as this study aimed to determine if health care utilisation was the underlying mechanism of the association between SES and HRQoL, a mediation analysis needed to be performed.

As the level of education was a multicategorical independent variable, indicator coding (also called dummy coding) is needed to fully represent the effect of educational level on HRQoL. Therefore, $k-1$ parameters coefficients are constructed. This implied that the level of education was recoded into two dummy variables: low educational level (D1) and middle educational level (D2) compared to high educational level (reference category).

There were two continuous mediation variables: (1) the number of appointments with primary health care providers and (2) the number of appointments with secondary health providers. However, using OLS in SPSS to estimate the coefficients and statistical significance, especially of the indirect effect in the mediation analysis, was difficult. Therefore, additional tests or the use of a macro extension in SPSS was required. This study used the macro extension PROCESS (Hayes, 2022) to estimate the coefficients and statistical inference.

Coefficients

First, univariate regression analyses were performed to assess the association between all variables (including control variables) and HRQoL. All variables with a significance level of $p < 0.01$ were included in the multivariate analyses, including mediation.

The mediation analysis method used was based on an expert tutorial on statistical mediation analysis with a multicategorical independent variable (Hayes & Preacher, 2014). Coefficients were calculated by hand in several steps:

- (1) *Relative total effect* of educational level on HRQoL (**model 1**) to test **hypothesis 1**: QFS, AQ and CQ patients with lower SES have a lower HRQoL compared to patients with a higher SES.
- (2) *Direct effects* between educational level and the number of primary/specialized health care appointments (**model 2**) to test **hypothesis 2**: The number of primary health care appointments is higher among patients with lower SES, while the number of specialised health care appointments is higher among patients with higher SES.
- (3) *Relative indirect effects* of educational level on HRQoL through the number of primary/specialized health care appointments.
- (4) *Relative direct effects* of educational level on HRQoL, adjusting for the number of health care appointments (**model 3**) to test **hypothesis 3**: SES has a direct impact on HRQoL and an indirect impact via health care utilisation.
- (5) *Total models of the association between educational level, number of primary/specialised health care appointments, and HRQoL, including control variables sex, age, diagnosis and number of health symptoms* (**model 4**) to test if **hypothesis 3** held when sociodemographic and medical variables were included.

Statistical significance

The coefficients and statistical significance were also estimated using SPSS Version 25 using linear regression analysis (steps 1, 2, 4 and 5) and the PROCESS macro (steps 3-5) (Hayes, 2022). For the statistical inference of the *relative indirect effects* between educational level and health care

utilization, an asymmetric bootstrapping technique with 5,000 samples was used as recommended by Hayes & Preacher (2014). For all outcomes of the regression analyses, statistical significance is indicated by asterisks: * $p < 0.01$; ** $p < 0.05$; *** $p < 0.001$.

Model assumptions

The linear regression model assumptions were checked for the total model using SPSS. Furthermore, it was also assessed if there were missing values, outliers and multicollinearity.

Model fit

For the model fit, the adjusted R^2 , F-change and significance values of the total models were given to indicate how well the models describe the observations.

3.4. Ethical considerations

Several ethical considerations were taken into account in this study. First, the Medical Ethics Review Board of Erasmus MC approved the data collection (METC-2018-1605). Second, participation in this study was voluntary. Before starting the questionnaire, participants were introduced to the topic and were informed about the estimated length of the questionnaire and the legal data retention period of 15 years. Participants needed to fill out an informed consent form stating that they were informed about the objective of the questionnaire, that participation was voluntary, and that they understood what happened to their data. Participants were also made aware that they could withdraw their data. Furthermore, only anonymised data was stored at EMC and available for research in this study. Also, the anonymised data were treated confidentially; only researchers at the Department of Public Health, EMC, can access the data. Third parties cannot view personal data without the consent of the participants.

Another consideration was the positionality of the researcher. The author acknowledged that the research process could be influenced by the research context, personal beliefs, and experiences. However, the author of this master thesis has no competing interests. The hypotheses were formulated based on existing theories and previous research, and were formulated before data analysis; the hypotheses were formulated based on scientific literature. Furthermore, the data were not gathered by the author of this paper. Although EMC and patient organisations gathered the data, the analysis was performed independently. To ensure honesty in data analysis and reporting in this study, the methods and reporting of the outcomes were described in detail.

4. RESULTS

4.1. Sociodemographic and medical characteristics

A total of 478 patients completed the online questionnaire (response rate of 54.3%). Forty-five participants were excluded from the analysis as they had missing values on the dependent variable. As these patients had similar sociodemographic and medical characteristics as the participants, the missing observations seemed random and were excluded from the data using listwise deletion. In total, 433 patients were included in the analyses.

The median age of the participants was 58.0 (*IQR*: 48.0-65.0), and 51.7% was male (Table 2). Participants with low educational levels were significantly older (*median*=61.0, *IQR*: 55.0-69.0) than participants with middle (*median*=55.5, *IQR*: 45.0-61.0) and high (*median*=56.0, *IQR*: 45.0-64.0) educational levels ($H(2)=35.870$, $p<0.001$). The majority of the participants lived together with a partner and/or children (61.2%).

Most participants were prescribed antibiotics when infected with Q-fever (71.8%), and 22.4% were hospitalised (Table 1). Of the participants, 59.1% had the diagnosis QFS, 10.6% CQ, and 30.3% AQ. There were significant differences in diagnosis between educational level groups ($X^2(4)=13.748$, $p=0.008$). The percentage of participants with CQ was highest in the low educational level group (16.4%), the percentage of participants with AQ was highest in the high educational level group (34.7%), and the percentage of participants with QFS was highest in the middle educational level group (69.0%). Participants had a median of 12.0 (*IQR*: 8.0-16.0) Q-fever-related health symptoms. The diagnostic groups also differed in all sociodemographic and medical characteristics, except for living together [Appendix A, Table A1].

4.2. Health-related quality of life

The median EQ-5D-5L utility index was 0.60 (*IQR*: 0.32-0.75). There was a considerable trend toward significance between the scores of the educational groups ($X^2(2)=5.527$, $p=0.063$). The EQ-5D-5L utility index was highest for participants with a high educational level (*median*=0.67; *IQR*: 0.39-0.81), and lowest for the low (*median*=0.58; *IQR*: 0.33-0.74) and middle educational levels (*median*=0.57; *IQR*: 0.26-0.74).

In general, the EQ-5D-5L utility index was significantly lower for women than for men ($U=20301.500$, $z=-2.388$, $p=0.017$), lower for participants younger than 40 and participants in their fifties compared to the other age categories ($H(4)=13.301$, $p=0.010$), and lower for QFS participants compared to CQ and AQ participants ($H(2)=26.676$, $p<0.001$) [Appendix A, Table A2]. QFS patients with a middle and high educational level had a significantly lower index (below 0.60) compared to the index

for patients with a middle and high educational level (above 0.73) of the other diagnosis groups [Appendix A, Table A3].

Participants reported most problems on the dimensions *usual activities* (89.6% reported any problems), *pain/discomfort* (88.5% reported any problems) and *mobility* (71.8% reported any problems) (Figure 3). Participants with a high educational level had significantly fewer problems with *mobility* ($X^2(8)=15.646, p=0.048$) and *usual activities* ($X^2(8)=16.748, p=0.033$) compared to participants with a low or middle educational level. There were also differences in four (all but *anxiety/discomfort*) dimensions by diagnosis: a higher percentage of CQ participants reported problems on *mobility* and *self-care*, and more QFS participants reported problems on *usual activities* and *pain/discomfort* [Appendix A, Figure A1].

Table 2: Sociodemographic and medical characteristics of the study participants, total and by educational level.

	Total	Low education	Middle education	High education	
	n=433	n=128	n=158	n=147	
	n (%)	n (%)	n (%)	n (%)	$X^2 (p)$
Sociodemographic characteristics					
Age in years, median (IQR)	58.0 (48.0-65.0)	61.0 (55.0-69.0)	55.5 (45.0-61.0)	56.0 (45.0-64.0)	35.870 (<0.001)*
Age categories					41.553 (<0.001)*
Under 40 years	52 (12.0)	3 (2.3)	25 (15.8)	24 (16.3)	
40-49 years	71 (16.4)	10 (7.8)	28 (17.7)	33 (22.4)	
50-59 years	122 (28.2)	40 (31.3)	52 (32.9)	30 (20.4)	
60-69 years	125 (28.9)	45 (35.2)	37 (23.4)	43 (29.3)	
70+ years	63 (14.5)	30 (23.4)	16 (10.1)	17 (11.6)	
Sex					0.360 (0.835)
Male	224 (51.7)	65 (50.8)	80 (50.6)	79 (53.7)	
Female	209 (48.3)	63 (49.2)	78 (49.4)	68 (46.3)	
Living situation					1.181 (0.554)
Living together	265 (61.2)	76 (59.4)	102 (64.6)	87 (59.2)	
Living alone	168 (38.8)	52 (40.6)	56 (35.4)	60 (40.8)	
Medical characteristics					
Diagnosis					13.748 (0.008)*
CQ	46 (10.6)	21 (16.4)	10 (6.3)	15 (10.2)	
QFS	256 (59.1)	66 (51.6)	109 (69.0)	81 (55.1)	
AQ	131 (30.3)	41 (32.0)	39 (24.7)	51 (34.7)	
Number of Q-fever related health symptoms	12.0 (8.0-16.0)	12.0 (7.3-16.0)	13.0 (8.0-17.0)	11.0 (7.0-15.0)	3.373 (0.185)
Antibiotics when infected					9.274 (0.055)
Yes	311 (71.8)	101 (78.9)	106 (67.1)	104 (70.7)	
No	102 (23.6)	19 (14.8)	44 (27.8)	39 (26.5)	
Not sure	20 (4.6)	8 (6.3)	8 (5.1)	4 (2.7)	
Hospitalisation when infected					3.935 (0.140)
Yes	97 (22.4)	36 (28.1)	29 (18.4)	32 (21.8)	
No	336 (77.6)	92 (71.9)	129 (81.6)	115 (78.2)	

Note. Kruskal Wallis H tests were used for ordinal and continuous variables (median and IQR), and χ^2 tests for binary or nominal variables.

* $p<0.05$

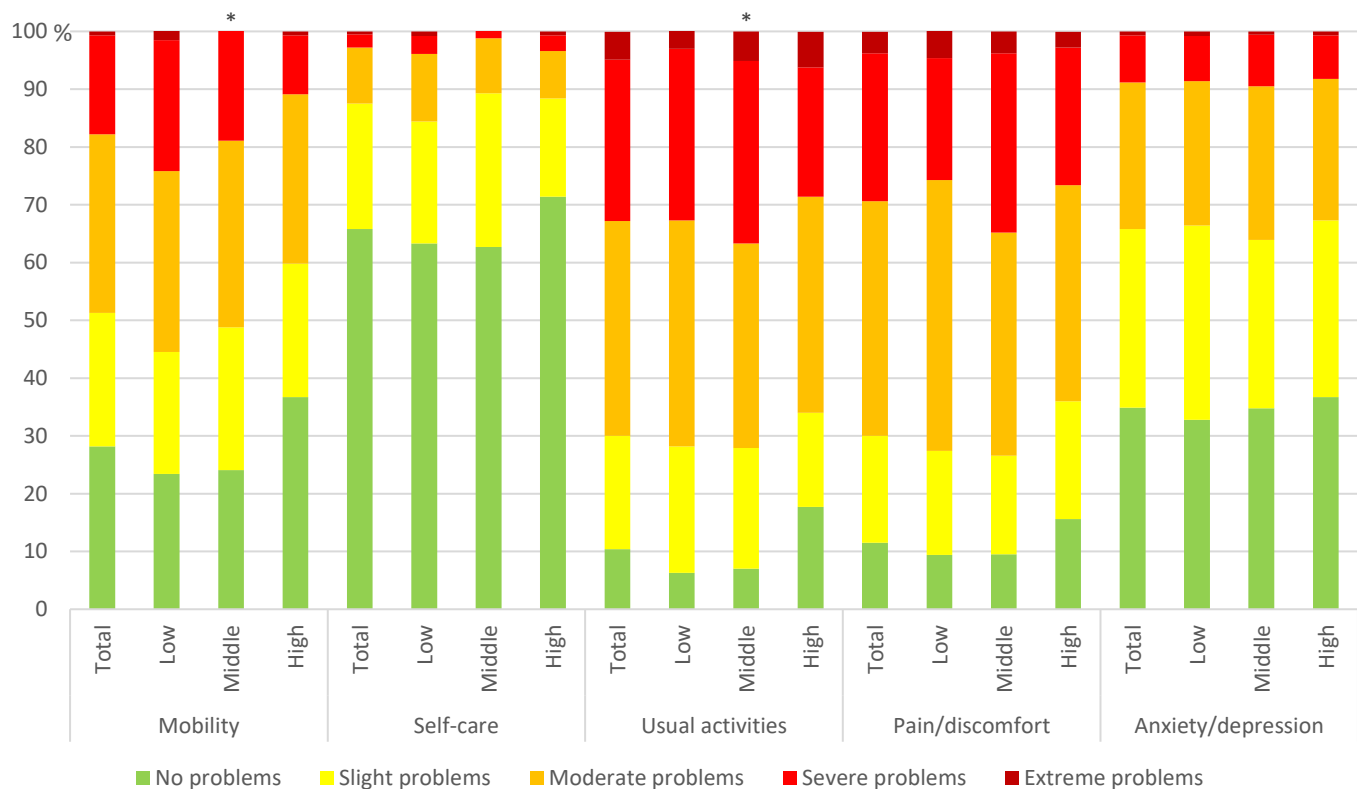


Figure 3. Distribution of responses by severity level (problems) on the EQ-5D-5L dimensions of the study participants, total and by educational level.

* $p < 0.05$

4.3. Health care utilisation

4.3.1. Health care providers

The median number of health care providers the participants had contact with related to Q-fever was 6.0 (*IQR*: 4.0-8.0) and did not statistically differ between educational groups. Participants with low educational level had significantly more contact with the cardiologist ($X^2(2)=10.384$, $p=0.006$), pulmonologist ($X^2(2)=14.980$, $p < 0.001$), rheumatologist ($X^2(2)=7.222$, $p=0.027$) and Cesar therapist ($X^2(2)=9.344$, $p=0.009$) (Figure 4). Significantly more participants with a high educational level had contact with the internist ($X^2(2)=7.356$, $p=0.025$) and osteopathic physician ($X^2(2)=7.825$, $p=0.020$). More participants with a middle educational level had contact with the social worker ($X^2(2)=10.502$, $p=0.005$) than participants with low and high educational levels (Figure 4).

A significantly higher percentage of CQ patients had contact with specialised health care (95.7%) providers compared to QFS and AQ patients ($X^2(2)=12.381$, $p=0.002$); with primary health care providers, CQ patients had significantly less contact compared to QFS and AQ patients ($X^2(2)=23.512$, $p < 0.001$) [Appendix A, Figure A2]. There were also differences in contact with different health care providers by diagnosis: a higher percentage of CQ participants had contact with the internist, cardiologist and surgeon, and more QFS participants had contact with the physical therapist,

occupational physician, psychologist, social worker, insurance doctor, acupuncturist, homoeopathic physician, occupational therapist, and manual therapist [Appendix A, Figure A2].

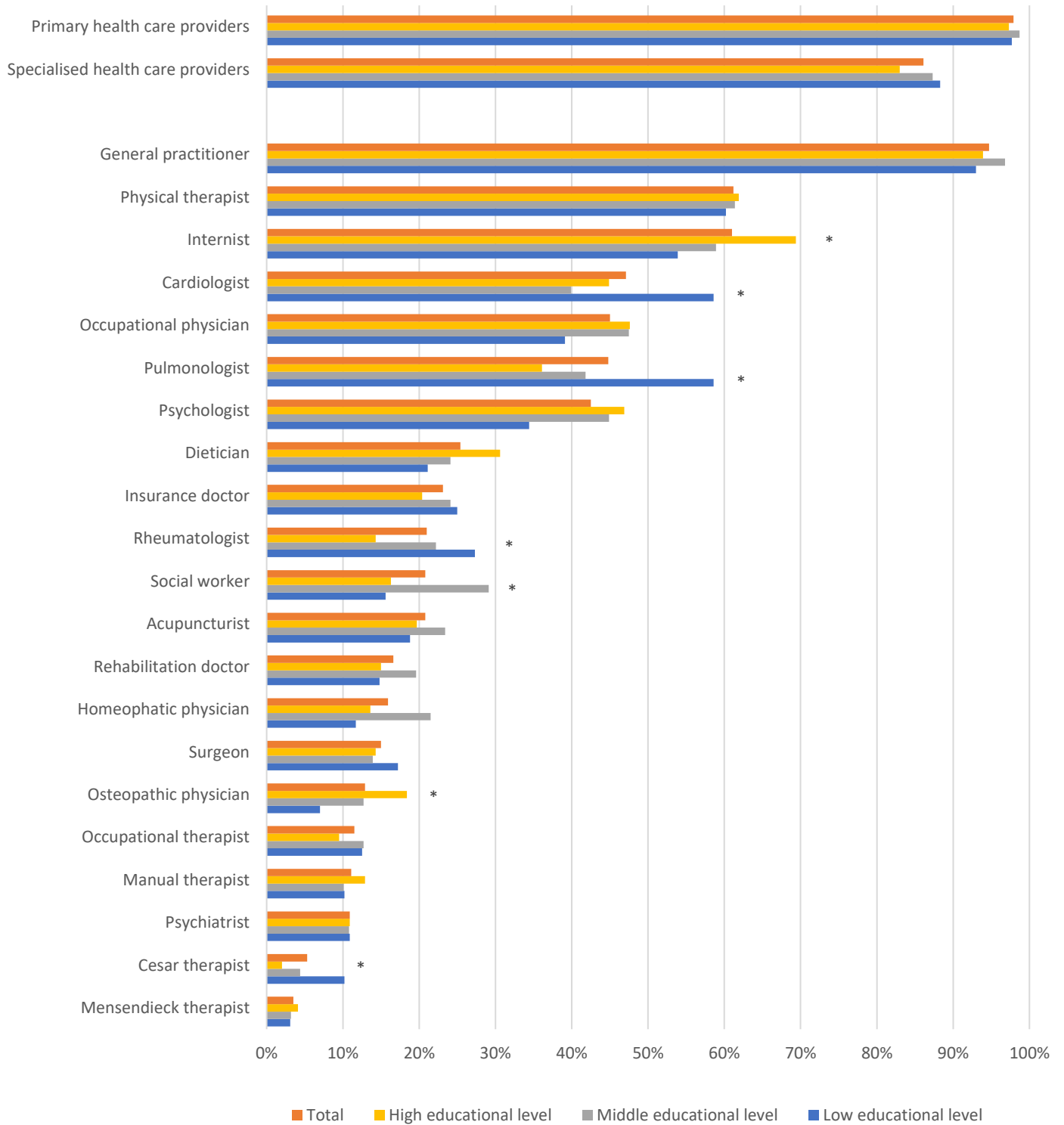


Figure 4. Percentage of participants (%) that had contact with health care providers, total and by educational level.
* p<0.05

4.3.2. Number of appointments with primary and specialised health care providers

Participants had a median of fifty appointments (*IQR*: 13.5-125.5) with the primary and ten appointments (*IQR*: 2.0-24.5) with specialised healthcare providers (Table 3). There were no statistical differences between educational groups on the number of appointments with health care providers. When categorising the number of appointments in three groups (no appointments, 1-9 appointments, ≥ 10 appointments), a higher percentage of the patients with a low educational level had ten or more appointments with specialised health care providers (60.2%) compared to middle (50.0%) and high educational level (44.9%) ($\chi^2(4)=8.924$, $p=0.063$), although not statistically significant (Table 3).

The number of appointments with primary health care providers was significantly higher for men compared to women ($U=20581.00$ -, $z=-2.173$, $p=0.030$), lower for participants older than 70 ($H(4)=12.581$, $p=0.014$), and highest for QFS participants compared to CQ and AQ participants ($H(2)=50.174$, $p<0.001$) [Appendix A, Table A2]. The number of appointments with specialised health care providers was lowest for patients with an age of 49 years or younger ($H(4)=11.966$, $p=0.018$), lower for females compared to males ($U=19217.500$ -, $z=-3.299$, $p=0.001$) and highest for patients with a CQ diagnosis ($H(2)=49.293$, $p<0.001$) [Appendix A, Table A2].

On all educational levels, CQ patients had a significantly higher number of appointments with specialised health care providers compared to AQ and QFS patients [Appendix A, Table A3]. For patients with a middle educational level, patients with CQ also had a significantly higher number of appointments with primary health care providers. For high educational level, the number of appointments with primary health care providers was highest for QFS patients [Appendix A, Table A3].

Table 3: The median number of appointments with primary and specialised healthcare providers, total and by educational level.

	Total	Low education	Middle education	High education	χ^2 (p)
Number of appointments with primary health care providers					
Median (<i>IQR</i>) appointments	50.0 (13.5-125.5)	47.0 (12.0-109.0)	59.5 (20.0-145.8)	46.0 (12.0-124.0)	2.625 (0.269)
<i>N</i> (%) appointments					7.506 (0.111)
None	22 (5.1)	12 (9.4)	5 (3.2)	5 (3.4)	
1-9 appointments	60 (30.9)	15 (11.7)	22 (13.9)	23 (15.6)	
≥ 10 appointments	351 (81.1)	101 (78.9)	131 (82.9)	119 (81.0)	
Number of appointments with specialised health care providers					
Median (<i>IQR</i>) appointments	10.0 (2.0-24.5)	13.5 (2.0-28.0)	9.5 (2.0-25.3)	8.0 (2.0-21.0)	2.781 (0.249)
<i>N</i> (%) appointments					8.924 (0.063)
None	71 (16.4)	22 (17.2)	24 (15.2)	25 (17.0)	
1-9 appointments	140 (32.3)	29 (22.7)	55 (34.8)	56 (38.1)	
≥ 10 appointments	222 (51.3)	77 (60.2)	79 (50.0)	66 (44.9)	

Note. Kruskal Wallis H tests were used for continuous variables (median and *IQR*), and χ^2 tests for nominal variables.

* $p<0.05$

4.4. Associations between SES, health care utilisation and EQ-5D-5L utility index

4.4.1. Coefficients and statistical significance

Several steps needed to be performed to test the hypothesis as stated in the Theoretical framework (pages 4-7). In these steps, different effects were calculated, of which the pathways are shown in Figure 5. The effects were calculated using descriptive statistics estimated by SPSS, shown in Table 4. The statistical inference was estimated by SPSS.

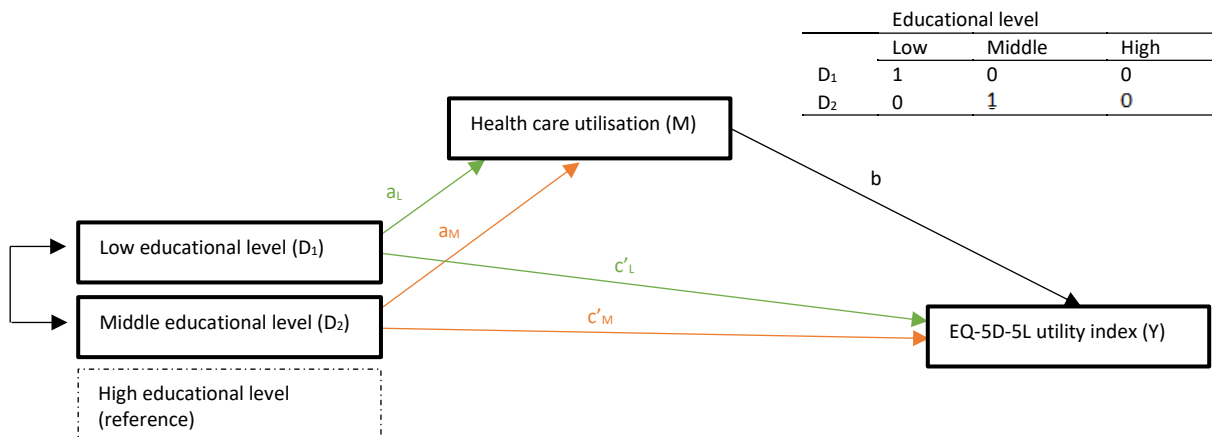


Figure 5. Model for the association between educational level, health care utilization and HRQoL, based on indicator coding.

Table 4: Means for the number of health care appointments and HRQoL by educational level and combined, estimated by SPSS.

	Number of appointments with primary health care providers (M _p)		Number of appointments with specialised health care providers (M _s)		Health-related Quality of Life (Y)			
	\bar{M}_p	SD	\bar{M}_s	SD	\bar{Y}	SD	$\bar{Y}^*_{p/s}$	\bar{Y}^*_s
	Low educational level	91.781	122.138	21.641	26.086	0.530	0.297	0.481
Middle educational level	107.854	145.684	19.177	29.677	0.511	0.299	0.471	0.512
High educational level	96.687	161.253	17.286	26.394	0.585	0.288	0.539	0.582
Combined	99.312	144.681	19.263	27.542	0.542	0.296	0.542	0.542

$\bar{Y}^*_{p/s}$ = adjusted mean, adjusted to the sample mean of the number of primary/specialised health care appointments.

(Step 1) Relative total effects

The relative total effects showed the effect of educational level on HRQoL and were equivalent to the mean difference in HRQoL between low and middle education relative to high education (Table 4):

The relative total effect of low compared to high educational level on HRQoL was

$$c_L = \bar{Y}_{\text{Low}} - \bar{Y}_{\text{High}} = 0.530 - 0.585 = -0.055$$

The relative total effect of middle compared to high educational level on HRQoL was

$$c_M = \bar{Y}_{\text{Middle}} - \bar{Y}_{\text{High}} = 0.511 - 0.585 = -0.074$$

Participants with a middle educational level had a significantly lower HRQoL than a high educational level ($b=-0.074$, $p=0.029$) (Table 5, Model 1). The coefficient of low education on HRQoL did not statistically differ from zero ($b=-0.055$, $p=0.121$) (Table 5, Model 1).

(Step 2) Direct effects

In Model 2, the association between educational level and health care appointments were calculated. The direct effects corresponded to the mean differences in health care utilization between the low and middle education relative to high education (Table 4):

The direct effect of low and middle educational levels compared to high educational level on the number of primary health care appointments was

$$a_{PL} = \hat{M}_{\text{Low}} - \hat{M}_{\text{High}} = 91.781 - 96.697 = -4.906$$

$$a_{PM} = \hat{M}_{\text{Middle}} - \hat{M}_{\text{High}} = 107.854 - 96.697 = 11.161$$

The direct effect of low and middle educational levels compared to high educational level on the number of specialised health care appointments was

$$a_{SL} = \hat{M}_{\text{Low}} - \hat{M}_{\text{High}} = 21.641 - 17.286 = 4.355$$

$$a_{SM} = \hat{M}_{\text{Middle}} - \hat{M}_{\text{High}} = 19.177 - 17.286 = 1.892$$

Although not significant, there was a difference in signs between low, middle and high education and the number of primary health care appointments (Table 5, Model 2_p). Low education lowered the number of primary health care appointments by 4.906 compared to high education. In contrast, middle education increased the number of primary health care appointments by 11.161 compared to high education. The coefficients of the direct effects of educational level on the number of specialised health care appointments were also not significant (Table 5, Model 2_s).

(Step 3) Relative indirect effects

The relative indirect effects of educational level on HRQoL through health care utilization were estimated by the SPSS macro PROCESS (Hayes, 2022). Relative to the control condition, participants with a middle educational level had an index value of 0.005 ($SE=0.004$) higher than participants with a high educational level due to the effect of education on the number of primary health care

appointments, which increased the HRQoL. Similarly, participants with a low educational level had an index value of 0.024 ($SE=0.015$) lower than participants with a high educational level due to the effect of education on the number of primary health care provider appointments, which, in turn, resulted in a lower HRQoL. However, using bootstrapping (5,000 samples) in the PROCESS procedure (Hayes, 2022) in SPSS to calculate the 95% confidence intervals showed that the relative indirect effect of educational level via the number of primary health care appointments was not significant: for low educational level, the 95% confidence interval was -0.009 to 0.009, and for the middle educational level, it was -0.010 to 0.007.

Relative to the control condition, participants with a middle educational level had an index value of 0.001 lower ($SE=0.004$) than participants with a high educational level due to the effect of education on the number of specialised health care appointments, which decreased the HRQoL. Similarly, participants with a low educational level had an index value of 0.002 lower ($SE=0.004$) than participants with a high educational level due to the effect of education on the number of primary health care provider appointments, which, in turn, resulted in a lower HRQoL. However, the bootstrapping method (5,000 samples) showed that the indirect effects were not significant. The 95% confidence interval for the low educational level was -0.036 to 0.026, while for the middle educational level, it was -0.035 to 0.026. The relative indirect effects did not straddle zero.

(Step 4) Relative direct effects

The relative direct effects of low and middle education compared to the high education on EQ-5D-5L utility index value were calculated using the adjusted means (\bar{Y}^* ; adjusted to the sample mean of the number of primary and specialised health care appointments) (Table 4).

The relative indirect effect of low and middle educational level compared to high educational level on HRQoL, adjusted for the number of primary health care appointments was

$$c_{P'L} = \bar{Y}^*_{Low} - \bar{Y}^*_{High} = 0.481 - 0.539 = -0.058$$

$$c_{P'M} = \bar{Y}^*_{Middle} - \bar{Y}^*_{High} = 0.471 - 0.539 = -0.068$$

The relative indirect effect of low and middle educational level compared to high educational level on HRQoL, adjusted for the number of specialised health care appointments was

$$c_{S'L} = \bar{Y}^*_{Low} - \bar{Y}^*_{High} = 0.536 - 0.582 = -0.046$$

$$c_{S'M} = \bar{Y}^*_{Middle} - \bar{Y}^*_{High} = 0.512 - 0.582 = -0.070$$

Adjusted for group differences in primary health care appointments, participants with a low and moderate educational level had lower HRQoL values than those with a high educational level, although

only the effect of a middle educational level was significant at a 95% confidence interval level ($b_{low}=-0.058, p=0.092$; $b_{Middle}=-0.068, p=0.038$) (Table 5, Model 3_P). For specialised care, only the effect of middle educational level was statistically different from zero ($b_{Low}=-0.046, p=0.187$; $b_{Middle}=-0.072, p=0.035$) (Table 5, Model 3_S).

In this model, a higher number of primary health care appointments was significantly associated with a lower HRQoL ($b=-0.001, p<0.001$) (Table 5, Model 3_P). Furthermore, participants with a higher number of specialised health care appointments had a significantly lower HRQoL ($b=-0.002, p<0.001$) (Table 5, Model 3_S).

Table 5: Estimated coefficients of educational level (Independent variable) on primary health care appointments (Mediator P), specialised health care appointments (Mediator S), and the EQ-5D-5L utility index (Dependent variable) using indicator coding.

	Number of primary health care appointments		Number of specialised health care appointments		EQ-5D-5L utility Index		
	Model 2 _P		Model 2 _S		Model 1	Model 3 _P	Model 3 _S
	M _P (SE)		M _S (SE)		Y (SE)	Y _P (SE)	Y _S (SE)
Constant	96.687 (11.948)***		17.286 (2.272)***		0.585 (0.024)***	0.638 (0.025)***	0.621 (0.025)***
Low education	a _{PL} -4.906 (17.512)		a _{SL} 4.355 (3.331)		-0.055 (0.036)	c _{P'L} -0.058 (0.034)*	c _{S'L} -0.046 (0.035)
Middle education	a _{PM} 11.161 (16.600)		a _{SM} 1.892 (3.157)		-0.074 (0.034)**	c _{P'M} -0.068 (0.034)**	c _{S'M} -0.070 (0.033)**
Number of primary health care provider appointments						b -0.001 (0.000)***	
Number of specialised health care provider appointments							b -0.002 (0.001)***
F-value	0.472		0.856		2.555*	13.064***	7.310***
Adjusted R²	-0.002		-0.001		0.012	0.084	0.042

* p<0.1; ** p<0.05; *** p<0.001

(Step 5) Total models, including control variables

All variables, including the significant control variables in the univariate analysis [Appendix B, Table B1], were included in the total model. The number of appointments with primary health care providers was significantly associated with HRQoL (Table 6, Model 4_P): holding the other variables constant, with every extra appointment with a primary health care provider, the HRQoL decreased ($b=0.000, p=0.009$). Of the control variables, controlling for the other variables, age between 50-59 significantly decreased HRQoL compared to the 70+ age category. Also, CQ and QFS, compared to AC, significantly decreased HRQoL and every additional health symptom.

The number of appointments with specialised health care providers was significantly associated with HRQoL (Table 6, Model 4_S). Controlling for the other variables, every additional appointment with a specialised health care provider decreased the HRQoL by 0.001 ($p=0.008$). Of the control variables, age between 50-59 years, QFS diagnosis and the number of Q-fever-related health symptoms significantly decreased HRQoL.

Table 6: Linear regression model for the hypothesis testing of the association between educational level, health care utilisation and HRQoL.

	Model 4_p: Educational level on HRQoL, via primary health care utilisation including controls	Model 4_s: Educational level on HRQoL, via specialised health care utilisation including controls
	<i>b</i> (SE)	<i>b</i> (SE)
Constant	0.976 (0.047)***	0.987 (0.047)***
Educational level		
Low	-0.037 (0.031)	-0.034 (0.031)
Middle	-0.030 (0.029)	-0.027 (0.029)
High (reference category)		
Number of appointments with primary health care providers	-0.000 (0.000)**	
Number of appointments with secondary health care providers		-0.001 (0.000)**
Sex		
Female	-0.017 (0.025)	-0.031 (0.025)
Males (reference category)		
Age		
Under 40 years	-0.021 (0.052)	-0.028 (0.052)
40-49 years	-0.005 (0.047)	-0.007 (0.047)
50-59 years	-0.082 (0.042)*	-0.078 (0.042)*
60-69 years	-0.021 (0.040)	-0.023 (0.040)
70+ years (reference category)		
Diagnosis		
CQ	-0.091 (0.045)**	-0.054 (0.049)
QFS	-0.057 (0.028)**	-0.067 (0.028)**
AQ (reference category)		
Number of Q-fever related health care symptoms	-0.025 (0.002)***	-0.025 (0.002)***
F-value	17.610***	17.628***
Adjusted R²	0.297	0.297

* p<0.01; ** p<0.05; *** p<0.001

Regression analyses by diagnosis

The EQ-5D-5L utility index was significantly lower for QFS patients than for CQ and AQ patients, and primary health care utilisation was highest among QFS patients, while specialised care was highest among CQ patients [Appendix A, Table A2]. The regression analyses were also conducted for the three diagnosis groups separately to assess if the diagnosis can explain differences in HRQoL and health care utilisation between the educational groups. These analyses did not show significant differences in the outcomes compared to the analyses of the total group of patients, as the coefficients of educational level were not significantly different from zero [Appendix B, Table B2-B5]. However, there was a change in the significance of the mediator variables: the mediators were only significant for the regression models of the diagnosis of QFS. In the models of AQ and CQ, only the coefficient of the number of Q-fever-related health symptoms was significantly different from zero.

4.4.2. Model fit

As there were no substantial violations of the linear model assumptions, no influential observations, and no signs of multicollinearity [Appendix C], no adjustments to the total models were made. Model 1, the association between educational level and HRQoL, had an adjusted R-square of 0.007 ($F=2.555$) (Table 5). The model improved significantly by adding the number of appointments with primary health care providers ($F\text{-change}=33.694$, $p<0.001$, $R^2\text{-adj}=0.077$) (Table 5, Model 3_p). The complete model, including control variables, had the best model fit ($F\text{-change}=17.782$, $p<0.001$, $R^2\text{-adj}=0.297$) (Table 6, model 4_p).

After adding the number of appointments with specialised health care providers to the model with educational level as the independent variable and HRQoL as the dependent variable, the model explained significantly more of the variance in HRQoL ($F\text{-change}=14.102$, $p<0.001$, $R^2\text{-adj}=0.037$) (Table 5, Model 3_s). After adding the control variables to get the total model significantly improved the model again ($F\text{-change}=20.661$, $p<0.001$, $R^2\text{-adj}=0.295$) (Table 6, Model 4_s).

5. DISCUSSION

This study assessed the link between inequalities of outcomes and opportunities for Q-fever patients with long-term health symptoms. Although the association between SES, HRQoL and health care utilisation had already been assessed for the general population (e.g., Mackenbach et al., 2008; Singh et al., 2005; Spronk, Haagsma, et al., 2021) and specific patient populations (e.g., Droomers & Westert, 2004; Schoofs et al., 2004; Verhagen et al., 2009), this was the first study that examined this association including mediation for Q-fever patients who experience long-term consequences.

As expected, the HRQoL in this study was highest for Q-fever patients with a high educational level (0.67), while it was lowest for those with low (0.58) and middle educational levels (0.57). Although this difference in HRQoL was only significant on a 90% confidence interval significance level, this outcome indicated that there are health inequalities of outcomes for Q-fever patients with long-term symptoms. Therefore, there is support for the hypothesis that QFS, AQ and CQ patients with lower SES have lower HRQoL than patients with higher SES. This finding is in line with results of the general population (Hoeymans et al., 2005) and previous studies of CFS and endocarditis, which are similar to CQ and QFS, that found that SES diminished quality of life (Schoofs et al., 2004; Verhagen et al., 2009).

Ideally, health care results in an improved quality of life or, in the case of progressive health conditions, maintaining the same level or slowing down the decline of quality of life. In the Capability Approach, the individual freedom to choose between health care providers can be seen as a capability to get the necessary health care, improving quality of life. However, for chronic diseases such as Q-fever, higher health care utilisation might not improve or even decrease the quality of life (Kaplan, 2003; Singh et al., 2005; Traino et al., 2021) due to ineffective treatment and care. In this study, the number of appointments negatively impacted participants' HRQoL. Every additional appointment with a primary and specialised health care provider decreased the HRQoL. This outcome may be explained by the diversity of complaints (participants had, on average, twelve different Q-fever-related health symptoms), which implies that patients have seen a range of health care providers and have a high health care utilisation (participants had consulted, on average, six different health care providers). Moreover, previous research showed that health care providers are often unaware of the long-term consequences of Q-fever, as underlying causes are not entirely known, and there is no effective treatment yet (Bronner et al., 2020). Combined with the longevity of the symptoms, this may lead to frustration and not feeling understood, and these feelings may decrease the patients' HRQoL. In this way, health care utilization may decrease the HRQoL of patients with chronic conditions (e.g., Kaplan, 2003; Traino et al., 2021).

Based on Sen's Capability Approach (Robeyns, 2005; Sen, 1992), it can be proposed that individuals have different choices regarding their health care utilisation. Looking at SES as a resource to transform capabilities into functionings, it was expected that there were health inequalities in opportunities: the number of appointments with primary health care providers would be higher among patients with lower SES, while utilisation of specialised health care would be higher for patients with higher SES. However, this study showed that both primary and specialised health care utilization is higher among lower SES patients. The differences in the number of appointments in this study were not explained by SES but only by the control variables: diagnosis, age, sex, and the number of health symptoms. This finding aligns with recent research, which concluded that lower SES was associated with higher healthcare utilization among Dutch adults but that these differences decreased when considering the patients' health status (Loef et al., 2021). The findings of this study do not support hypothesis 2: it cannot be concluded that higher SES is a resource to get more specialised health care for this specific patient population.

The results partly supported hypothesis 3, the expectation that SES directly impacts HRQoL and has an indirect impact via health care utilization. As expected and also shown by the descriptive results, the regression analysis showed that HRQoL of patients with middle and low educational levels were significantly lower compared to patients with high educational level. However, the results did not show a modifying role of health care utilization in HRQoL: the number of appointments with primary and specialised health care providers were both associated with HRQoL, but health care utilisation did not mediate the association between SES and HRQoL. Therefore, health care utilisation does not explain the association between SES and HRQoL. Nevertheless, health care utilisation does seem to be an explaining factor of HRQoL on its own.

5.1. Strengths and limitations

This study has several strengths. To the best of the authors' knowledge, this research is the first to study the association between SES, health care utilisation, and HRQoL for Q-fever patients, assessing possible mechanisms to understand the association between SES and HRQoL. Furthermore, the number of participants in this study is high, especially for individuals with a high rate of fatigue and a diversity of other health symptoms.

However, this study has also some limitations. First of all, the data in this research is self-reported. Patients were asked to estimate the total number of appointments per health care provider, which may be challenging because of the long follow-up period. Most patients got ill during the Q-fever epidemic (2007-2010), implying that the questionnaire was up to twelve years after Q-fever infection. Consequently, there is a high risk of recall bias due to this long follow-up period. The risk is

significantly higher for this group of patients as the study for which the data was gathered showed that these patients frequently report memory problems (Bronner et al., 2020).

Regarding the choice of the EQ-5D-5L instrument as a measurement for HRQoL, two possible factors may have limited the reliability of the data in this specific patient population. First, the EQ-5D-5L utility indexes is a very brief questionnaire and may limit the sensitivity and the ability to measure long-term consequences (Lin, Longworth, & Pickard, 2013). Second, patients in this study had severe fatigue and concentration problems (Bronner et al., 2020) that may have been insufficiently measured by the five dimensions of the EQ-5D-5L (Geraerds et al., 2022; Spronk, Polinder, Bonsel, Janssen, & Haagsma, 2022; Spronk, Polinder, Janssen, & Haagsma, 2021). Therefore, the validity of the HRQoL measure is a limitation as there is a possibility that it may not completely correspond to the actual HRQoL of patients.

Third, educational level was included in this study, and it was used as a proxy for SES. Future studies might consider including income and occupation to provide information on the SES of patients and information on possible financial barriers for health care utilisation. On the other hand, educational level might be the most accurate proxy for SES due to the long follow-up period, as occupation and income have changed for a large proportion of this group of patients (Bronner et al., 2020).

There may have been a selection and non-response bias. The questionnaire was sent to Q-fever more than 800 patients who were registered at Q-support and Q-uestion. However, there are more than 4000 notified cases of Q-fever in the Netherlands (RIVM, 2021). Therefore, the representativeness of the study population is unknown: there is no information on the HRQoL and health care utilisation of patients not registered at the patient organisations. On the other hand, it is possible that patients with severe fatigue and concentration problems did not fill out the questionnaire, leading to a possible non-response bias.

5.2. Recommendations

This study showed that there are socioeconomic health inequalities in outcomes regarding HRQoL for Q-fever patients with long-term health symptoms. This outcome implies that interventions for improving HRQoL need to be tailored to SES groups (Mielck et al., 2014). For example, (interventions for) improving the locus of control and/or self-management are found to improve HRQoL for patients with chronic diseases (e.g., Bringsvor et al., 2019; Zimbudzi, 2019). However, studies showed that interventions for improving the self-management of patients with chronic diseases are less successful among low SES cohorts: a systematic review showed that the low SES group engaged less in self-management strategies due to several barriers, including lower knowledge and literacy (Hardman,

Begg, & Spelten, 2020). Thus, interventions based on locus of control or self-management may be less effective for lower SES groups than for higher SES groups. Therefore, different interventions are needed to improve the HRQoL of different SES groups.

In order to provide the needed support to Q-fever patients with long-term health symptoms, it is necessary to assess factors that influence health outcomes and identify the underlying patterns and processes. Therefore, it is recommended to research the causes that underlie the low health outcomes of Q-fever patients. This research showed that a mediation analysis is suitable for assessing the underlying patterns of this patient population. Mediation analyses assess what processes underlie an association between a factor and a health outcome. Especially since this group of patients experience chronic disease, interventions are less about treatment and more about support. It is necessary to investigate which factors and processes influence health outcomes to determine how support can be improved. In this way, support can be better tailored toward the needs of patients.

5.3. Conclusion

To conclude, this research increased the scientific knowledge on the association between SES and HRQoL for patients with a chronic disease and expanded the knowledge about the long-term consequences of Q-fever. This study showed that there are socioeconomic health inequalities in outcomes regarding HRQoL for Q-fever patients with long-term health symptoms. Therefore, tailoring future interventions to different SES groups might improve the HRQoL of Q-fever patients with long-term health symptoms. However, no health inequalities in opportunities were found, nor that health care utilization is the process that underlies the association between educational level and HRQoL. Nevertheless, this study showed that it is possible to and accentuates the need to assess explanations for associations between health outcomes and opportunities for patients who experience long-term health impairment due to the sequela of a zoonosis, such as Q-fever and COVID-19. Especially for a disease about with many unknowns, justifying the name Query-fever, research into the underlying mechanisms is needed to improve patients' long-term health outcomes by identifying possible leads for interventions.

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APPENDIX A. ELABORATION ON THE DESCRIPTIVE RESULTS

Table A1: Sociodemographic and medical characteristics of the study participants, total and by diagnosis.

	Total	CQ	QFS	AQ	
	n=433	n=128	n=158	n=147	
	n (%)	n (%)	n (%)	n (%)	χ^2 (p)
Sociodemographic characteristics					
Age in years, median (IQR)	58.0 (48.0-65.0)	70.0 (61.0-73.3)	56.0 (47.0-63.0)	57.0 (48.0-65.0)	47.666 (<0.001)*
Age categories					68.956 (<0.001)*
Under 40 years	52 (12.0)	0 (0.0)	37 (14.5)	15 (11.5)	
40-49 years	71 (16.4)	1 (2.2)	47 (18.4)	23 (17.6)	
50-59 years	122 (28.2)	6 (13.0)	78 (30.5)	38 (29.0)	
60-69 years	125 (28.9)	15 (32.6)	72 (28.1)	38 (29.0)	
70+ years	63 (14.5)	24 (52.2)	22 (8.6)	17 (13.0)	
Sex					12.287 (0.002)*
Male	224 (51.7)	33 (71.7)	117 (45.7)	74 (56.5)	
Female	209 (48.3)	13 (28.3)	139 (54.3)	57 (43.5)	
Living situation					0.650 (0.722)
Living together	265 (61.2)	26 (56.5)	160 (62.5)	79 (60.3)	
Living alone	168 (38.8)	20 (43.5)	96 (37.5)	52 (39.7)	
Educational level					13.748 (0.008)*
Low	128 (29.6)	21 (45.7)	66 (25.8)	41 (31.3)	
Middle	158 (36.5)	10 (21.7)	109 (42.6)	39 (29.8)	
High	147 (33.9)	15 (32.6)	81 (31.6)	51 (38.9)	
Medical characteristics					
Number of Q-fever related health symptoms	12.0 (8.0-16.0)	10.0 (6.0-12.0)	13.0 (10.0-18.0)	10.0 (6.0-14.0)	31.696 (<0.001)*
Antibiotics when infected					18.039 (<0.001)*
Yes	311 (71.8)	44 (95.7)	180 (70.3)	87 (66.4)	
No	102 (23.6)	1 (2.2)	61 (23.8)	40 (30.5)	
Not sure	20 (4.6)	1 (2.2)	15 (5.9)	4 (3.1)	
Hospitalisation when infected					23.639 (<0.001)*
Yes	97 (22.4)	23 (50.0)	53 (20.7)	21 (16.0)	
No	336 (77.6)	23 (50.0)	203 (79.3)	110 (84.0)	

Note. Mann-Whitney U tests and Kruskal-Wallis H tests were used for ordinal and continuous variables (median and IQR), and χ^2 tests for binary or nominal variables.

* p < 0.05.

Table A2: Median (IQR) EQ-5D-5L utility index and health care utilisation, by sex, age, and diagnosis.

	EQ-5D-5L Utility Index		Appointments with primary health care providers		Appointments with specialised health care providers	
	Median (IQR)	H or U (p)	Median (IQR)	H or U (p)	Median (IQR)	H or U (p)
Age categories		13.301 (0.010)*		12.581 (0.014)*		11.966 (0.018)*
Under 40 years	0.57 (0.27-0.75)		49.5 (18.5-124.0)		5.5 (1.3-19.5)	
40-49 years	0.68 (0.36-0.79)		50.0 (22.0-144.0)		5.0 (1.0-20.0)	
50-59 years	0.53 (0.24-0.72)		63.0 (15.8-135.3)		10.0 (2.0-22.8)	
60-69 years	0.65 (0.38-0.75)		49.0 (20.0-97.0)		12.0 (4.0-31.0)	
70+ years	0.67 (0.45-0.81)		12.0 (3.0-131.0)		14.0 (3.0-42.0)	
Sex		20301.500 (0.017)*		20581.000 (0.030)*		19217.500 (0.001)*
Male	0.65 (0.35-0.79)		45.5 (10.0-114.3)		14.0 (3.0-33.5)	
Female	0.57 (0.27-0.74)		55.0 (20.0-150.5)		8.0 (2.0-20.0)	
Diagnosis		26.676 (<0.001)*		50.174 (<0.001)*		49.293 (<0.001)*
CQ	0.67 (0.31-0.81)		29.5 (2.8-170.0)		46.0 (15.0-72.3)	
QFS	0.56 (0.26-0.72)		70.0 (29.3-156.8)		11.5 (3.0-24.0)	
AQ	0.72 (0.45-0.83)		22.0 (7.0-57.0)		5.0 (1.0-14.0)	

Note. Mann-Whitney U tests and Kruskal-Wallis H tests were used.

* p < 0.05

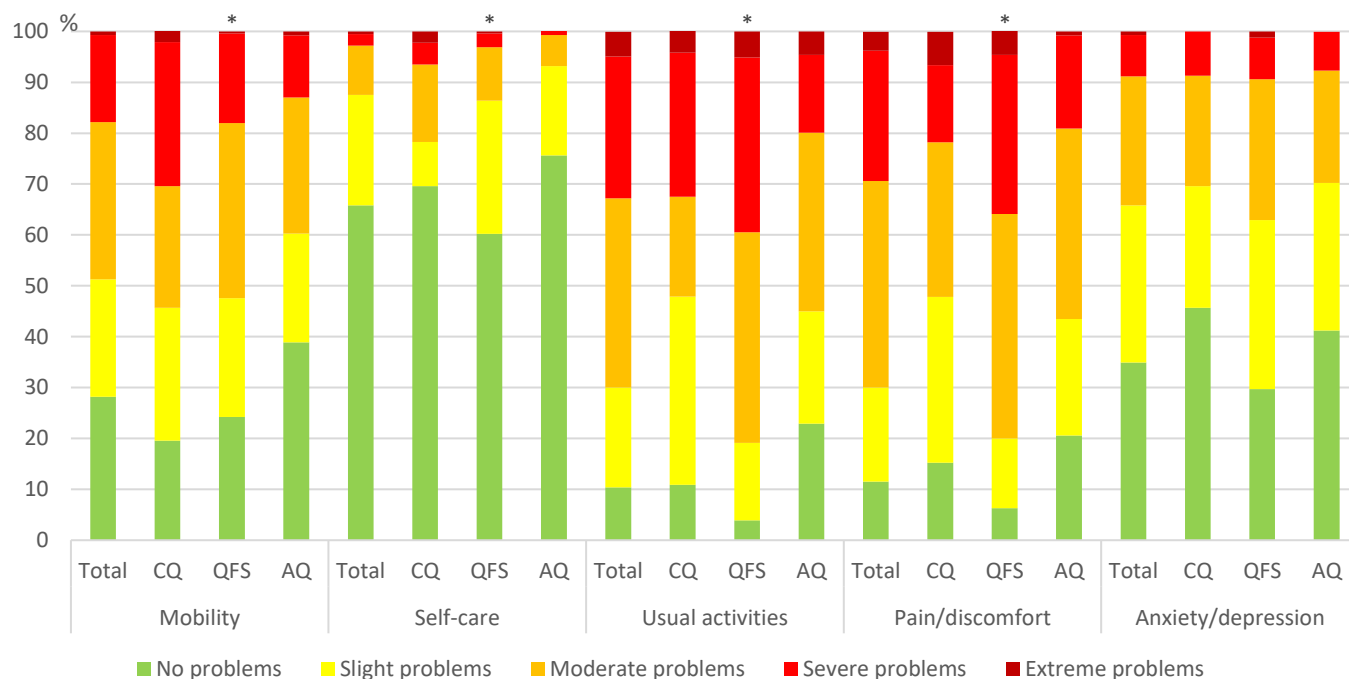


Figure A1. Distribution of responses by severity level (problems) on the EQ-5D-5L dimensions of the study participants, total and by diagnosis.

* p<0.05

Table A3: EQ-5D-5L utility index values and appointments with health care providers by diagnosis and educational level.

	CQ	QFS	AQ	H (p)
	Median (IQR)	Median (IQR)	Median (IQR)	
EQ-5D-5L utility index				
Education low	0.556 (0.221-0.722)	0.568 (0.282-0.719)	0.705 (0.434-0.765)	4.015 (0.134)
Education middle	0.744 (0.338-0.833)	0.539 (0.234-0.709)	0.735 (0.427-0.891)	15.475 (<0.001)*
Education high	0.765 (0.548-0.879)	0.590 (0.289-0.745)	0.739 (0.468-0.856)	9.629 (0.008)*
Appointments with primary health care providers				
Education low	30.0 (1.0-136.0)	61.0 (21.5-130.8)	40.0 (10.5-89.0)	2.921 (0.232)
Education middle	129.5 (21.8-253.3)	79.0 (36.0-160.0)	10.0 (6.0-40.0)	29.767 (<0.001)*
Education high	11.0 (2.0-61.0)	73.0 (31.5-169.0)	17.0 (9.0-50.0)	28.477 (<0.001)*
Appointments with specialised health care providers				
Education low	40.0 (11.5-82.5)	11.5 (2.0-20.3)	14.0 (2.0-27.0)	11.881 (0.003)*
Education middle	42.5 (6.0-70.3)	14.0 (3.0-28.0)	3.0 (1.0-10.0)	16.484 (<0.001)*
Education high	50.0 (20.0-56.0)	9.0 (3.0-22.0)	4.0 (0.0-9.0)	33.124 (<0.001)*

Note. Kruskal-Wallis H tests were used.

*p<0.05

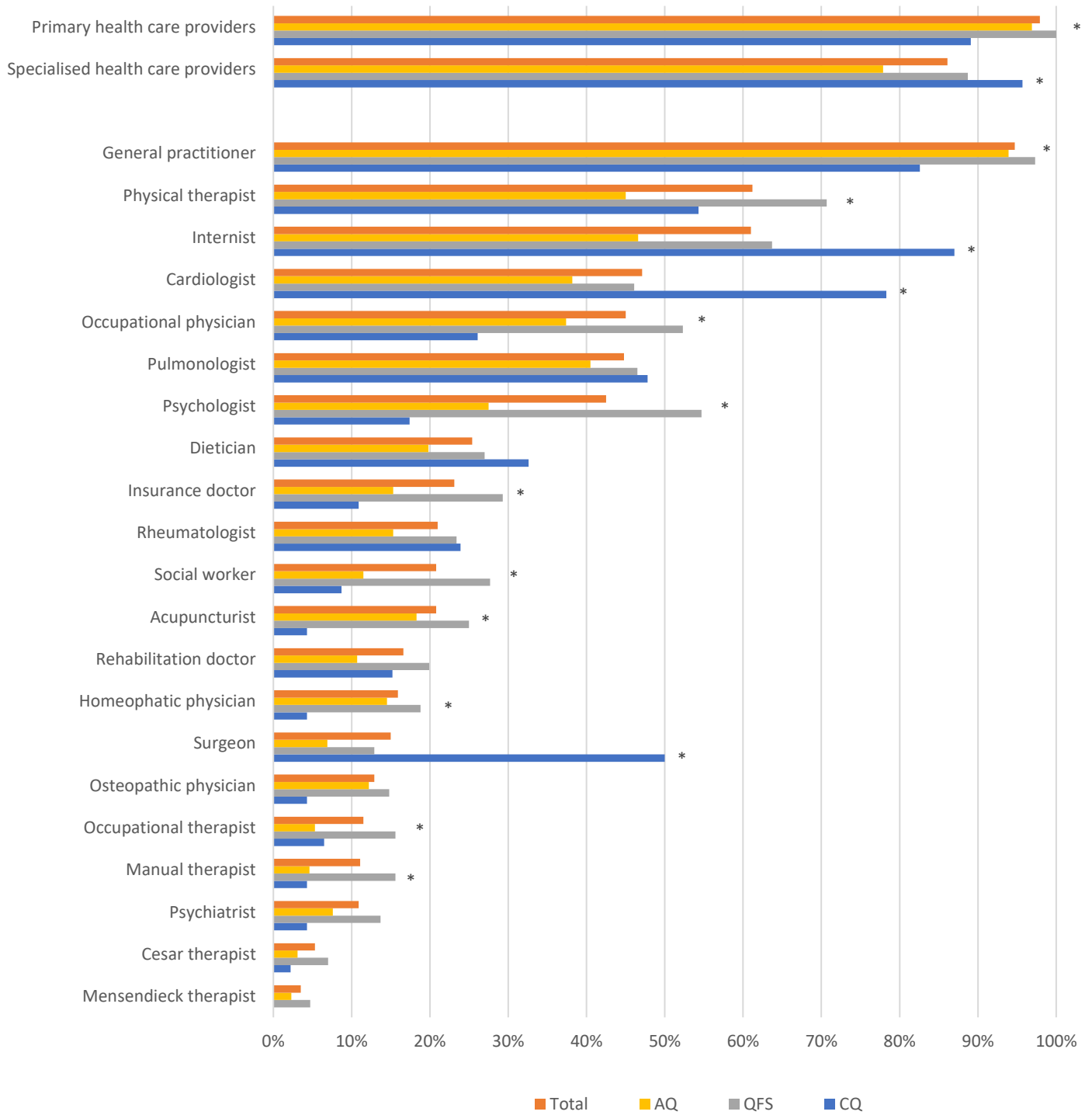


Figure A2. Percentage of participants (%) that had contact with health care providers, total and by diagnosis.
* p<0.05

APPENDIX B. ELABORATION ON THE REGRESSION ANALYSES

Table B1: Univariate linear coefficients for the association between SES, health care utilization and HRQoL.

	EQ-5D-5L utility index <i>b</i> (SE)
Educational level	
Low	-0.055 (0.036)
Middle	-0.074 (0.034)**
High (reference category)	
Appointments with primary health care providers	-0.001 (0.000)***
Appointments with secondary health care providers	-0.002 (0.001)***
Sex	
Female	-0.066 (0.028)**
Males (reference category)	
Age	
Under 40 years	-0.104 (0.055)*
40-49 years	-0.047 (0.051)
50-59 years	-0.143 (0.045)**
60-69 years	-0.049 (0.045)
70+ years (reference category)	
Diagnosis	
CQ	-0.080 (0.049)
QFS	-0.151 (0.031)***
AQ (reference category)	
Number of Q-fever related health care symptoms	-0.028 (0.002)***

* p<0.1; ** p<0.05; *** p<0.01

Table B2: Estimated coefficients of model 1 by diagnosis: educational level (Independent variable) on the EQ-5D-5L utility index.

	EQ-5D-5L utility index		
	Model 1		
	AQ	CQ	QFS
	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)
Constant	0.661 (0.039)***	0.649 (0.086)***	0.526 (0.032)***
Low education D ₁	-0.061 (0.058)	-0.170 (0.113)	-0.023 (0.047)
Middle education D ₂	-0.008 (0.059)	-0.051 (0.136)	-0.073 (0.042)*
F-value	0.619	1.207	1.654
Adjusted R²	-0.006	0.009	0.005

* p<0.1; ** p<0.05; *** p<0.001

Table B3: Estimated coefficients of model 2 by diagnosis: educational level (Independent variable) on primary health care appointments (Mediator P) and specialised health care appointments (Mediator S).

	Number of appointments with primary health care providers			Number of appointments with specialised health care providers		
	Model 2 _P			Model 2 _S		
	AQ	CQ	QFS	AQ	CQ	QFS
	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)
Constant	37.392 (9.479)***	70.733 (35.288)**	138.827 (18.484)***	6.608 (3.072)**	55.067 (12.481)***	17.012 (2.278)***
Low education D ₁	34.583 (14.200)**	18.522 (46.203)	-33.948 (27.585)	11.953 (4.602)**	-7.495 (16.342)	-1.709 (3.399)
Middle education D ₂	-1.315 (14.400)	80.767 (55.796)	-9.295 (24.403)	5.674 (4.667)	-1.667 (19.734)	1.492 (3.007)
F-value	3.802**	1.105	0.797	3.376**	0.117	0.507
Adjusted R²	0.041	0.005	-0.002	0.035	-0.041	-0.004

* p<0.1; ** p<0.05; *** p<0.001

Table B4: Estimated coefficients of model 3 by diagnosis: educational level (Independent variable) on primary health care appointments (Mediator P), specialised health care appointments (Mediator S), and the EQ-5D-5L utility index (Dependent variable).

	Model 3P			Model 3S		
	AQ b (SE)	CQ b (SE)	QFS b (SE)	AQ b (SE)	CQ b (SE)	QFS b (SE)
Constant	0.696 (0.040)***	0.697 (0.088)***	0.582 (0.034)***	0.671 (0.039)***	0.775 (0.099)***	0.577 (0.034)***
Low education	-0.029 (0.058)	-0.157 (0.110)	-0.037 (0.046)	-0.043 (0.60)	-0.187 (0.108)*	-0.028 (0.046)
Middle education	-0.009 (0.058)	0.004 (0.136)	-0.077 (0.041)*	0.001 (0.059)	-0.055 (0.130)	-0.069 (0.041)*
Number of appointments with primary health care providers	-0.001 (0.000)**	-0.001 (0.000)*	0.000 (0.000)***			
Number of appointments with specialised health care providers				-0.001 (0.001)	-0.002 (0.001)**	-0.003 (0.001)***
F-value	2.726**	2.016	6.122***	1.007	2.610*	5.273**
Adjusted R²	0.038	0.063	0.057	0.000	0.097	0.048

* p<0.1; ** p<0.05; *** p<0.001

Table B5: Estimated relative indirect effects and 95% Confidence Interval by diagnosis: educational level (Independent variable) on HRQoL (Dependent variable) via primary health care appointments (Mediator P) and specialised health care appointments (Mediator S).

	AQ		CQ		QFS	
	b (SE)	95% CI	b (SE)	95% CI	b (SE)	95% CI
Coefficient of education on HRQoL via primary health care appointments						
Low educational level	-0.013 (0.014)	-0.009; 0.019	0.000 (0.018)	-0.149; 0.058	0.008 (0.007)	-0.008; 0.021
Middle educational level	0.002 (0.007)	-0.047; 0.009	-0.002 (0.030)	-0.225; 0.150	0.003 (0.006)	-0.011; 0.014
Coefficient of education on HRQoL via specialised health care appointments						
Low educational level	-0.002 (0.019)	-0.059; 0.013	0.025 (0.030)	-0.026; 0.095	0.003 (0.008)	-0.015; 0.016
Middle educational level	-0.001 (0.006)	-0.012; 0.013	-0.005 (0.038)	-0.106; 0.055	-0.001 (0.008)	-0.020; 0.013

Note. 95% Confidence Interval (95% CI) was estimated using the asymmetric bootstrapping method with 5,000 samples in the SPSS Macro PROCESS (Hayes, 2022).

Table B6: Estimated coefficients of model 4 by diagnosis: educational level (Independent variable) on EQ-5D-5L utility index (Dependent variable), via number of primary health care appointments (Mediator P) and specialised health care appointments (Mediator S) including control variables.

	AQ		CQ		QFS	
	Model 4P	Model 4S	Model 4P	Model 4S	Model 4P	Model 4S
	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)	<i>b</i> (SE)
Constant	0.971 (0.075)***	0.978 (0.075)***	1.036 (0.108)***	1.072 (0.108)***	0.831 (0.074)***	0.858 (0.075)***
Educational level						
Low	-0.017 (0.054)	-0.028 (0.054)	-0.004 (0.087)	-0.029 (0.087)	-0.031 (0.044)	-0.028 (0.044)
Middle	0.003 (0.051)	0.007 (0.051)	0.033 (0.104)	0.037 (0.100)	-0.048 (0.038)	-0.045 (0.038)
High (reference category)						
Appointments with primary health care providers	0.000 (0.000)		0.000 (0.000)		0.000 (0.000)**	
Appointments with secondary health care providers		0.000 (0.001)		-0.001 (0.001)		-0.002 (0.001)**
Sex						
Female	-0.028 (0.044)	-0.035 (0.044)	-0.069 (0.086)	-0.072 (0.083)	-0.009 (0.034)	-0.031 (0.034)
Males (reference category)						
Age						
Under 40 years	-0.053 (0.089)	-0.062 (0.090)	No data	No data	0.035 (0.073)	0.017 (0.073)
40-49 years	0.013 (0.080)	0.002 (0.080)	-0.391 (0.292)	-0.471 (0.286)	0.042 (0.068)	0.033 (0.068)
50-59 years	-0.064 (0.072)	-0.081 (0.071)	-0.102 (0.141)	-0.067 (0.139)	-0.030 (0.063)	-0.035 (0.062)
60-69 years	-0.035 (0.072)	-0.051 (0.071)	-0.027 (0.084)	-0.025 (0.080)	0.028 (0.063)	0.015 (0.063)
70+ years (reference category)						
Number of Q-fever related health care symptoms	-0.024 (0.004)***	-0.025 (0.004)***	-0.041 (0.010)***	-0.038 (0.010)****	-0.021 (0.003)***	-0.022 (0.003)***
F-value	6.403***	6.141***	6.200***	6.786***	7.711***	7.814***
Adjusted R²	0.272	0.262	0.480	0.507	0.192	0.194

* p<0.1; ** p<0.05; *** p<0.01

APPENDIX C. LINEAR REGRESSION ASSUMPTIONS

Several assumptions were tested to test if linear regression analyses were appropriate for this dataset: (1) independent observations, (2) normality of the residuals, (3) linearity, and (4) homoscedasticity. Furthermore, it was tested if the variables did not have multicollinearity, how many missing values were in the dataset, and if influential observations should be deleted.

Missing values

Based on the Missing Value Analysis in SPSS, 45 missing values were identified. As these observations all had missing values on the dependent variable HRQoL, the observations were filtered out of the dataset using listwise deletion.

Assumption 1. Independent observations

The observations were assumed to be independent, as they did not have a hierarchical structure.

Assumption 2. Normality of the residuals

A P-P Plot and histogram of the standardised residuals were made (Figure C1 for the model with primary health care appointments and Figure C2 for the model with specialised health care appointments) to assess the normality of residuals.

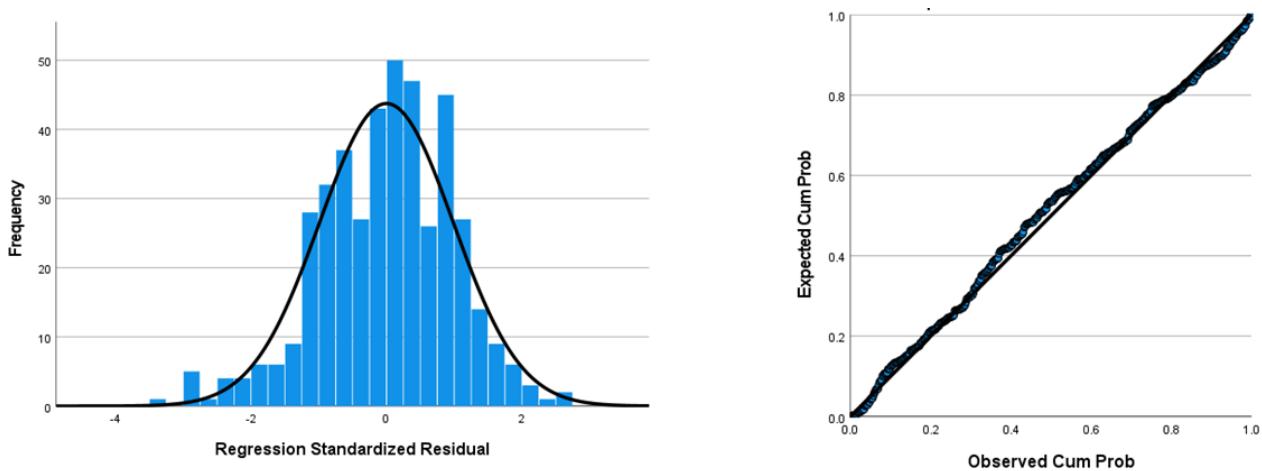


Figure C1. Histogram and P-P Plot of the standardized residuals for the model with primary health care appointments.

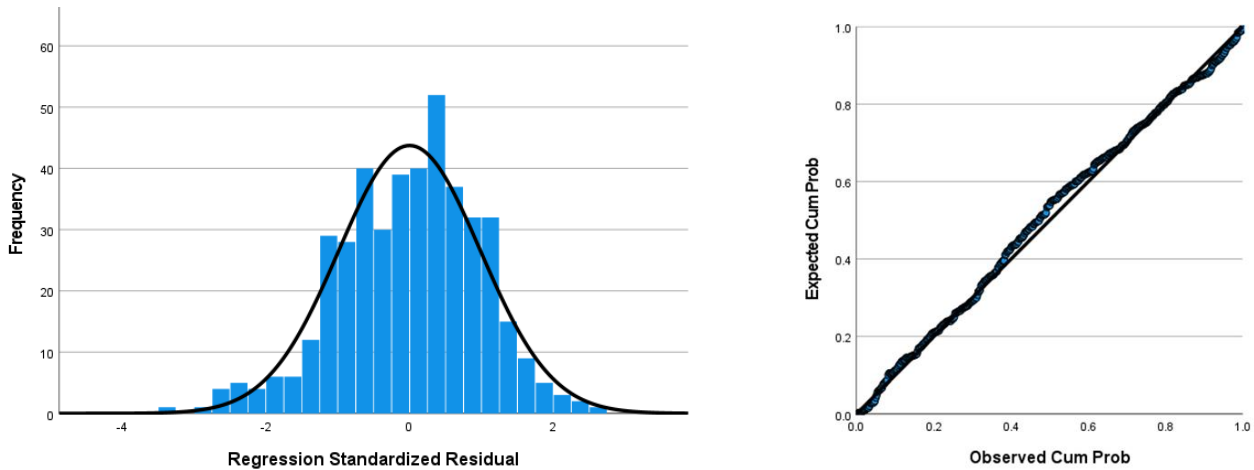


Figure C2. Histogram and P-P Plot of the standardized residuals for the model with specialised health care appointments.

The histogram and PP-plot showed no significant violations of the normality of residuals for the models with primary and specialised health care appointments. The points in the PP-Plot did not precisely fit the diagonal line, but there were no significant violations of the normality of residuals.

Assumption 3. Linearity

A residual plot was made of the standardized residuals against the standardized predicted values to test the assumption of linearity. Furthermore, several partial regression plots were made to check the association between the dependent and independent variables.

The residual plot for primary health care appointments (Figure C3) shows a systematic deviation from the horizontal zero-line. However, as the HRQoL variable has scores ranging from -0.45 to 1.0, there are enough different scores. The violation of the assumption of linearity did not seem substantial. The partial plots of educational level on HRQoL and number of primary health care appointments did not systematically deviate from the zero-line.

The residual plot for specialised health care appointments (Figure C4) did not show a systematic deviation from the horizontal zero-line. The partial plots of educational level on HRQoL and the number of specialised health care appointments also did not systematically deviate from the zero-line.

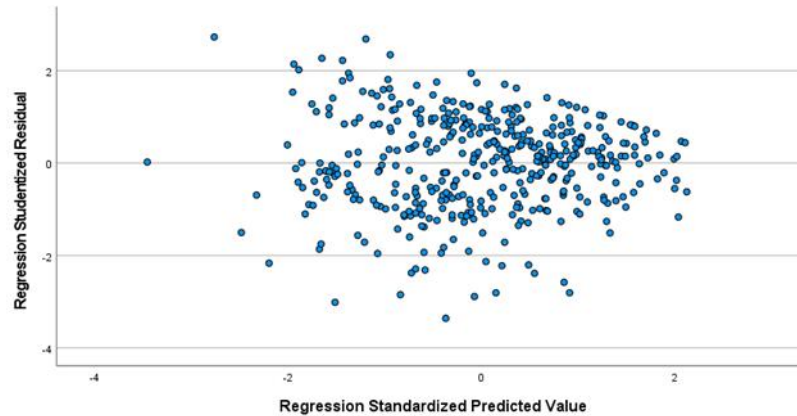


Figure C3. Scatterplot of the studentized residuals plotted against the standardized predicted values for the model with primary health care appointments.

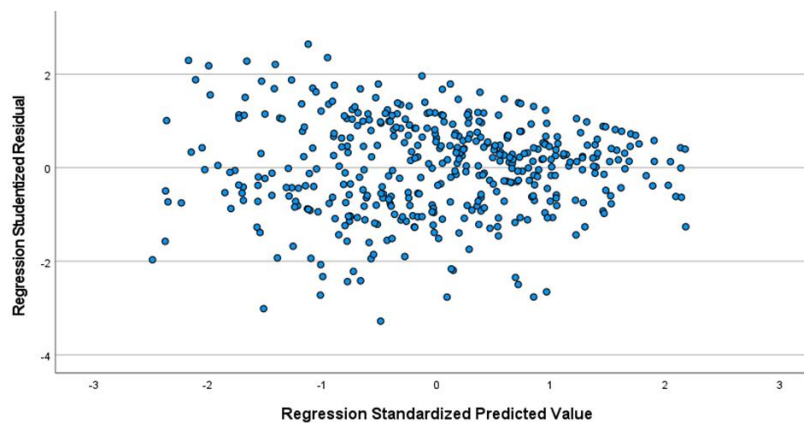


Figure C4. Scatterplot of the studentized residuals plotted against the standardized predicted values for the model with specialised health care appointments.

Assumption 4. Homoscedasticity

Homoscedasticity means that the variation of the residuals of the dependent variables was the same for every value of the independent variables. The descriptive statistics show that the mean of the EQ-5D-5L utility index (0.542) is higher than the middle of the range (-0.45 to 1.0). This may imply that there were some problems with heteroscedasticity. However, the violations did not seem substantial in the residual plot (Figure A2): the scatter seems similar on both sides of the zero line.

Assumption 5. Multicollinearity

The independent variables were checked for multicollinearity (variance inflation factor (VIF)>4 and tolerance <0.2) to check if the correlation between the two variables is acceptable. In both models, all variables did not have a VIF >4 and tolerance <0.2. Therefore, all variables were included in the analysis.

Outliers

The residual plot and the residual statistics were checked for outliers on the y-axis. The mean of the standardized residuals was zero. HRQoL is slightly skewed (more patients with a more negative HRQoL than positive). However, none of the studentised residuals had a value of 4 or higher or -4 or lower, which indicates that there were probably no outliers on the y-axis.

The Leverage and Cook's Distance (CD) were assessed to test for outliers on the x-axis. Observations with a leverage higher than $3p/n = 3*12/433 = 0.083$ were identified as possible outliers. For CD, the rule of thumb is that observation might be an outlier when $CD > 4/433 = 0.009$.

In the model with primary health care appointments, there were three observations with high Leverage, 21 with a high CD, and two with both a high Cook's Distance and high Leverage. The linear regression was repeated without the two observations to test whether these two points were outliers. The results slightly changed: ages 50 to 59 were no longer significant at the 95% confidence level. However, the significance, sign and strength of coefficients of the dependent and independent variables did not change drastically. Removing the outliers from the models caused a loss of data, which is not acceptable in this case, as the outliers did not drastically change the results.

For the model with specialised health care appointments, there were three observations with a leverage > 0.083 and 21 with a CD > 0.009 . Two observations have both high Leverage as well as a high CD. Excluding these variables from the analysis did not change the significance and sign of the coefficients. The effects of the coefficients slightly changed, but not drastically. Therefore, the regression analysis was performed with all 433 observations included in the analysis.