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# Quality of life and coping in Dutch homozygous familial hypercholesterolemia patients: A qualitative study

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ABSTRACT

*Background and aims:* Homozygous familial hypercholesterolemia (HoFH) is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C) levels leading to extremely premature atherosclerotic cardiovascular disease. Therefore, healthcare professionals consider HoFH to have major impact on patients' life. Remarkably, little is known on how patients deal with their condition. The aim of this study is to investigate how Dutch patients experience and cope with HoFH in daily life.

*Methods:* Adult patients with genetically confirmed HoFH, treated at the 3 specialized HoFH-centers in the Netherlands, were interviewed in-depth. Interview transcripts were analyzed according to grounded theory. Health-related quality of life (QoL) and coping were measured with the EuroQol (EQ)-5D-5L questionnaire and the Threatening Medical Situations Inventory (TMSI), respectively.

*Results:* 20 Dutch HoFH patients were interviewed: 50% women, median age 38 years, 60% with cardiovascular disease, 10% on apheresis. Coding of the transcripts resulted in a conceptual model, with disease perception as the central theme. Individual TMSI-results corresponded to the interviews, with most patients showing both monitoring (information-seeking behavior) and blunting (distractive strategies) coping styles. The median EQ-5D-5L health utility score (0.839) was only 5% below the Dutch population (0.887). Transient anxiety was reported when confronted with the consequences of HoFH in daily life. Patients reported high confidence in treatment by a dedicated HoFH center, which helped them cope with their disease.

*Conclusions:* Dutch HoFH patients use a variety of effective coping mechanisms in such a way that their subjective QoL is only slightly affected. Healthcare professionals can use this knowledge to tailor their care to the specific needs of these patients.

## 1. Introduction

With a prevalence of approximately 1 in 250, heterozygous familial hypercholesterolemia (HeFH) is the most common hereditary disorder associated with hypercholesterolemia, leading to premature cardiovascular disease (CVD), such as coronary heart disease [1,2]. Homozygous familial hypercholesterolemia (HoFH) is considered a rare disease affecting approximately 1 in 300,000 to 1,000,000 individuals [3]. Compared to HeFH, patients with HoFH have even more elevated low-density lipoprotein cholesterol (LDL-C) levels leading to a further increased risk of premature CVD [3,4]. Some HoFH patients experience their first CVD event before the age of twenty years [3]. Even though HoFH is regarded as one entity, HoFH patients show a wide variety of genetic background and LDL-C levels, resulting in a diversity in lipid-lowering treatment and prognosis [4–6].

Treatment options consist of a combination of lipid lowering medications, such as statins and ezetimibe, and/or lipoprotein apheresis, and/or novel medications such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and microsomal triglyceride transfer protein (MTP) inhibition [7]. Even with combination therapy, reaching target LDL-C levels remains a challenge for HoFH patients [4].

Although HoFH is considered a serious disorder by healthcare

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professionals and its severity is often mentioned in literature [6,8,9], little is known about how HoFH patients cope with their condition in daily life [10–13]. Therefore, the aim of our study is to obtain knowledge about (1) the quality of life (QoL) and (2) the coping style of HoFH patients in the Netherlands.

## 2. Patients and methods

### 2.1. Study design

A qualitative cross-sectional study was performed, consisting of in-depth interviews with Dutch HoFH patients, face-to-face or, due to the coronavirus disease 2019 (COVID-19) pandemic, using video conferencing. The study protocol was approved by the Medical Ethics Committee of Erasmus University Medical Center (Erasmus MC) (MEC-2019-0377).

### 2.2. Patients

HoFH patients were invited to participate by their treating HoFH specialist from the 3 specialized HoFH centers in the Netherlands: Erasmus MC, Rotterdam, Amsterdam University Medical Center, Amsterdam, or Radboud University Medical Center, Nijmegen. Inclusion criteria were: 1) HoFH patient with genetically confirmed HoFH: homozygous, compound heterozygous or double heterozygous familial hypercholesterolemia with pathogenic mutations in the *LDLR* and/or *APOB* and/or *PCSK9* gene or having 2 mutations in the *LDLRAP* gene; 2) $\geq$ 18 years old; and 3) sufficient understanding of the Dutch or English language. Patients were enrolled consecutively, meaning that each HoFH patient visiting the outpatient clinic, who met the inclusion criteria, was invited for study participation. In doing so, we aimed to include a representative group of the Dutch HoFH population.

### 2.3. Measures and procedures

The research team created a topic list as guideline for every interview (Supplementary data 1). For the in-depth interviews, an open approach was chosen to allow for further elaboration on the patients' responses, since little is known about QoL and coping of HoFH patients [10,11,14]. Interviews were performed at home or at the hospital, according to the patient's preference. The first three interviews were held by LK and JM, and further interviews by JM, supervised by LK.

Prior to the interview, patients filled in the Threatening Medical Situations Inventory (TMSI) including extra statements on HoFH to assess coping style, and the EQ-5D-5L to assess QoL.

The TMSI questionnaire measures 'monitoring' (information seeking) and 'blunting' (distraction seeking) coping styles [15]. The questionnaire contains three situations, with 6 items each: 3 measuring a monitoring and 3 measuring a blunting coping style. Items are scored on a 5-point Likert scale, resulting in scores ranging from 9 to 45 for both monitoring and blunting coping strategies.

The EQ-5D-5L resulted in Visual Analogue Scale (VAS) scores (range 0–100) and a 'utility score' [16,17]. The utility score has a maximum score of 1.00 being perfect health and where 0.00 is representing death (scores below 0.00 possible).

### 2.4. Data analyses

Interviews were audio recorded and transcribed verbatim. Subsequently, transcripts were analyzed according to the principles of 'grounded theory' [14,18]. The transcribed data were analyzed in Nvivo software by two researchers (JM and WT), with supervision of a psychologist (LK) in joint weekly "small team" meetings. They went through the coding phases of open, axial and selective coding [14]. In doing so, the coders compared their coding frameworks on all levels of coding and discussed differences until consensus was reached. Analysis continued until a sufficient level of "saturation" had been reached - referring to a point where no new codes or categories emerged anymore [19]. The interview findings were also compared to the results of the questionnaires. Furthermore, findings were discussed in the larger research team including both physicians and psychologists at three meetings over time. After careful consideration and adjustments, the final conceptual model was established (Fig. 1).

Results of the EQ-5D-5L and TMSI questionnaires are presented as means and SD when the data is normally distributed. Otherwise, median and interquartile ranges are applied.

## 3. Results

### 3.1. Participants

21 HoFH patients were invited to participate. One patient refrained, fearing a possible negative impact on his mental state. The interviews were held between October 2019 and September 2020. Due to COVID-19 pandemic measures, 15 (75%) interviews were held via video calling. Median age of participants was 38 years during the interview and 50% was female. Of the participants, 12 (60%) had suffered from a CVD-event and 2 (10%) were receiving lipoprotein apheresis. In addition to regular treatment, four patients were participating in an open-label trial, receiving study treatment (n = 2 evinacumab, n = 2 gene therapy). Further baseline characteristics are presented in Table 1.

### 3.2. Conceptual model

After 20 interviews saturation was reached. The central theme in the resulting model is the patient's perception of HoFH in terms of four themes: Daily life impact; Long-term impact; Generic coping; and Specific coping through appreciation of HoFH-specialist care (Fig. 1). The patient's perception of HoFH as central theme influences all other 4 themes and they, in turn, have an influence on the patient's perception of HoFH. How a patient copes with HoFH influences both daily life and the long-term impact. The theme (appreciation of) specialist care also influences life in the short- and long-term. Finally, through the patient's perception of HoFH, specialist care has an influence on coping and vice versa.

#### 3.2.1. The central theme: perception of HoFH

Although several participants (n = 7, 35%) consider other HoFH patients as having a disease, they do not consider themselves as ill. One of the participants mentioned: "*Taking medicines is annoying, but I don't consider familial hypercholesterolemia a disease*". Also, 6 participants thought of HoFH as a condition more than an illness (Table 2, quote 1). This is mainly the case for patients who are not impaired in daily life. One patient said: "*I can do everything, I work, I exercise, I can go away with friends. I can go on vacation*" (Table 2, quote 2). A patient without CVD

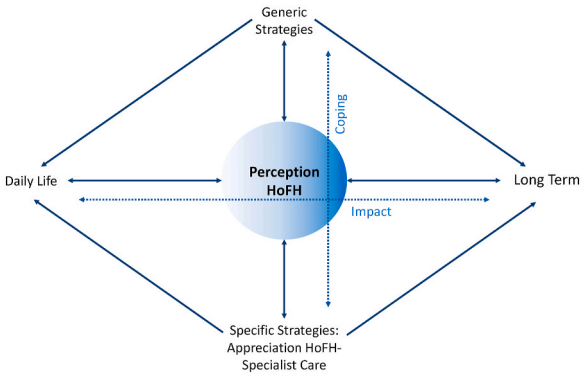


**Fig. 1.** Conceptual model with relationships between the five themes.

**Table 1**
Baseline characteristics of HoFH participants.

| Baseline characteristics | N (%) |
|---|---|
| Age, years | |
| 20-29 | 3 (15%) |
| 30-39 | 8 (40%) |
| 40-49 | 6 (30%) |
| 50-59 | 2 (10%) |
| 60-69 | 1 (5%) |
| Median [IQR] | 38 [32; 46] |
| Female | 10 (50%) |
| Socioeconomic status (SD), 0 = population mean (−1, 1) | −0.33 (1.19) |
| Established atherosclerotic CVD | 12 (60%) |
| Coronary artery disease | 9 (45%) |
| Aortic stenosis (n = 17) | 7 (41%) |
| Normal ejection fraction (n = 15) | 15 (100%) |
| Diabetes mellitus type 2 | 1 (5%) |
| Hypertension | 3 (15%) |
| Smoking | 2 (10%) |
| Years since diagnosis/start treatment[a] | 21 (10.91) |
| Age at diagnosis/start treatment (years), median [IQR] | 18 [9; 27] |
| Mutation | |
| True homozygous | 6 (30%) |
| Compound heterozygous | 11 (55%) |
| Double heterozygous | 3 (15%) |
| Affected gene | |
| *LDLR* | 19 (95%) |
| *APOB* | 2 (10%) |
| *PCSK9* | 1 (5%) |
| *LDLRAP1* | 1 (5%) |
| Treatment | |
| Statins | 19 (95%) |
| Ezetimibe | 19 (95%) |
| Lomitapide | 7 (35%) |
| PCSK9-inhibitor | 12 (60%) |
| Apheresis | 2 (10%) |
| Trial medication | 4 (20%) |
| Psychotropic medication[b] | 1 (5%) |
| Lipid levels[a] | |
| Untreated levels | |
| Total cholesterol (mmol/L) (n = 18) | 13.87 (5.13) |
| LDL-C (mmol/L), median [IQR] | 9.91 [8.03; 14.43] |
| HDL-C (mmol/L) (n = 17) | 1.04 (0.27) |
| Triglycerides (mmol/L) (n = 16), median [IQR] | 1.28 [1.03; 2.08] |
| Most recent lipid levels | |
| Total cholesterol (mmol/L), median [IQR] | 4.07 [2.65; 6.66] |
| LDL-C (mmol/L), median [IQR] | 2.42 [1.44; 4.59] |
| HDL-C (mmol/L) | 1.04 (0.29) |
| Apo B (g/L) (n = 14), median [IQR] | 0.97 [0.68; 1.93] |
| Triglycerides (mmol/L), median [IQR] | 1.03 [0.64; 1.43] |
| LDL-goal attained[c] | 7 (35%) |

N≠20 for all lipid levels. N will be mentioned per lipid level-variable if not 20.
CVD = cardiovascular disease; SES = socioeconomic status; PCSK9 = proprotein convertase subtilisin/kexin type 9; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Apo B = apolipoprotein B.
[a] Presented as mean (SD) unless stated otherwise.
[b] Being methylphenidate for ADHD.
[c] LDL-goal attainment is defined according to the 2016 ESC/EAS guideline for the management of dyslipidemias [36]: target LDL-cholesterol <2.6 mmol/L in primary prevention, target LDL-cholesterol <1.8 mmol/L in secondary prevention (CVD presence).

said he would consider himself as ill when he had a cardiovascular event. Interestingly, another HoFH patient who had CVD did not consider HoFH a disease. Only two participants, one with a recent myocardial infarction and one with extreme premature CVD mortality in the family, were quite firm in their opinion that HoFH is a disease.

### *3.2.2. Disease impact: daily life and long-term consequences*

*3.2.2.1. Daily life.* The majority of patients (n = 15, 75%) indicated in normal circumstances not to be preoccupied with HoFH in daily life. They expressed to perceive HoFH not as a limitation in their education, employment, sports, hobbies, friends and family life. Impact on daily life was experienced at specific times: time of diagnosis, and when something reminds them of HoFH, for instance when their medication is adjusted (Table 2, quotes 3–4).

In general, patients mentioned that they experience little understanding about their condition by their social environment (excluding direct family). They also assumed that others would not understand (the severity of) their condition, because it is not visible (Table 2, quote 5). Therefore, most patients do not actively talk about HoFH.

**Table 2**
Example quotes per theme.

| Theme | Quotes |
|---|---|
| Perception of HoFH | 1 "*Yes, I know that it is [a disease], but I am not literally ill because of it. …. I never tell people that I have a disease. …. Maybe more a condition. … it already feels less .. Because it doesn't contain the word ill.*" – Female, 46 years |
| | 2 "*No, I don't regard HoFH as a disease. … I work, I exercise, I can go away with friends. I hardly have any pain. Sometimes I have side-effects from my medication, but for the rest I can do almost everything. I can go on a holiday. … Yes, I do consider HoFH as a disease, but to me it does not feel that way every day.*" – Female, 37 years |
| Impact of HoFH on daily life | 3 "*Only in the beginning it had an influence, but not anymore.*" – Female, 38 years |
| | 4 "*Of course, you know with cholesterol, … something is there, but you are not continuously thinking about it. … It is more that you think and talk about it when something happens that reminds you*" – Male #1, 32 years |
| | 5 "*I don't think it is relevant enough to tell others. … If I would have a different disease where I couldn't walk or stand or whatever, then yes, I would explain what I have and why I couldn't be doing certain things.*" – Male #2, 32 years |
| Long-term impact of HoFH | 6 "*No I don't think HoFH influences my life. I have it all under control.*" – Female, 35 years |
| | 7 "*The emotional side is indeed the most difficult. Look, the physical side with the examinations etc. …. . It is something you have to go through and then it's done. The mental aspect is something that can haunt you, which is really the toughest aspect.*" – Female, 46 years |
| | 8 "*Physically, I don't experience any limitations because of HoFH. Psychologically, I am also not affected at the moment, except that you have a certain insecurity. In fact, the only certainty you have is the knowledge that you have something [HoFH].*" – Male #1, 32 years |
| | 9 "*I haven't been able to get children. …. that also does a lot to you psychologically. …. I've always wanted children, but I always said to the outside world: No I don't want children. Even though I really wanted to.*" – Female, 40 years |
| Coping with HoFH | 10 Active coping style: "*The moment I get a list, I will comply with it. And that's what I have done. So losing weight till a certain target and also just walking. …. In terms of nutrition and lifestyle, it is executable, and I went the extra mile with that.*" – Male, 42 years |
| | 11 Relativism: "*Yes, I think that is the only thing that works. I mean, you can really continue to spiral, but of course you should not allow that, because that is no way of living. So that is why I always try to put everything into perspective as quickly as possible.*" – Female, 46 years |
| | 12 Avoidance: "*When the sun is shining or at other good moments, I don't like answering questions [about HoFH]. … You can ask me some other time.*" – Male, 24 years |
| Appreciation HoFH-specialist care | 13 "*Now I have the feeling I am at the right place for treatment. I have a good relationship with the doctors that help me. They take me seriously and I think they try to achieve the maximum with the current knowledge.*" – Male #1, 32 years |
| | 14 "*Mainly it gave me peace of mind that I was with someone who knows everything about it. But also that he was specialized in it. Yes, I have a lot of confidence in that doctor. And that made a big difference for me.*" – Female, 37 years |

*3.2.2.2. Long-term impact.* Most patients stated to value the present instead of thinking about the long-term future too much. However, most participants did mention the uncertainty of living with HoFH on the long-term, especially in case of disease-related events (e.g. onset of CVD) or invasive questions. Although some patients did mention the physical aspects of symptoms (e.g. CVD or xanthomas), most of them reported that what they consider emotionally most bothersome is the uncertainty these symptoms represent (Table 2, quotes 7–8). Some patients (n = 10, 50%) specifically mentioned that they experienced the issue of family planning as complicated. Compared to women, more men stated that HoFH had no influence on family planning (2 women *vs*. 5 men). Mainly women mentioned the mental struggle they went through regarding passing on the disease and mentioned medical issues relating to pregnancy, for example having to stop lipid lowering medications. Besides, two women with CVD were advised that a pregnancy could have serious consequences on their already fragile cardiovascular system. Therefore, they were impaired from ever having children and in turn not becoming parent or grandparent (Table 2, quote 9).

### 3.2.3. Coping: individual strategies and professional support

*3.2.3.1. Coping.* Various ways of coping with HoFH could be identified in the interviews. The most common styles were: an active coping style, seeking social support, positive thinking, relativism, acceptance and avoidance. Examples of some of these coping styles are provided in Table 2 (quotes 10–12). Other coping styles that respondents applied were: seeking distraction, downplaying, exercising self-control, expressing emotions, worrying, prophesying. All participants showed a combination of coping styles.

*3.2.3.2. Appreciation HoFH-specialist care.* In general, patients have great appreciation of the care given at specialized lipid clinics. They value a physician who is specialized in HoFH with in-depth and current knowledge of their illness (Table 2, quotes 13–14). All patients mentioned to feel more comfortable with a dedicated physician, and also to feel assured in receiving the most optimal treatment available. To illustrate, one patient said: "*Since I feel I am at the right place for it [HoFH], that does help me*". All patients mentioned to profit from the information from their treating physician. Several examples of ways of providing information were given. One patient stressed the importance of educational sessions about HoFH, wherein his family members could attend as well. Another patient mentioned the treating physician provided a short film which explained HoFH: "*It is easy to look at yourself, but also to show to others in case you get questions about your illness*".

For some patients, it is also important to frequently see their physician as it helps them comply with their medication regime.

### 3.3. Questionnaires – EQ-5D-5L & TMSI

The median EQ-5D-5L utility score was 0.839 [0.755; 0.887] and the mean visual analogue score was 75 (16.42) on a scale of 0–100.

For the TMSI, two scores were calculated: a score for a monitoring coping style (information seeking and need for control) and a score for a blunting coping style (distractive strategies). In general, both coping styles were applied by the participants (Table 3). Individually, some participants showed a preference for one over the other, which corresponded to how they talked about their dealing with the disease during the interviews.

## 4. Discussion

In this qualitative study, the views of Dutch HoFH patients regarding their QoL, as well as how they deal with their disease in daily life, was explored. This resulted in a theoretical model with the perception of HoFH as central theme. Disease perception influenced how they dealt with having HoFH in the present and with regard to their future. Results of the TMSI questionnaires showed that individual scores on coping style corresponded to interview results, with most patients showing both monitoring (information-seeking behavior) and blunting (distractive strategies) coping styles. The median EQ-5D-5L health utility score (0.839) was only 5% below the Dutch population (0.887) [17].

One of the most striking findings of our study was that 75% of the Dutch HoFH patients did not regard themselves as ill. This is in line with studies amongst HeFH patients [20–22]. However, our findings seem somewhat conflicting with previous studies in HoFH patients in other countries [13]. A qualitative French study in 24 HoFH patients found

that only 54% considered themselves "normal" or "not ill" [10]. The main difference with our study is that all patients in the aforementioned study were treated with lipoprotein apheresis, opposed to only 10% of our patients. The frequent confrontation with their illness, fueled by (bi) weekly hospital-based treatment, may explain the lower QoL. Indeed, our study found that at moments when HoFH becomes more apparent, e.g. time of diagnosis, adjustment of their medication, and CVD events, patients become more aware of their illness. The triggers first diagnosis [20–23], and CVD of self/family member were also noted in HeFH patients [24–27]. Strikingly, when talking about family members with FH, the worry of a family member developing CVD becomes tangible even though some patients estimate their CVD risk as low. This contradiction has also been observed in previous HeFH studies and may be related to coping [25,26,28]. That is, seeing oneself as "not ill", may serve the purpose of (continuing) to focus on life and not losing oneself in worrying over future illness.

The QoL reported by HoFH patients in our study ranged from negative (−0.050) to maximum (1.000) EQ-5D-5L utility scores (further descriptive data shown in Supplementary Data 2). The two HoFH patients receiving apheresis were on the outer ends of the spectrum (−0.050 and 1.000). Overall QoL is quite good, with median EQ-5D-5L health utility scores (0.839) only 5% below the Dutch population (0.887) [17]. These scores seem somewhat better compared to QoL findings in two studies which have assessed QoL in HoFH [10,11]. These studies, however, employed different measures for QoL, one study being fully qualitative and the other employing the Short Form-36 questionnaire (SF-36). The before mentioned French qualitative study identified considerable burdens (physical, psychosocial, educational, work-related) [10]. The other study from Turkey consisting of 88 HoFH patients, all receiving apheresis, found that, except for vitality, all domains of QoL were significantly lower on the SF-36 compared to the general Turkish population [11]. Moreover, 30.4% had an increased risk of depression based on the Hospital Anxiety and Depression Scale (HADS), which is associated with a negative impact on QoL [29].

An important finding of our study was the difference between male and female participants concerning family planning. We received a broad range of answers on the impact of HoFH on family planning. Women more often mentioned a negative impact. Similar diverse answers, from no effect at all to not being physically able to have children, were also observed in French HoFH patients receiving apheresis [10]. However, no gender differences were described. In HeFH patients, women seemed to more often worry about the impact of their disease on their own and children's future [22]. Also, they are insecure about the effects of long-term medication on their own health as well as on becoming pregnant in the future [21]. Most lipid-lowering therapies are contraindicated in pregnancy and during lactation [30]. This impact was recently investigated in a study consisting of Dutch and Norwegian HeFH patients, which showed a median total length off-statin period of 2.3 years per pregnancy and lower frequency and duration of breastfeeding compared to the general population [31].

The participants in this study emphasized the value of referral to a specialized lipid clinic and specialist. They especially stressed the importance of information exchange and professional and dedicated care. In HeFH patients this appreciation and trust were also observed [20,28]. Specialized care also contributes to the patient's perception of CVD risk and treatment adherence, especially in patients without CVD [22,24].These findings underline the importance of dedicated centers for rare disorders such as the European reference networks (ERN) for rare diseases and the recently initiated Lipid clinics network [32,33]. Professionals play an important role to improve QoL and treatment compliance in the patient and to come to a fine balance in awareness of risk *versus* continuous threat-awareness and worrying in patients. Understanding of coping mechanisms can help patients find this balance through patient-physician interaction.

**Table 3**
Results EQ-5D-5L and TMSI questionnaire.

| Participant | EQ-5D-5L | | TMSI | |
|---|---|---|---|---|
| | Utility score | VAS | TM | TB |
| **1** | 0.267 | 50 | 24 | 27 |
| **2** | 1.000 | 100 | 37 | 33 |
| **3** | 0.883 | 80 | 25 | 22 |
| **4** | 1.000 | 85 | 32 | 25 |
| **5** | 0.817 | 80 | 17 | 32 |
| **6** | 0.887 | 90 | 37 | 26 |
| **7** | 0.887 | 95 | 33 | 38 |
| **8** | 0.861 | 75 | 40 | 31 |
| **9** | 0.743 | 40 | 36 | 37 |
| **10** | 0.887 | 80 | 40 | 26 |
| **11** | 0.817 | 50 | 18 | 36 |
| **12** | 0.791 | 90 | 29 | 37 |
| **13** | 0.817 | 70 | 21 | 30 |
| **14** | −0.050 | 50 | 30 | 29 |
| **15** | 0.642 | 65 | 34 | 21 |
| **16** | 0.718 | 75 | 19 | 39 |
| **17** | 1.000 | 85 | 37 | 44 |
| **18** | 1.000 | 85 | 24 | 25 |
| **19** | 0.883 | 80 | 18 | 27 |
| **20** | 0.808 | 70 | 31 | 19 |
| **Total** | | | | |
| Mean (SD) | 0.783 (0.255) | 74.8 (16.42)[a] | 29.10 (7.79) | 30.20 (6.71) |
| Median [IQR] | 0.839 [0.755; 0.887][a] | 80.0 [66.3; 85.0] | 30.50 [21.75; 36.75][a] | 29.50 [25.25; 36.75][a] |

EQ-5D-5L = EuroQol 5D on a 5-point Likert scale, with utility score and VAS-score (VAS = Visual Analogue Scale, ranging from 0 to 100).
TMSI = Threatening Medical Situations Inventory.
TM = Monitoring (information-seeking behavior), on a scale from 9 to 45.
TB = Blunting (distractive strategies), on a scale from 9 to 45.
[a] For all scores, except the VAS-score, the median is prevalent due to the distribution of data.

### 4.1. Strengths and weaknesses

A strength of this study is the diverse study population from different parts of the Netherlands, which we consider representative for the Dutch HoFH population. Also, our research team consisted of FH specialists and psychologists, giving it a multi-disciplinary approach. Furthermore, the COVID pandemic might have influenced the QoL outcome of some participants. However, this possibility was explored in the interviews, but no influence was found. Undeniably, the pandemic could have influenced the QoL in other ways, which are unmeasured.

Another limitation could be that our results might not be extrapolatable to countries with different health care systems and treatments such as apheresis. Until 2014 a nationwide FH cascade screening was performed in the Netherlands. Presently, HoFH patients are diagnosed by genotyping, as DNA-testing is part of routine practice. Previously, the phenotypical characteristic of the HoFH population in the Netherlands was described by Sjouke et al. [34,35]. They showed a wide variability in phenotype of the Dutch HoFH population with the majority of patients having a relatively mild phenotype. The patients in our study are comparable in age, LDL-C levels and CVD prevalence compared to the population described by Sjouke et al. and therefore representative of Dutch HoFH patients. Moreover, the other non-participating HoFH patients treated at the Dutch HoFH centers at the time of our study show similar baseline characteristics and have less CVD. Only one of the Dutch non-participating patients had CVD, which was angina pectoris at age 40 followed-up by a PCI. In the Netherlands, LDL-apheresis is not a standard treatment for HoFH patients, as for a long-time it has not been reimbursed. Therefore, the findings of this study might not be representative of all HoFH populations in other countries and the possible influence of apheresis-treatment on QoL should be examined further in this population. This research has shown some first insights into the QoL

of the heterogeneous Dutch HoFH population. Previous QoL research has only focused on HoFH patients receiving apheresis treatment, while the recently published data from the HICC-registry shows that the majority (61%) of international HoFH patients is not on apheresis treatment [12,13]. It is therefore valuable to further investigate QoL in a larger HoFH population receiving a variety of treatments. Additionally, future quantitative research on HoFH patients is needed exploring possible influencing factors (e.g. sex, extent of CVD, years since diagnosis, LDL-goal attainment, etc.), which may provide more knowledge on where improvements can be made in HoFH care.

### 4.2. Conclusion

In this study, the subjective quality of (daily) life of HoFH patients seems to be only slightly affected by the objective elevated risk of premature CVD and death. There are moments in life, however, when being confronted with having HoFH (e.g. CVD events, family planning), that the burden becomes more apparent. On those occasions, most patients seem to be able to make use of effective coping mechanisms to deal with it.

An important aspect in this process, besides their family contacts, is the treatment and guidance from HoFH specialists. From the patient's perspective, referral to a specialized lipid clinic is esteemed as particularly valuable for a combination of reasons, ranging from early diagnosis, information, reassurance, motivation, to understanding. It is important that HoFH-specialists understand the various coping strategies of HoFH patients to optimize, tailor care and help HoFH patients deal with their condition. Future quantitative research in a larger international HoFH study population is essential to gain more insights into QoL of HoFH patients worldwide.

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## CRediT authorship contribution statement

**Janneke W.C.M. Mulder:** Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. **Leonieke W. Kranenburg:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Visualization, Supervision. **Willemijn J. Treling:** Formal analysis, Validation, Visualization, Writing – review & editing. **G. Kees Hovingh:** Resources, Writing – review & editing. **Joost H.W. Rutten:** Resources, Writing – review & editing. **Jan J. Busschbach:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Jeanine E. Roeters van Lennep:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – review & editing, Visualization, Funding acquisition, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.03.015.

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