Mind your heart: health care, quality of life, and biological pathways in adults with congenital heart disease

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Mind your Heart

Health Care, Quality of Life, and Biological Pathways in Adults with Congenital Heart Disease

op donderdag 6 december 2012
om 14.00 uur in de Agnietenkapel
aan de Oudezijds Voorburgwal 231
in Amsterdam

Aansluitend is er een receptie ter plaatse

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Mind your Heart

Health Care, Quality of Life, and Biological Pathways in Adults with Congenital Heart Disease

Dounya Schoormans
Mind your Heart: Health Care, Quality of Life, and Biological Pathways in Adults with Congenital Heart Disease

Academic Medical Center - University of Amsterdam, the Netherlands
Thesis, with a summary in Dutch
Proefschrift, met een samenvatting in het Nederlands

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Mind your Heart

Health Care, Quality of Life, and Biological Pathways in Adults with Congenital Heart Disease

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof.dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op donderdag 6 december 2012, te 14:00 uur

door

Dounya Schoormans
geboren te Tilburg
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- Prof.dr. J.C.J.M. de Haes
- Prof.dr. P. Moons
- Prof.dr. J.K.L. Denollet
- Prof.dr. N.K. Aaronson

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Chapter 1

Introduction
ADULTS WITH CONGENITAL HEART DISEASE

Annually, eight out of 1000 live births are diagnosed with a congenital heart defect (CHD). CHD is defined as a malformation of the heart or the large blood vessels that develops during the fetal period. There is great variety within CHD ranging from mild to complex defects. Thanks to the successes of cardiac surgery and medical care, nowadays approximately 90% of CHD-patients reach adulthood. At present, the adult CHD-population outweighs the children with an estimated population of 1 million in the United States and 1.3 million in Europe. Despite cardiac surgery most patients have residual lesions affecting daily life, possibly leading to impairments in quality of life (QoL). To manage the congenital malformation, and improve patients’ outcome, lifelong care is needed. Within the field of CHD, outcome research has focused on the clinical evaluation (e.g. mortality and morbidity). Additionally, health care and patient-reported outcomes such as QoL are important as well.

HEALTH CARE

In order to diminish the negative impact of the condition, expert lifetime care for adults with CHD is needed. Recommendations on how health care should be organized have been given in several reports. Often heard is the advocacy for a multidisciplinary care structure. That is, care should not solely be provided by the general practitioner and cardiologist, but also by other health care providers, such as nurses, physician assistants, social workers and psychologists. Although this structure is ideally needed, it will be challenging as there are too few trained and experienced specialists.

To optimize care, empirical studies on current health care utilization are needed. Due to a lack of empirical studies, there is little insight into the level of agreement between recommended and actual provided care. Empirical research focusing on at least the following topics is needed. First, health care utilization needs to be studied. To date, only three empirical studies have examined health care use in adult CHD-patients. All three focused solely on health care provision by the traditional health care providers, namely the general practitioner and cardiologist, and on inpatient health care use. To our knowledge, no studies have examined health care use for other health care providers representing a multidisciplinary health care structure. Second, we need to identify patient characteristics related to health care use. Identifying which patients use much or little health care, will enable the prediction and allocation of future health care utilization in a cost-effective manner. Third, to provide tailored care, patients’ need for health care has to be studied. Finally, it is important to study patient-satisfaction levels regarding the provided care as this information gives insight into the impact of treatment and the quality of care, which can ultimately direct the future delivery of care. To our knowledge only three studies have been published on CHD-patients’ experiences with the care they received with regard to their CHD. Two studies focused on the transfer from paediatric to adult cardiology. The third study examined the level of satisfaction in adult patients receiving follow-up care in a pediatric setting. There is thus a need for patient satisfaction studies focusing on other aspects of the provided care.
QUALITY OF LIFE

Patient-reported outcomes are measurements based on a report that comes directly from the patient without amendment or interpretation of the patient’s response by a clinician or anyone else.\(^{15}\) The most popular and often used patient-reported outcome is QoL, which can be defined in many ways. In general, there is consensus that it is a multidimensional concept including at least physical, psychological and social functioning.\(^{16}\)

In clinical practice, the most commonly assessed aspect of QoL is patients’ physical functioning. Within the field of CHD this is often measured in terms of functional status. During consultation, a cardiologist assesses patients’ functional status according to the New York Heart Association (NYHA) classification.\(^{17}\) To date; no patient-based equivalent of this NYHA classification is available.

Over the last years, research on QoL has gained increasing attention within the field of CHD. Results are mixed; on the one hand, studies report that CHD-patients have impairments in their QoL compared to their healthy counterparts,\(^ {18-21}\) whereas others describe that the QoL of patients is similar to that of their peers.\(^ {22-26}\) These differences seem to be region dependent as the QoL of West-European CHD-patients is generally less impaired than the QoL of patients from other countries or continents. Therefore this discrepancy may represent differences in health care organization, social inequity or cultural differences. This discrepancy may additionally be the result of differences in methodology and measurements across studies.\(^ {27}\)

Relatively little is known about factors explaining CHD-patients’ QoL. Few studies have related socio-demographic, clinical and psychosocial factors to patients’ QoL. Results show that a high age, low educational level, complex defect, poor functional status, depressive predisposition and limited social support are related to poor QoL.\(^ {18,28-30}\) Whereas insight into these associating factors is important, the therapeutic value of these studies is limited, since these variables are not (easily) modifiable. To improve patients’ QoL, studies need to be conducted identifying modifiable determinants.

BIOLOGICAL PATHWAYS

Research on the relation between patient-reported (e.g. depression) and clinical outcomes (e.g. mortality and morbidity) has gained increasing attention. It is well-known that psychological co-morbidities such as depression and anxiety are common among patients with various conditions such as diabetes, respiratory diseases, arthritis, and heart diseases.\(^ {31-33}\) Numerous studies have examined the effects of these psychological co-morbidities for the onset and progression of disease.\(^ {31,34,35}\) For example, within the field of acquired heart disease, it is well known that depressed patients have an increased risk of death, irrespective of the traditional risk factors.\(^ {36,37}\) Moreover, depression is linked to the development of heart failure.\(^ {36}\) However, little is known about underlying mechanisms responsible for these interactions. A direct biological pathway may be an immunological imbalance.

The prevalence of life-time depression and anxiety among adult CHD-patients is around 50%.\(^ {38}\) Despite this high number, studies about the (negative) effects of depression and anxiety on long-
term complications such as heart failure are lacking. As far as we know, there are no studies within the field of CHD that focus on the relation between patient-reported and clinical outcomes and consequently on the biological pathways involved.

**OUTLINE OF THIS THESIS**

The overall aims of this thesis are: (1) to examine health care use and its predictors, patients’ need for health care and patients’ evaluation of health care (*chapters 2 through 6*); (2) to study QoL and its predictors (*chapters 7 through 10*); and (3) to relate patient-reported and clinical outcomes through biological pathways (*chapters 11 and 12*), in adults with CHD.

The results described in chapters 3 to 5 and 8 to 10 are part of a longitudinal study in adult patients. At baseline, patients from five tertiary and three regional Dutch centers are randomly selected from the CONCOR database, a Dutch registry for adult patients with CHD. All patients complete questionnaires assessing health care use and needs, Type D personality, QoL, depressive symptoms, trait-anxiety, happiness, optimism, illness perceptions, symptomatology, and perceived health. After two years, first-time respondents are asked to fill-out a second questionnaire set assessing health care use and QoL once again.

The outline of future research on health care in CHD-patients is provided in *chapter 2*. A first study on health care utilization and needs in a multidisciplinary health care structure of adult CHD-patients is described in *chapter 3*. Here we report on the number of contacts patients have with various health care providers within a one-year time-frame. Moreover, patients’ need for contact with these health care providers is assessed. Finally, patients evaluate the communication skills and expertise of their general practitioner and cardiologist. Additionally, we assess patients’ perceptions of the need for health care improvements.

The first study relating personality to health care use is provided in *chapter 4*. Here, we study the distressed (Type D) personality type, which is the tendency to experience negative affect and to be socially inhibited. The prevalence of a Type D personality and its cross-sectional relation to functional status, QoL, and health care use is described.

In addition, we examine to what extent disease complexity, functional status, and psychological patient characteristics (i.e. Type D personality, QoL, depressive symptoms, trait-anxiety, happiness, optimism, and illness perceptions) are predictive of health care use at two-year follow-up in *chapter 5*. During their adult life patients with CHD undergo several medical procedures. Probably the most invasive procedure is open-heart surgery. Given the complex character and the high impact of open-heart surgery, high quality of care during this procedure is of paramount importance. In *chapter 6* we describe the first study exploring the level of satisfaction with peri-operative care of consecutive adult patients undergoing open-heart surgery at a single referral center. Moreover, we examine whether involvement of a specialized nurse is associated with higher levels of patient satisfaction.
In large research projects, when cardiologists cannot assess the NYHA class for all included patients, it is beneficial when patients could self-assess their functional status. To date, no patient-based equivalent of the NYHA classification to assess functional status is available. In chapter 7, consecutive adult outpatients complete the following three patient-based questionnaires assessing their NYHA class; a patient-based translation of the NYHA classes, a self-constructed questionnaire based on the NYHA classes and the specific activity scale. The level of agreement between these three questionnaires and the assessment of the treating cardiologist are calculated to enable ‘best choice’. We moreover explore the level of agreement for patients without co-morbidity, as co-morbidity is known to affect self-perceived health.

In CHD, disease complexity is only marginally related to perceived health. In chapter 8 we study whether the symptomatology is responsible for this weak relation. A secondary data analysis on two separate patient samples (Belgian and Dutch patients) is performed exploring patients’ symptomatology (i.e. symptom frequency and symptom distress) and its relation to perceived health, independent of disease complexity.

Chapter 9 and chapter 10 describe predictors of QoL. In chapter 9 we examine the predictive value of negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) and whether positive affect can function as a buffer for the detrimental consequences of negative affect on QoL at two-year follow-up. In chapter 10, we compare illness perceptions of CHD-patients to those of patients with cystic fibrosis, diabetes mellitus, and asthma. We moreover, relate patient characteristics to illness perceptions. Furthermore, we examine to what extent illness perceptions are predictive of the QoL of CHD-patients two-years later.

In the last two chapters we relate patient-reported and clinical outcomes through biological pathways. In chapter 11 we associate gene expressions and single nucleotide polymorphisms (SNPs) with QoL in a population of patients with the Marfan syndrome (MFS). In addition, we explore MFS-patients’ QoL and its relation to demographics and MFS-related symptoms. Lastly, in chapter 12 we suggest that depressed CHD-patients are possibly at risk of developing heart failure through an immunological mechanism.

A discussion with suggestions for future research on providing appropriate care is given in chapter 13. In chapter 14 we summarize the results of our studies.
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PART I

Health Care
Chapter 2

Letter to the editor regarding the article “Recommendations for improving the quality of interdisciplinary care of grown-up with congenital heart disease (GUCH)”

International Journal of Cardiology, 2011; 151(1):121

Dounya Schoormans
Barbara JM Mulder
Mirjam AG Sprangers
TO THE EDITOR

In their article, Kaemmerer et al. state that current health care for patients with a congenital heart defect (CHD), is insufficient. We agree with their advocacy for a needs-based interdisciplinary medical care structure. Care for CHD-patients should not be provided by a cardiologist only. Rather other health care providers such as a general practitioner, rheumatologist, gynecologist, neurologist, and psychologist, may need to be involved, depending on the disease severity, disease course and underlying problems. Kaemmerer and colleagues point out that the achievement of multidisciplinary health care provision will be challenging as there are not enough highly trained and experienced specialists. Consequently, in order to deliver multidisciplinary optimal care to those who need it, we have to relocate the scarce resources that are available.

To enable such relocation and to optimize tailored care, not only the view of professionals is important, but empirical studies on current health care utilization are needed as well. So far, many studies have described guidelines for optimal care for CHD-patients based on the expert opinion. However, due to a lack of empirical studies, there is little insight in the discrepancy between these guidelines and the care provided. Ultimately, knowledge about this possible discrepancy is vital for the identification of those aspects of care that need to be changed.

The facilitation of optimal care for CHD-patients requires future empirical research focusing on at least the following three topics. First, patterns of health care utilization in countries with different health care systems have to be studied. To our knowledge only four studies, conducted in the Netherlands, Canada, Belgium, and the UK, have explored health care use of adult CHD-patients. Three of these focused solely on the quantity of care provided by a cardiologist or general practitioner or the use of inpatient health care (i.e. hospitalizations, operations, and emergency room (ER) visits). Given the multidisciplinary character of the guidelines on the management of CHD-patients, not only care provided by cardiologists, but also visits to other health care providers (e.g. neurologist, and psychologist), and inpatient health care have to be documented. The results of these future studies will provide insight into the country-specific use of current health care resources.

Second, patient characteristics associated with health care use have to be identified, enabling the prediction and allocation of future health care utilization. Research on the prediction of health care use in other patient groups, has shown that in addition to clinical (e.g. disease severity), and enabling factors (e.g. health care system), patient characteristics such as anxiety, depression, personality, quality of life, and illness perceptions are also related to health care use. For example, an anxious patient with a mild malformation might visit an ER twice a year because of concerns about his/her heart condition, while there is no clinical reason for it. For such a patient psychological care might be more appropriate, reducing the number of visits to the ER. Insight into patient characteristics related to health care use will direct the development of future health care facilities and tailoring it to those who need it.

Third, patients’ perceived needs for health care have to be investigated, as these are essential for the provision of tailored care. Additionally, barriers experienced by patients to use health care...
also have to be studied, as this knowledge might help design interventions to prevent patients from being lost to follow-up.

In summary, insight into current health care utilization, including the patient perspective is vital to direct the development of future health care facilities for CHD-patients, and to rearrange the scant resources to those who need it.
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Chapter 3

The perspective of patients with congenital heart disease: Does health care meet their needs?

*Congenital Heart Disease, 2011; 6(3):219-227*

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Arie PJ van Dijk
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Mariët S Hulsbergen-Zwarts
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ABSTRACT

Objective A first step in the delivery of tailored care is answering the following question: does health care meet the needs of patients? Therefore patients’ perspective on health care use and their needs was examined. The design used was a cross-sectional questionnaire study.

Patients A total of 1109 adult congenital heart defect (CHD) patients attending one of eight Dutch hospitals were randomly selected from a national database (10% of all registered patients).

Main outcome measures Patient-reported questionnaires on in- and outpatient health care use during the past year and need for additional care.

Results A total of 66% and 40% of patients had contact with their cardiologist and general practitioner, respectively. Six to 10% were hospitalized, operated upon, or visited the emergency room. For the majority the amount of contact was sufficient. Most patients indicated that the communication skills and expertise of the cardiologist and general practitioner were sufficient, and health care improvements were not necessary. Frequent health care users had a poor functional status and frequent contact with their cardiologist and general practitioner. Patients who want more contact with their cardiologist rated the communication skills of the cardiologist as insufficient.

Conclusions For most patients, the amount and quality of care are both sufficient. Patients who rate the communication skills of the cardiologist as insufficient have a need for more contact. In addition to the recommended training program as described in the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines, we recommend the incorporation of communication training. This is the first study to provide insight into health care use and needs of CHD-patients in countries with a compulsory health insurance system from the patient perspective.
INTRODUCTION

Annually, eight out of 1000 live births are diagnosed with a congenital heart defect (CHD). Thanks to the successes of cardiac surgery, almost 85% of CHD-patients reach adulthood. Most patients have residual lesions possibly resulting in impaired quality of life. To manage the congenital malformation and to reduce the negative impact on daily life, life-long care is needed.

In most European countries, the health care system is based on a National Health Service, as in the United Kingdom, Ireland, and Spain, or compulsory health insurance as in Belgium, Germany, France, Switzerland and the Netherlands. Primary and hospital care is accessible to Dutch citizens without extra costs. This system is found to be effective in the care of chronically ill patients.

In the Netherlands, primary care for adult CHD-patients is provided by the general practitioner and the cardiologist. As a result of the malformation or its treatment, patients may visit additional health care providers, such as a pulmonologist, psychologist or physical therapist.

Little is known about health care utilization or the need for health care of adult CHD-patients. The few studies that have investigated health care use of adult CHD-patients used database records to calculate health care utilization. Consistent with follow-up recommendations, a higher level of disease severity was found to be associated with more health care utilization. To the best of our knowledge, no studies have been published that investigated health care use of CHD-patients, using patient-based measures. Self-reports enable the enquiry of disease-specific health care use. To deliver tailored care to patients who need it, patients’ need for health care also has to be studied. Moreover, no studies are known to us, in which health care needs of CHD-patients are investigated.

This is the first study to assess (disease-specific) health care use and need for health care from the CHD-patient perspective. The objectives are as follows: (1) to identify the types and amount of health care used by CHD-patients, (2) to examine patients’ need for additional health care, (3) to examine patients’ perception of their primary care givers (i.e. cardiologist and general practitioner) and need for health care improvement, and (4) to identify patient characteristics affecting health care use and need for additional health care. This knowledge will ultimately enable the delivery of tailored care.

METHODS

Study population and procedure

In March 2009, 1670 adult CHD-patients from five tertiary referral and three regional centers were randomly selected from the congenital corvitia (CONCOR) database, a nationwide registry for CHD-patients, representative of CHD-patients in the Netherlands. Patients who were diagnosed with Marfan syndrome, mentally impaired, or illiterate in Dutch were excluded from this study.

Under Dutch law, ethical approval is not required for questionnaire studies. Therefore, this study was exempted from approval of the Medical Ethics Committee of the Academic Medical Center in Amsterdam. This study was conducted in accordance with the principles of the “Declaration of Helsinki.”
Measurements

Outpatient health care use
Outpatient health care use was operationalized as the number of contacts with regular (medical and psychosocial) and complementary health care providers during the previous year, for disease-specific reasons. Nineteen health care providers were included e.g., cardiologist, general practitioner, pulmonologist, and acupuncturist.

Inpatient health care use
Inpatient health care use was measured by three questions asking how often patients were hospitalized, visited the emergency room, and were operated upon in relation to their CHD during the previous year.

Health care needs
Health care needs were assessed for each of the 19 health care providers. Patients were asked whether they wanted to have more or less contact during the past year, or whether the number of contacts was sufficient. Response options were “more contact”, “enough contact”, and “less contact”.

Patients’ perception of cardiologist and general practitioner
Patients’ perception of the communication skills (one item) and expertise (one item) of their cardiologist and general practitioner were assessed per provider. Answers could be given on a 4-point Likert scale ranging from “not good at all” to “very good”. We added the option “not applicable” for the two questions concerning the general practitioner because patients may not have visited their general practitioner regarding their CHD during the past year.

Patients’ perception of the need for health care improvement
Patients’ perceptions of the need for health care improvement were assessed with nine statements describing such improvements (e.g. “The collaboration between hospitals should be improved”). A 4-point Likert scale was employed, ranging from “not necessary, good as it is” to “definitely necessary”, with an added option of “no opinion”.

Construction of the questionnaire and pilot study
Two independent cardiologists and two specialist CHD-nurses identified health care providers to be incorporated in the questionnaire. A pilot-study was conducted in 20 patients who evaluated the list of health care providers, leading to extension of the list. These patients also identified aspects of health care that should be improved. These aspects were subsequently translated into nine statements.
**Patient characteristics**

Sex, age, work status, education, religion, marital status, and the presence of co-morbidity were measured through self-report. Functional status was measured by a patient-based questionnaire assessing the New York Heart Association (NYHA) classification. Type of congenital heart defect was extracted from the CONCOR database and categorized into disease severity (i.e. mild, moderate and severe) according to Warnes and colleagues.

**Statistical analysis**

To identify the types and amount of care used, to examine patients’ need for additional care, and to explore patients’ perception of their cardiologist and general practitioner, and need for health care improvement, frequencies and percentages were calculated for all items. To identify patient characteristics affecting health care use, we first created five health care use variables; number of contacts with cardiologist and general practitioner, hospitalizations, emergency room visits, and operations. Three groups were created for each of these variables, according to no contact, one contact (once), and having more than one (frequent) contact (similar for hospitalization/emergency room visit/operation). Additionally, we formulated two health care needs variables; need for contact with cardiologist and general practitioner. The following patient characteristics were included as independent predictors of health care use and needs; patient characteristics listed in Table 1 (except for type of CHD, due to small subsample sizes), patients’ perceptions of their cardiologist and general practitioner, the number of contacts with their cardiologist and general practitioner and type of center (tertiary referral versus regional center). The effect of these patient characteristics on the five health care use and two health care need variables was examined by means of chi-square ($\chi^2$) tests for categorical variables and ANOVA’s for continuous variables. All comparisons were tested at the significance level of 10% ($p=0.10$). Significantly related independent variables were then tested by means of multinomial logistic regression analyses at a significance level of 1% ($p=0.01$). Patients who have contacted their health care provider (being hospitalized, visiting the emergency room, or being operated upon) once were identified as reference category because the comparison with frequent health care users is clinically most interesting. If multinomial logistic regression on health care use variables was not possible due to small subsample sizes, groups were clustered. All analyses were conducted in SPSS 16.0 (SPSS, Chicago, IL, USA).

**RESULTS**

**Response and patients’ characteristics**

Of the 1670 eligible patients, 1109 participated in this study (response rate 66.4%). Almost 78% of patients were treated in a tertiary referral center, whereas 22% were treated in regional centers, which is in line with the distribution of patients across centers in the CONCOR database. Patients who were treated in a tertiary referral center were older and had more often a severe congenital malformation than patients treated in regional centers, whereas no differences were found...
regarding functional status and sex (data not shown). Approximately half of the patients were male, with a median age of 38.0 years (Table 1). Little over 50% of patients reported one or more co-morbidities, and almost 70% of patients reported a NYHA class I. Almost 60% was diagnosed with a mild congenital malformation. The most common diagnoses were ventricular septal defect (15.8%), and atrial septal defect (15.3%), which is in concordance with the distribution of diagnoses of the CONCOR database. Non-respondents were comparable to respondents according to type of congenital heart defect and disease severity.

Table 1: *Patient characteristics*

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (n=1109) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (male)</strong></td>
<td>502 (45.3)</td>
</tr>
<tr>
<td><strong>Age in median years (range)</strong></td>
<td>38.0 (18-87)</td>
</tr>
<tr>
<td><strong>Work status (paid labor)</strong></td>
<td>785 (71.7)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>64 (5.8)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>410 (37.2)</td>
</tr>
<tr>
<td>Higher education</td>
<td>627 (56.9)</td>
</tr>
<tr>
<td><strong>Religion</strong></td>
<td></td>
</tr>
<tr>
<td>Christian</td>
<td>630 (58.0)</td>
</tr>
<tr>
<td>No-religion</td>
<td>406 (37.4)</td>
</tr>
<tr>
<td>Other</td>
<td>50 (4.6)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Married / living together</td>
<td>753 (68.7)</td>
</tr>
<tr>
<td>Single</td>
<td>257 (23.4)</td>
</tr>
<tr>
<td>Divorced / widowed</td>
<td>55 (5.0)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (2.8)</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
</tr>
<tr>
<td>No co-morbidity</td>
<td>544 (49.1)</td>
</tr>
<tr>
<td>One co-morbidity</td>
<td>278 (25.1)</td>
</tr>
<tr>
<td>Two or more co-morbidities</td>
<td>287 (25.9)</td>
</tr>
<tr>
<td><strong>NYHA classification</strong></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>754 (69.9)</td>
</tr>
<tr>
<td>Class II</td>
<td>232 (21.5)</td>
</tr>
<tr>
<td>Class III/IV</td>
<td>92 (8.5)</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>644 (58.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>366 (33.0)</td>
</tr>
<tr>
<td>Severe</td>
<td>99 (8.9)</td>
</tr>
</tbody>
</table>
### Types and amount of health care use

#### Outpatient health care use

Two-thirds of the patients (n=724; 65.9%) had contact with their cardiologist during the previous year, and 316 had more than one contact (Table 2). Forty percent of patients (n=438) had contact with their general practitioner during the past year for disease-specific reasons, and 210 patients had more than one contact.

Other medical specialists were contacted less often, ranging from 1.9% for a rheumatologist to 14.2% for a nurse. Few patients (0.6-1.9%) had contact with complementary health care providers (Table 2). Slightly more than a quarter of the patients (n=302; 27.2%) had frequent contact with more than one health care provider, and 116 patients had contact with two health care providers.

#### Inpatient health care use

Nearly 10% of patients (n=108) were hospitalized during the previous year, while 9% of patients (n=99) visited the emergency room, and 6.1% (n=67) were operated upon for disease-specific reasons (Table 2). Only three patients were hospitalized, visited the emergency room, and were operated upon during the past year.

#### Need for health care

Most patients indicated that the number of contacts with their cardiologist (n=948; 86.9%) and general practitioner (n=977; 90.1%), was sufficient, while 9.6% and 3.4% of the patients, respectively, indicated to need more contact. Interestingly, 3.5% and 6.5% wanted less contact with their cardiologist and general practitioner (Table 2).

For most of the other health care providers, about 5% of patients indicated to want additional contact. Interestingly, these patients named different health care providers, and only 17.6%
(n=195) wanted additional contact with two or more health care providers. Only 15 patients (1.4%) wanted less contact with more than one health care provider.

Table 2: Health care use and needs

<table>
<thead>
<tr>
<th>HEALTH CARE USE (n, %)</th>
<th>HEALTH CARE NEEDS (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Once</td>
</tr>
<tr>
<td>Less contact</td>
<td>Sufficient contact</td>
</tr>
<tr>
<td>Outpatient care</td>
<td></td>
</tr>
<tr>
<td><strong>Regular</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiologist</td>
<td>375 (34.1)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>658 (60.0)</td>
</tr>
<tr>
<td>Internist</td>
<td>979 (90.7)</td>
</tr>
<tr>
<td>Nurse</td>
<td>916 (85.8)</td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>994 (93.2)</td>
</tr>
<tr>
<td>Genetic counselor</td>
<td>1030 (97.6)</td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>1038 (98.1)</td>
</tr>
<tr>
<td>Surgeon</td>
<td>973 (91.7)</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>997 (93.7)</td>
</tr>
<tr>
<td>Physical therapist</td>
<td>933 (87.3)</td>
</tr>
<tr>
<td>Dietitian</td>
<td>1011 (95.1)</td>
</tr>
<tr>
<td>Pacemaker specialist</td>
<td>971 (90.7)</td>
</tr>
<tr>
<td>Thrombosis specialist</td>
<td>960 (89.6)</td>
</tr>
<tr>
<td>Home care aid</td>
<td>1033 (96.9)</td>
</tr>
<tr>
<td>Psychologist</td>
<td>1018 (95.3)</td>
</tr>
<tr>
<td>Social worker</td>
<td>1029 (96.6)</td>
</tr>
<tr>
<td><strong>Complementary</strong></td>
<td></td>
</tr>
<tr>
<td>Homeopath</td>
<td>1059 (98.1)</td>
</tr>
<tr>
<td>Acupuncturist</td>
<td>1065 (98.8)</td>
</tr>
<tr>
<td>Magnetizer</td>
<td>1071 (99.4)</td>
</tr>
<tr>
<td><strong>Inpatient care</strong></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>989 (90.2)</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>994 (90.9)</td>
</tr>
<tr>
<td>Operations</td>
<td>1028 (93.9)</td>
</tr>
</tbody>
</table>

Note: All numbers are given in frequencies (percentages). A time-frame of one year was employed. – = not applicable.

Patients’ perception of cardiologist and general practitioner

Communications skills of the cardiologist and general practitioner were rated as sufficient (i.e. “very good”, “good” or “reasonable”) according to 97.4% and 88.0% of patients, respectively. Expertise
of the cardiologist was rated as sufficient according to 98.7%, and of the general practitioner by 76.7% of the patients.

**Patients’ perception of the need for health care improvement**

For six statements on health care improvements more than half of the patients (51.0-68.0%) indicated that it is good as it is (Table 3). A quarter of the patients (25.2%, 24.5%, and 24.2%) agreed ("necessary" and "definitely necessary") with the following statements on health care improvements; “improving communication between physicians”, “shortening waiting time”, and “improving collaboration between hospitals”.

<table>
<thead>
<tr>
<th></th>
<th>Not necessary, fine as it is</th>
<th>Somewhat necessary</th>
<th>No opinion</th>
<th>Necessary</th>
<th>Definitely necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improving information giving</td>
<td>595 (54.5)</td>
<td>204 (18.7)</td>
<td>83 (7.6)</td>
<td>160 (14.7)</td>
<td>49 (4.5)</td>
</tr>
<tr>
<td>Improving joint decision making</td>
<td>674 (60.7)</td>
<td>111 (10.2)</td>
<td>122 (11.2)</td>
<td>141 (12.9)</td>
<td>45 (4.1)</td>
</tr>
<tr>
<td>Better listening to you as a patient</td>
<td>697 (64.1)</td>
<td>133 (12.2)</td>
<td>86 (7.9)</td>
<td>114 (10.5)</td>
<td>57 (5.2)</td>
</tr>
<tr>
<td>Taking more time for you as a patient</td>
<td>741 (68.0)</td>
<td>135 (12.4)</td>
<td>83 (7.6)</td>
<td>98 (9.0)</td>
<td>32 (2.9)</td>
</tr>
<tr>
<td>Improving flexibility in appointment making</td>
<td>621 (57.0)</td>
<td>163 (15.0)</td>
<td>93 (8.5)</td>
<td>152 (13.9)</td>
<td>61 (5.6)</td>
</tr>
<tr>
<td>Improving communication between physicians</td>
<td>472 (43.2)</td>
<td>153 (14.0)</td>
<td>191 (17.5)</td>
<td>160 (14.7)</td>
<td>115 (10.5)</td>
</tr>
<tr>
<td>Shortening waiting time</td>
<td>492 (45.0)</td>
<td>179 (16.4)</td>
<td>155 (14.2)</td>
<td>170 (15.6)</td>
<td>97 (8.9)</td>
</tr>
<tr>
<td>Improving collaboration between hospitals</td>
<td>386 (35.5)</td>
<td>106 (9.7)</td>
<td>333 (30.6)</td>
<td>153 (14.1)</td>
<td>110 (10.1)</td>
</tr>
<tr>
<td>Expanding the expertise of physicians</td>
<td>556 (51.0)</td>
<td>123 (11.3)</td>
<td>238 (21.8)</td>
<td>116 (10.6)</td>
<td>58 (5.3)</td>
</tr>
</tbody>
</table>

Note: All numbers are given in frequencies (percentages).

**Patient characteristics affecting health care use and need for health care**

Based on the results of the univariate analyses (data not shown), for each of the seven outcome variables different background variables were included in the multivariate analyses.

**Outpatient health care use**

Patients with a high NYHA class (i.e. NYHA-III/IV) have a 2.23 times higher odds (95% confidence interval (CI) 1.22-4.06) than patients with NYHA-I to have had frequent contact (i.e. more than one contact, instead of one contact) with the cardiologist during the previous year. Thus, patients with frequent contact with the cardiologist during the past year were characterized by a higher NYHA class and had frequent contact with the general practitioner (odds ratio (OR)=5.65, 95% CI=3.65-8.76).

Similarly, patients with frequent contact with the general practitioner during the past year, had a high NYHA class (OR=2.51, 95% CI=1.25-5.04) and had frequent contact with their cardiologist (OR=4.28, 95% CI=2.37-7.73) (Table 4).
Table 4: Multivariate analyses – Odds ratios (95% confidence interval) for the individual independent variables

<table>
<thead>
<tr>
<th></th>
<th>OUTPATIENT CARE (ref. once)</th>
<th>INPATIENT CARE (ref. once)</th>
<th>NEEDS (ref. sufficient)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contacts with cardiologist</td>
<td>Contacts with general practitioner</td>
<td>Hospitalizations</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>&gt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>NYHA (ref. I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1.60(1.07,4.21)</td>
<td>1.19(0.75,1.91)</td>
<td>2.02(0.66,6.20)</td>
</tr>
<tr>
<td>III/IV</td>
<td>2.23(1.22,4.06)*</td>
<td>2.51(1.25,5.04)*</td>
<td>2.95(0.88,9.90)</td>
</tr>
<tr>
<td>Communication skills cardiologist (ref. satisfied)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unsatisfied</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Contacts cardiologist (ref. none)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>N/A</td>
<td>1.20(0.65,2.23)</td>
<td>0.08(0.00,1.34)</td>
</tr>
<tr>
<td>More than once</td>
<td>N/A</td>
<td>4.28(2.37,7.73)*</td>
<td>0.27(0.03,2.19)</td>
</tr>
<tr>
<td>Contacts general practitioner (ref. none)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>1.59(1.05,2.40)</td>
<td>N/A</td>
<td>1.72(0.38,7.84)</td>
</tr>
<tr>
<td>More than once</td>
<td>5.65(3.65,8.76)*</td>
<td>N/A</td>
<td>1.96(0.52,7.43)</td>
</tr>
</tbody>
</table>

Note: Displayed are the odds ratios (95% confidence interval) for patients in a certain category of an independent variable (versus the reference category) (column), to be in a certain category of a dependent variable (versus the reference category) (row); ref. = reference category; ER = emergency room; N/A = not applicable, since the predictor was not included in multivariate analysis; * p<0.01.
Inpatient health care use

Patients, who had been frequently hospitalized during the past year, were not statistically significantly different from patients who were hospitalized once (Table 4). Patients who had visited the emergency room during the past year, had a high NYHA class (OR=4.05, 95% CI=2.06-7.96), and had frequent contact with their cardiologist (OR=8.32, 95% CI=3.11-22.29) and general practitioner (OR=3.58, 95% CI=1.88-6.81). Patients who were operated upon had frequent contact with their cardiologist (OR=49.33, 95% CI=6.56-370.05) (Table 4).

Need for health care

The number of patients in need of additional or less contact with their general practitioner was too small to conduct a multivariate analysis. Univariate analyses showed that both dissatisfaction with the communication skills of the cardiologist and the expertise of the general practitioner, were significantly (p≤0.01) associated with a need for additional contact with the general practitioner (data not shown).

Patients with a need for less contact with the cardiologist were not significantly different from patients who had sufficient contact. Patients in need for additional contact with their cardiologist had a higher NYHA class (OR=3.23, 95% CI=1.59-6.60), were unsatisfied with the cardiologists’ communication skills (OR=8.19, 95% CI=2.70-24.87), and had at least one contact with their general practitioner (OR=2.65, 95% CI=1.48-4.76 for one contact and OR=4.23, 95% CI=2.24-8.01 for frequent contact) (Table 4).

DISCUSSION

This is the first study that used a patient-based questionnaire to investigate patients’ perspective on health care use and need. Although the provision of care for CHD-patients is suboptimal,12 most patients find both the amount and quality of care sufficient, thus meeting patients’ needs.

Furthermore, results show that CHD-patients use many different types of health care, i.e. regular and psychosocial outpatient care, and inpatient care. Patients have had most frequent contact with their cardiologist and general practitioner. As can be expected from satisfaction surveys, most patients rated the provided care in general as sufficient. However, a substantial number of patients indicated that the communication between physicians and collaboration between hospitals can be improved, and the waiting time shortened. Frequent health care users are, as expected, functionally more impaired, and also had frequent contact with the primary care givers. Patients in need of more contact with their cardiologist had a lower functional status, had frequent contact with their general practitioner and, interestingly, rated the communication skills of their cardiologist as insufficient.

Adult CHD-patients have contact with several health care providers, other than their cardiologist and general practitioner. Residual lesions, impairments in quality of life, and high prevalence of co-morbidity, might be contributing factors. Having contact with several health care
providers is in line with the current opinion on health care provision for CHD-patients – care should be multidisciplinary to facilitate the comprehensive care for this emerging patient group.\textsuperscript{11-14}

Mackie et al.,\textsuperscript{5} Billet et al.,\textsuperscript{6} and Moons et al.\textsuperscript{7} studied health care use of CHD-patients in the UK, Canada and Belgium respectively, using database records. Although the designs of these studies were also different in other aspects (e.g. time-frame and inclusion of non-CHD related health care use), several comparisons can be made. The number of patients who had contact with the cardiologist in our study (65.9\%) is quite comparable to the number found by Mackie and colleagues (54.8\%).\textsuperscript{5} The number of patients visiting their general practitioner (> 90.0\%),\textsuperscript{5,6} being hospitalized (51.3\%, 20.3\%),\textsuperscript{5,7} and visiting the emergency room (67.9)\textsuperscript{5} were higher than the numbers found in our study (40\%, 9.8\%, 9.1\%, respectively). Factors that may have contributed to the higher numbers of patients found in these studies\textsuperscript{5-7} include the wider time-frame employed (four and two years, respectively),\textsuperscript{5,6} and the inclusion of visits and hospitalizations unrelated to CHD.\textsuperscript{5-7} Moons et al.\textsuperscript{7} reported a smaller number of patients being operated in one year (3.7\%) than we did (6.1\%), which might be explained by their selection of patients through convenient sampling of in- and outpatients, patients’ younger age and better functional status.

According to our patients and health care professionals,\textsuperscript{13} the communication between physicians and the collaboration across hospitals should be improved. These findings underline the importance of one of the guidelines on the management of adult CHD-patients formulated by the European Society of Cardiology (ESC),\textsuperscript{15} i.e. to initiate a medical passport for each patient. This passport facilitates easy access to and communication between physicians. Patients’ dissatisfaction with waiting time is a common finding in patient satisfaction studies.\textsuperscript{16} Informing patients about the predicted waiting time and the reason for the delay is found to increase patients’ satisfaction levels.\textsuperscript{16}

Contrary to what might be expected based on clinical practice, older age and being female were not associated with more health care use. This might be explained by the young age of this patient group (median = 38.0 years), since only 17 percent of patients were 55 years or older. Additionally, the difference in health care use between men and women seen in clinical practice might represent a difference in clinical and psychological functioning, as patients’ sex was related to functional status and quality of life, with women reporting poorer functional status and lower quality of life scores than men.

As expected, patients with a low functional status have frequent contact with their cardiologist. Moreover, they want even more contact with their cardiologists. Interestingly, patients who rate the communication skills of their cardiologist as insufficient are in need of more contact with their cardiologist, but are not frequent visitors of their cardiologist. One might speculate that patients have a need for better contact, instead of more contact. Alternatively, Type D personality, which is a combination of negative affect and social inhibition, has been found to be associated with less health care use in heart-failure and CHD-patients even if they are functionally more impaired.\textsuperscript{17,18} It might be hypothesized that the CHD-patients, rating the communication skills as negative and wanting additional contact, do not visit their cardiologist frequently, because they have a Type D personality. The general tendency to experience negative emotions might influence the negative
rating of the communication skills of their cardiologist, while the social inhibition may prevent them to contact the cardiologist.

The limitations of this study merit attention. First, results might be influenced by patients’ recall-bias; the involuntary or voluntary over- or underreporting. Second, health care use and needs were measured with a one-year time-frame, possibly leading to underestimation, since contacts of patients visiting their health care provider once every few years were not all counted. Third, the results stem from a cross-sectional study, leaving questions about cause and effect unanswered.

We would also like to emphasize the strengths of this study. The inclusion of 1109 randomly selected patients, which is 10% of all registered patients in the national database, represents a broad spectrum of CHD-patients in the Netherlands. Moreover, this is the first study that identifies types of health care used by CHD-patients, examines their need for health care, and explores the effect of patient characteristics on their health care use and needs. Finally, we are the first to use patient-based measures, enabling the specification of CHD-specific health care utilization.

In conclusion, for most patients both the amount and quality of care is sufficient, thus meeting patients’ needs. As expected, patients with a poor functional status are at risk of becoming frequent health care users and in need of additional contact with their cardiologist. A small minority of patients who rate the communication skills of the cardiologist as insufficient indicate to want more contact with the cardiologist. In addition to the recommended training program for congenital cardiologists, as described in the American College of Cardiology/ American Heart Association (ACC/AHA) and ESC guidelines, we recommend the incorporation of communication training. This training will improve cardiologists’ communication skills and reduce the perceived needs of patients for additional contact. This study provides insight into health care use and needs of CHD-patients and their evaluation of the health care system. Results are relevant to other countries employing a similar compulsory insurance health care system, like Belgium, Germany, France, and Switzerland.

ACKNOWLEDGEMENTS
We are very grateful to all patients. Moreover, we thank Mrs. F. van Ommen of the Academic Medical Center for her help with the data collection.
REFERENCES


Patients with a congenital heart defect and Type D personality feel functionally more impaired, report a poorer health status and quality of life, but use less health care

*European Journal of Cardiovascular Nursing, 2012*
ABSTRACT

Background Type D personality, characterized by a high level of neuroticism and social inhibition, is related to mortality, morbidity, poor health status, quality of life (QoL), and less health care utilization in various cardiovascular patient groups. To date, studies in patients with congenital heart disease (CHD) are lacking.

Aims (1) To examine the prevalence of Type D personality in CHD-patients; (2) to compare Type D to non-Type D patients with regard to disease severity, functional status, health status and QoL; and (3) to examine the extent to which Type D personality is independently related to health care utilization.

Methods A total of 1109 adult CHD-patients were included in a questionnaire survey. Due to missing data, 302 patients were excluded.

Results The prevalence of Type D personality was 20.4%. Type D patients reported a poorer functional status, health status and QoL than non-Type D patients (p<0.05). Type D patients reported less health care use than non-Type D patients (i.e. primary and cardiac outpatient health care: adjusted OR=0.56, 95% CI=0.35-0.90 and inpatient health care: adjusted OR=0.38, 95% CI=0.17-0.83). Results of a post-hoc analysis showed a high prevalence of Type D personality in patients with a poor functional status who did not to consult their cardiologist.

Conclusion Type D patients report a poorer functional status, health status, and QoL, but less health care utilization. In clinical practice patients should be screened for Type D personality, since social inhibition may prevent them from contacting a health care provider in the event of symptom aggravation.
INTRODUCTION

Over the past ten years, Type D (distressed) personality has been extensively studied in various cardiovascular patient groups. Developed by Denollet a Type D personality is characterized by high scores on both negative affect and social inhibition.\textsuperscript{1} Around 25% of cardiovascular patients were found to have a Type D personality.\textsuperscript{2} Several studies have shown that Type D personality is a predictor of mortality\textsuperscript{1-3} and adverse health outcomes, such as myocardial infarction,\textsuperscript{4} independent of traditional biomedical risk factors.

Moreover, Type D patients report a poorer health status and quality of life (QoL),\textsuperscript{5,7} more symptoms,\textsuperscript{6} and more disabilities than non-Type D patients.\textsuperscript{9} Conversely, Type D patients display adverse health behavior, such as smoking,\textsuperscript{10,11} and report less health care utilization\textsuperscript{8}. These studies have been performed in patients with acquired heart disease. To date, studies in patients with congenital heart disease (CHD) are lacking.

Given the clear prognostic value of Type D personality in various cardiovascular diseases and its relation with health care utilization, information about the prevalence of Type D personality in CHD-patients is important. Relating Type D personality to health outcomes such as functional status and QoL provides information about a possible determinant of poor health outcomes in CHD-patients. Moreover, knowledge about the relation between Type D and health care utilization provides a target for intervention, as patients can be stimulated to visit their physician in case of need. The aims of this study are, therefore: (1) to establish the prevalence of Type D personality in CHD-patients; (2) to examine the extent to which Type D and non-Type D patients differ with regard to disease severity, functional status, health status, and QoL; and (3) to examine the extent to which Type D personality is independently associated with health care utilization.

METHODS

Study population and procedure

This study utilized data from a larger study on patient-reported outcomes of adult CHD-patients.\textsuperscript{12} In March 2009, 1670 adult CHD-patients from eight hospitals were randomly selected from the CONCOR database – a nationwide registry for CHD-patients.\textsuperscript{13} Eligible patients were diagnosed with a CHD (patients with Marfan syndrome were excluded), literate in Dutch and 18 years or older. Patients were invited by letter to complete a web-based questionnaire. Non-respondents were sent reminders after six and 12 weeks. Ethical approval is not required for questionnaire studies in the Netherlands. Therefore, this study was exempted from approval of the Medical Ethics Committee of the Academic Medical Center in Amsterdam. This study was conducted in accordance with the principles of the “Declaration of Helsinki”.\textsuperscript{14}

Measurements

Type D personality

The 14-item Type D Scale (DS14) was used to assess Type D personality; it consists of two subscales, Negative Affectivity (seven items) and Social Inhibition (seven items).\textsuperscript{1} A Type D personality is
defined as a cut-off score of ≥ 10 on both subscales of the DS14, and is coded as a dichotomous variable. Following Denollet, patients with versus without a Type D personality were labeled “Type D patients” versus “non-Type D patients”.1 The DS14 is standardized and validated, and has good psychometric properties.1

Disease severity and functional status
Type of congenital heart defect was extracted from the CONCOR database and categorized as mild, moderate and severe according to Warnes and colleagues15 to determine disease severity. Functional status was assessed according to the New York Heart Association (NYHA) class.16 One patient-based question to assess NYHA class was administered.17 Previous research has shown adequate levels of agreement between this patient-assessed and cardiologist-assessed NYHA-class.17

Health status and quality of life
Health status was measured by the Short Form Health Survey-36 (SF-36), yielding a physical (PCS) and mental component summary (MCS).18 QoL can be defined in many ways. We adopt the definition as proposed by Moons et al., who defined QoL as “the degree of overall life satisfaction that is positively or negatively influenced by individuals’ perception of certain aspects of life important to them, including matters both related and unrelated to health” (p. 17).19 QoL was measured by two questionnaires. The five-item Satisfaction With Life scale (SWL),20 and the TNO/AZL Adult Quality Of Life-CHD (TAAQOL-CHD) forming the three subscales Symptoms (e.g. palpitations) (nine items), Worries (about e.g. their relationships or career perspective) (ten items), and Impact Cardiac Surveillance (e.g. the number of hospitalizations) (seven items).21 For each (sub)scale, higher scores reflect a better health status or QoL. Both the SF-36 and SWL are well validated.22,23 There has been only one study that validated the TAAQOL-CHD,21 making its validity less clear.24,25

Health care use
A study-specific questionnaire was developed to assess clinical and psychological health care use for CHD-related reasons during the last year.12 Clinical health care yields three types of health care, i.e. primary and cardiac outpatient health care, additional medical outpatient health care, and inpatient health care. Primary and cardiac outpatient health care constituted the number of contacts with the general practitioner (one item) and cardiologist (one item). Additional medical outpatient health care (nine items) constituted the number of contacts with nine health care providers (e.g. rheumatologist, internist, and nurse). Inpatient health care use was measured by three questions asking how often patients visited the emergency room, were hospitalized or operated upon in relation to their CHD. Finally, two items assessed the number of contacts with a psychologist and social worker, forming psychological health care.
Statistical analyses

Exploratory analyses showed that for all four health care use variables, missing data were less than 10%. We ran our analyses with missings imputed (i.e. imputing a zero score) and by excluding all missings. Results were compared via a sensitivity analysis and showed unstable results for one outcome variable. We therefore chose the conservative estimate where no missing data were present. In other words, only patients with complete data on the health care use variables were included in the subsequent analyses.

To establish the prevalence of Type D personality, we calculated percentages. In addition, we examined the extent to which patients with a Type D personality differed from non-Type D patients with respect to clinical factors (i.e. disease severity, functional status, and congenital heart defect), health status (both the PCS and MCS of the SF-36), QoL (the SWL scale, and the Symptoms and Worries subscales of the TAAQOL-CHD), and the potential confounders: sex and age. Possible differences between Type D and non-Type D patients were examined by means of chi-square tests for categorical variables and t-tests for continuous variables. The subscale Impact Cardiac Surveillance of the TAAQOL-CHD was not included, because items overlapped with the health care use items.

We examined the extent to which Type D personality was independently related to the different forms of health care use (i.e. primary and cardiac outpatient health care, additional medical outpatient health care, inpatient health care and psychological health care) while controlling for potential confounders (i.e. age, sex, disease severity, functional status, health status, and QoL). All variables were simultaneously included in four generalized linear model analyses with Poisson distribution. Heterogeneity in our sample was corrected using robust standard errors.

All analyses were conducted in SPSS 16.0 and comparisons were tested at the significance level of 5%. We chose not to use a more stringent alpha level for two reasons: first, since this is the first study exploring Type D personality in CHD-patients we wanted to avoid making a type-2 error, and second, our hypotheses were theory driven.

RESULTS

Response and patient characteristics

Of the 1670 eligible patients, 1109 participated in this study (response rate 66.4%). Non-respondents were not significantly different in terms of disease severity, but were more often male and younger than respondents (data not shown). For the 1109 patients, there was missing data on the health care use and the independent variables (i.e. DS-14, NYHA, SF-36, SWL, and TAAQOL-CHD) which led to the exclusion of 302 patients. The final number of included patients was thus 807. Excluded patients were similar according to disease severity, yet younger and more often female than the included patients (data not shown).

Patient characteristics of the included 807 patients stratified by Type D personality are displayed in Table 1. Of the total 807 patients more than half of the patients were female, with a mean age of 39.5 years (Table 1). Almost 57% was diagnosed with a mild congenital defect. Most
patients (71.1%) had a NYHA-I classification. The most common diagnoses were ventricular septal defect (16.2%), atrial septal defect (15.2%), and aortic coarctation (13.1%) which is in concordance with the distribution of diagnoses of the CONCOR database.

Table 1: Patient characteristics for the total patient group and stratified by Type D personality

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (n=807)</th>
<th>Type D patients (n=165)</th>
<th>Non-Type D patients (n=642)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>422 (52.3)</td>
<td>90 (54.5)</td>
<td>332 (51.7)</td>
<td>0.516</td>
</tr>
<tr>
<td>Age in mean years (SD)</td>
<td>39.5 (13.4)</td>
<td>40.0 (12.4)</td>
<td>39.3 (13.6)</td>
<td>0.682</td>
</tr>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
<td>0.601</td>
</tr>
<tr>
<td>Mild</td>
<td>459 (56.9)</td>
<td>99 (60.0)</td>
<td>350 (56.1)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>276 (34.2)</td>
<td>51 (30.9)</td>
<td>225 (35.0)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>72 (8.9)</td>
<td>15 (9.1)</td>
<td>57 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
<td></td>
<td>0.000*</td>
</tr>
<tr>
<td>NYHA-I</td>
<td>574 (71.1)</td>
<td>88 (53.3)</td>
<td>486 (75.7)</td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>168 (20.8)</td>
<td>47 (28.5)</td>
<td>121 (18.8)</td>
<td></td>
</tr>
<tr>
<td>NYHA-III</td>
<td>46 (5.7)</td>
<td>19 (11.5)</td>
<td>27 (4.2)</td>
<td></td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>19 (2.4)</td>
<td>11 (6.7)</td>
<td>8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td></td>
<td></td>
<td></td>
<td>0.339</td>
</tr>
<tr>
<td>VSD / ASD / ASD-I / PDA</td>
<td>290 (35.9)</td>
<td>58 (35.2)</td>
<td>232 (36.1)</td>
<td></td>
</tr>
<tr>
<td>TOF / PS</td>
<td>161 (20.0)</td>
<td>31 (18.8)</td>
<td>130 (20.2)</td>
<td></td>
</tr>
<tr>
<td>BAV / AS / SubvAS</td>
<td>107 (13.3)</td>
<td>28 (17.0)</td>
<td>79 (12.3)</td>
<td></td>
</tr>
<tr>
<td>CoA</td>
<td>106 (13.1)</td>
<td>16 (9.7)</td>
<td>90 (14.0)</td>
<td></td>
</tr>
<tr>
<td>TGA/ ccTGA</td>
<td>32 (4.0)</td>
<td>5 (3.0)</td>
<td>27 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Other CHD-diagnoses</td>
<td>111 (13.8)</td>
<td>27 (16.4)</td>
<td>84 (13.1)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Numbers are given in frequencies (percentages), age in mean years (standard deviation). Type D patients = patients with a Type D personality; non-Type D patients = patients without a Type D personality; n = numbers; p = p-value; SD = standard deviation; NYHA = New York Heart Association functional class; VSD = Ventricular Septum Defect; ASD = Atrial Septum Defect; ASD-I = Atrial Septum Defect primium; PDA = Patent Ductus Arteriosus; TOF = Tetralogy of Fallot; PS = Pulmonary Stenosis; BAV = Bicuspid Aortic Valve; AS = Aortic Stenosis; SubvAS = Subvalvar Aorta Stenosis; CoA = Coarctation of the Aorta; TGA = Transposition of the Great Arteries; ccTGA = Congenital corrected Transposition of the Great Arteries; CHD = Congenital heart defect; * p < 0.01.

Prevalence of Type D personality and comparisons with non-Type D patients

The prevalence of Type D personality was 20.4% (n=165). Comparisons between Type D and non-Type D patients showed that Type D patients did not differ significantly regarding sex (p=0.516), age (p=0.682), disease severity (p=0.601), and congenital heart defect (p=0.339) from non-Type D patients (Table 1). Type D patients reported a poorer functional status (p<0.001) than non-Type D patients. Figure 1 shows that Type D patients have a significantly poorer health status and QoL (all p’s <0.01) than non-Type D patients.
Figure 1: Differences in health status and quality of life between Type D and non-Type D patients

![Figure 1: Differences in health status and quality of life between Type D and non-Type D patients](image)

Note: PCS = Physical component scale of the SF-36; MCS = Mental component scale of the SF-36; SWL = Satisfaction With Life scale; Symptoms = Symptoms subscale of the TAAQOL-CHD; Worries = Worries subscale of the TAAQOL-CHD.

### Association of Type D personality with health care use

Results of the three generalized linear model analyses relating Type D personality to clinical health care use (i.e. primary and cardiac outpatient health care, additional medical outpatient health care and inpatient health care) while controlling for confounders, are shown in Table 2. Type D patients reported less health care use than non-Type D patients (i.e. primary and cardiac outpatient health care: \( \text{adjusted OR}=0.56, \ 95\% \ CI=0.35-0.90 \) and inpatient health care: \( \text{adjusted OR}=0.38, \ 95\% \ CI=0.17-0.83 \)) independent of confounders. In general, a lower disease severity score and a better functional status (lower NYHA class) were independently associated with less clinical health care utilization (see Table 2 for specific contrasts). Patients who reported a better health status or QoL also reported less health care use.

Results of the generalized linear model explaining variance in psychological health care use showed that Type D was not independently related to psychological health care use. A better health status was independently related to less psychological health care use (PCS: \( \text{adjusted OR}=0.93, \ 95\% \ CI=0.90-0.97 \), MCS: \( \text{adjusted OR}=0.92, \ 95\% \ CI=0.89-0.96 \)).

### Further exploration of Type D patients’ consultation behavior

Since Type D patients reported a poorer functional status and less health care use, they may be at risk of inadequate consultation behavior. In post-hoc analysis, we compared patients who had a poor functional status (NYHA-III or NYHA-IV) but did not consult their cardiologist during the last year to all other patients. Results showed that of the nine patients who had a poor functional status, but did not consult their cardiologist, four patients (44.4%) had a Type D personality, compared to 20.2% of the remaining patients (n=798). Fisher’s exact test showed a trend for this effect (\( p=0.09 \)).
### Table 2: Relating Type D personality to health care use, while controlling for confounders

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL HEALTH CARE</th>
<th>PSYCHOLOGICAL HEALTH CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary and cardiac outpatient health care (n=803)</td>
<td>Additional medical outpatient health care (n=773)</td>
</tr>
<tr>
<td><strong>Personality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type D‡</td>
<td>0.56(0.35-0.90)</td>
<td>0.68(0.42-1.11)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>1.11(0.89-1.38)</td>
<td>0.98(0.71-1.36)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00(1.00-1.01)</td>
<td>0.99(0.98-1.01)</td>
</tr>
<tr>
<td><strong>Disease severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.30(1.07-1.59)</td>
<td>1.11(0.76-1.62)</td>
</tr>
<tr>
<td>Severe</td>
<td>2.21(1.38-3.54)</td>
<td>1.06(0.65-1.73)</td>
</tr>
<tr>
<td><strong>Functional status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>1.38(1.03-1.83)</td>
<td>1.49(0.98-2.78)</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>1.89(0.92-3.88)</td>
<td>1.70(0.76-3.79)</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>1.33(0.70-2.52)</td>
<td>1.75(0.79-3.87)</td>
</tr>
<tr>
<td>PCS</td>
<td>0.98(0.95-1.01)</td>
<td>0.95(0.92-0.67)</td>
</tr>
<tr>
<td>MCS</td>
<td>0.99(0.98-1.00)</td>
<td>0.99(0.96-1.01)</td>
</tr>
<tr>
<td>SWL</td>
<td>1.02(1.00-1.04)</td>
<td>1.01(0.96-1.07)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.99(0.98-0.99)</td>
<td>0.99(0.98-1.01)</td>
</tr>
<tr>
<td>Worries</td>
<td>0.98(0.96-1.00)</td>
<td>1.00(0.99-1.02)</td>
</tr>
</tbody>
</table>

Note: Adjusted OR are given for a one year increase for age, and a one-point increase on the health status and quality of life scales; Adjusted OR = odds ratio adjusted for the other included predictors; n = numbers; 95% CI = 95% confidence interval; p = p-value; Type D = patients with a Type D personality; NYHA-class = New York Heart Association functional class; PCS = Physical component scale of the SF-36; MCS = Mental component scale of the SF-36; SWL = Satisfaction With Life scale; Symptoms = Symptoms subscale of the TAAQOL-CHD; Worries = Worries subscale of the TAAQOL-CHD; ‡ reference category is non-Type D; * reference category is mild; † reference category is NYHA-I; ** p < 0.01; *** p < 0.05; * p < 0.10.
DISCUSSION
To our knowledge, this is the first study in CHD-patients focusing on Type D personality and its relation to health care utilization. The main result is that Type D patients report a poorer functional status, health status and QoL than non-Type D patients, but report less health care use.

We found that 20.4% of patients have a Type D personality, which is quite similar to the prevalence of Type D personality in the general adult Dutch population (18-21%). A study by Pedersen et al. also found similar prevalence levels of Type D personality in myocardial infarction (MI) patients and the general Danish population. The prevalence level found in CHD-patients is slightly lower than in other cardiac populations. In CHF- and MI-patients, 24% and 25% had a Type D personality, respectively. One might speculate that the slightly higher prevalence of Type D personality in cardiovascular patients stems from the fact that the presence of a Type D personality is found to be predictive for the development of acquired heart diseases.

We also found a negative relation between Type D personality and poor functional status, health status and QoL in our CHD-sample. As in studies in various cardiovascular patient groups, Type D personality was not related to disease severity. This is also in line with other studies in CHD-patients that found that disease severity is only minimally related to the patient-reported outcomes health status and QoL. Furthermore, we found that Type D personality is negatively related to health care use while adjusting for disease severity, functional status, health status, and QoL. Although various studies in patients with chronic heart failure report that Type D patients show inadequate consultation behavior (e.g. use less health care) Michal et al. found that Type D personality is associated with more health care use in the general population. In the Michal et al. study the authors did not correct for co-morbid conditions which can explain the higher level of health care use, as Type D personality is also associated with an increased risk for the development of diseases.

Although Type D patients report a poorer functional status, they report less health care use. Results of the post-hoc analysis indicated that Type D personality may be responsible for the inadequate health care use as the prevalence of Type D personality was higher in patients who reported a poor functional status, yet did not consult a cardiologist. It has been suggested that this inadequate consultation behavior is a mechanism underlying the negative relation between Type D personality and poor health outcomes. This hypothesis is supported by a vast amount of literature indicating that negative emotions are related to poor prognosis and unhealthy behaviors. Moreover, social inhibition may prevent patients contacting a health care provider, because patients feel insecure and less competent in communicating. Furthermore, persons with a Type D personality may have a passive and avoiding coping style, thereby not acting upon the symptoms they are experiencing.

This study has a number of limitations that merit attention. The main limitation is that we solely focused on Type D personality. Since research on personality development in this patient population is lacking, studies investigating other personality types – the Big Five personality traits – are needed as well. Second, the one-year time frame used in the health care use items, might have introduced patients’ recall-bias. Third, patients included in the analyses differed on age and
sex from both non-respondents and patients excluded due to missing data. Although sex, and age are neither associated with personality type or health care use, caution is warranted in the extrapolation of these results.

We would also like to emphasize the strengths of this study. First, the inclusion of 807 patients is 7.5% of all registered patients in the national database and around 3% of the estimated total adult CHD-population in the Netherlands. Our sample therefore represents a broad spectrum of Dutch CHD-patients. Second, diverse types of health care use were measured, i.e. primary and cardiac outpatient health care, additional medical outpatient health care, inpatient health care, and psychological health care. Finally, we used standardized measures that are widely used.

In conclusion, one fifth of our CHD-patients have a Type D personality. Type D patients report a poorer functional status, health status and QoL than non-Type D patients, but are less likely to use health care. In clinical practice, patients might be screened for Type D personality, since this patient group is reluctant to contact a health care provider in case of need. Due to the social inhibition present in Type D patients, doctor-patient communication may be hampered. Therefore, physicians should pay extra attention to physical symptoms displayed during consultation. Additionally, whereas most physicians nowadays are aware of the importance of a good doctor-patient relation, they may need to help Type D patients to disclose their symptoms and concerns. For example, Type D patients could fill out a questionnaire prior to the consultation reporting on symptoms and concerns. Physicians can then discuss patients’ answers during the consultation, thereby lowering patients’ threshold to disclose these issues. Finally, behavioral interventions targeted at patients with a Type D personality may need to be developed to improve their health behaviors, such as consulting a doctor when necessary, and to reduce their social inhibition.

ACKNOWLEDGEMENT

We are very grateful to all patients. Moreover, we thank Mrs. F. van Ommen of the Academic Medical Center for her help with the data collection.
REFERENCES


Chapter 5

Clinical and psychological characteristics of adults with congenital heart disease predict future health care use

Submitted

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Joost P van Melle
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ABSTRACT

Background To deliver adequate care to patients with congenital heart disease (CHD), it is important to know which patients use what type of care and to what extent. This knowledge will enable the allocation of future health care utilization in a cost-effective manner. Our objective was to examine the extent to which psychological characteristics are predictive of future health care use, independent of clinical characteristics.

Methods A longitudinal questionnaire study in 845 adult CHD-patients was conducted. Linear regression analyses with negative binomial log link function were performed predicting health care use at two-year follow-up. Independent variables were Type D personality, quality of life (QoL), depressive symptoms, trait-anxiety, happiness, optimism, and illness perceptions, independent of disease complexity and functional status.

Results Patients who reported more health care use had a complex defect, a poor functional status, no Type D personality, and a poor QoL. They moreover felt their CHD had a severe impact on their life and believed their CHD could be managed by themselves or treatment.

Conclusions Health care use is not entirely determined by disease complexity and functional status but also for a large part by psychological patient characteristics. This indicates that in some cases psychosocial care may be more appropriate. Nurse practitioners, social workers and psychologists should focus on improving patients’ QoL, helping them to reduce the negative impact of CHD and informing them about strategies to manage their CHD. Consequently, providing psychosocial care will not only be more appropriate but probably also more cost-effective.
INTRODUCTION

The number of adults with congenital heart disease (CHD) has grown expansively over the last few decades. As a consequence of their residual lesions, patients with CHD experience a number of physical symptoms, psychological impairments, and social problems. Therefore, it is highly recommended that care for adults with CHD is multidisciplinary. Various articles have described what optimal care for CHD-patients should look like based on expert opinion. Although expert opinion is important, empirical studies are needed to gain insight into a possible discrepancy between existing recommendations and currently provided care.

To facilitate optimal care for CHD-patients, we need to focus on health care utilization provided by not only cardiologists, but also by other health care providers such as pulmonologists or social-workers. To the best of our knowledge there is only one study that examined the number of contacts that CHD-patients have with this wide range of health care providers. Furthermore, it is important for health care providers and policy makers to know which patients use what type of health care and to what extent. This knowledge will enable the prediction and allocation of future health care utilization in a cost-effective manner. In patients with other chronic diseases, research has shown that not only clinical characteristics, such as disease severity, determine patients’ health care use. Psychological characteristics also related to health care utilization, are patients’ quality of life (QoL), whether they are depressed or anxious and the way they perceive their illness.

In the present study we therefore examined to which extent psychological characteristics (i.e. personality, QoL, depressive symptoms, trait-anxiety, happiness, optimism and illness perceptions) were independently predictive of health care use at two-year follow-up.

METHODS

Study population and procedure

This study is part of a larger longitudinal study on health care use of adults with CHD. Adult CHD-patients from five tertiary referral and three regional centers were randomly selected from the CONCOR database, a nationwide registry for CHD-patients. Upon registration in the CONCOR database, patients gave informed consent to be contacted for future scientific research. Eligible patients were sent an information letter explaining the nature and procedure of this study. Exclusion criteria were: a diagnosis of Marfan syndrome, being mentally impaired, or illiterate in Dutch. In total, 1670 eligible patients were invited to fill-out the questionnaire. At two-year follow-up another questionnaire was sent to all patients who completed the baseline questionnaire. Since approval is not required for questionnaire studies under Dutch law, this study was exempted from approval of the Medical Ethics Committee of the Academic Medical Center in Amsterdam. This study was conducted in accordance with the principles of the “Declaration of Helsinki”.
Measurements

Demographic and clinical characteristics

At baseline, patients’ sex, age, disease complexity, and functional status were measured. Both sex and age were assessed by self-report. The type of congenital heart defect was extracted from the CONCOR database and categorized into simple, moderate and complex defects according to Warnes and colleagues.\textsuperscript{18} Patients’ functional status was operationalized according to the New York Heart Association (NYHA) classification and assessed by a patient-based question.\textsuperscript{19}

Psychological characteristics

At baseline, the presence of a Type D personality, QoL, negative (i.e. depressive symptoms and trait-anxiety) and positive emotions (i.e. happiness and optimism), and patients’ illness perceptions were assessed by standardized well validated questionnaires (see Table 1).\textsuperscript{20-27} The DS14, measuring the presence of a Type D personality, is coded as a dichotomous variable, either having a Type D personality or not. Patients with a Type D personality have a high tendency to experience negative affect and to be socially inhibited. For the other questionnaires, higher scores indicate a better QoL, more depressive symptoms, a stronger tendency to be anxious, more happiness, a stronger tendency to be optimistic and stronger perceptions about their illness.

Health care use

Two years after the baseline assessment, a study-specific questionnaire (see Schoormans and colleagues for a detailed description\textsuperscript{11}) was administered to assess clinical and psychological health care use during the last year for CHD-related reasons. \textit{Clinical health care} yields three types; primary and cardiac outpatient health care, additional medical outpatient health care, and inpatient health care. For \textit{primary and cardiac outpatient health care} the number of contacts with the cardiologist (one item) and general practitioner (one item) were assessed. \textit{Additional medical outpatient health care} (nine items) was operationalized as the number of contacts with nine health care providers (e.g. rheumatologist, internist, and nurse). Three questions asking how often patients were hospitalized, visited the emergency room, or were operated upon in relation to their CHD, formed \textit{inpatient health care use}. Finally, \textit{psychological health care} was operationalized by two items assessing the number of contacts with a psychologist and social worker.

Statistical analyses

First, to identify the amount of primary and cardiac outpatient, additional medical outpatient, inpatient and psychological health care use we calculated the frequency and percentages for all items.

Second, we examined the extent to which psychological characteristics were predictive of the different types of health care use at two-year follow-up, while controlling for demographic and clinical characteristics, and type of center (regional versus tertiary referral). Four generalized linear models with negative binominal log link function were run separately for the different types of health care use (primary and cardiac outpatient health care, additional medical outpatient health care, inpatient health care and psychological health care). Sex, age, disease complexity, functional
status, type of center, Type D personality, the four QoL scales, depressive symptoms, trait-anxiety, happiness, optimism, and the six illness perception scales were simultaneously included in the analyses.

Table 1: *Questionnaires used to measure the psychological characteristics*

<table>
<thead>
<tr>
<th>Psychological characteristics</th>
<th>Questionnaire</th>
<th>Scales/Items</th>
</tr>
</thead>
</table>
| Type D personality, *is the tendency to experience negative affect and be socially inhibited* | DS-14<sup>20</sup> | − Negative affect (7 items)  
− Social inhibition (7 items)  
A patient with a score of 10 or more on both scales has a Type D personality |
| Quality of life                                                   | Short Form Health Survey-36 (SF-36)<sup>21</sup> | − Mental component scale (MCS)  
− Physical component scale (PCS)  
Total of 36 items |
| Quality of life                                                   | TNO/AZL Adult Quality Of Life-CHD (TAAQOL-CHD)<sup>22</sup> | − Symptoms (9 items)  
− Worries (10 items)  
− Impact Cardiac Surveillance (7 items) |
| Depressive symptoms                                              | Depression subscale of the Hospital Anxiety and Depression Scale (HADS)<sup>23</sup> | 7 items |
| Trait-Anxiety, *the tendency to be anxious*                       | Trait-subscale of the State Trait Anxiety Inventory (STAI)<sup>24</sup> | 20 items |
| Happiness                                                         | Subjective Happiness Scale (SHS)<sup>25</sup> | 4 items |
| Optimism, *the tendency to be optimistic*                         | Life Orientation Test (LOT)<sup>26</sup> | 8 items |
| Illness perceptions, *how patients perceive their illness*        | The six illness representation scales of the Illness Perception Questionnaire-Revised form (IPQ-R),<sup>27</sup> which was adapted to CHD-patients | − Consequences (5 items) *the impact on patients’ lives*  
− Personal control (6 items) *self-management*  
− Treatment control (3 items) *management by treatment*  
− Illness coherence (4 items) *patients’ understanding*  
− Timeline-cycle (3 items) *changeability of the illness*  
− Emotional representation (5 items) *experienced negative feelings* |

Exploratory analyses showed that there was no multicollinearity among the predictors (data not shown). The Impact subscale of the TAAQOL-CHD was not included, because items overlap with the health care use items. Heterogeneity in our sample was corrected using robust standard errors.
RESULTS
Response rate and demographic and clinical characteristics
At baseline 1670 eligible patients were invited to participate. A total of 1109 patients filled out the first questionnaire (response rate 66.4%). Two years later the follow-up questionnaire was sent to these respondents (n=1100, nine patients died during the follow-up period). Of the 1100 eligible patients, 845 patients returned the second questionnaire (response rate 76.8%).
More than half of the 845 patients were female (Table 2). Median age was 39 years. Almost 60% of patients were diagnosed with a simple malformation, and 71.2% had a NYHA-I classification. Ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA) (together 36.3%), were the most common diagnoses (Table 2), which is in concordance with the distribution of diagnoses of the CONCOR database. Non-respondents were not significantly different in terms of type of congenital heart defect and disease complexity (data not shown).

Table 2: Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Total (n=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>457 (54.7)</td>
</tr>
<tr>
<td>Age in median years (range)</td>
<td>39 (18-85)</td>
</tr>
<tr>
<td>Disease complexity</td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>502 (59.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>270 (32.0)</td>
</tr>
<tr>
<td>Complex</td>
<td>72 (8.5)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
</tr>
<tr>
<td>NYHA-I</td>
<td>591 (71.2)</td>
</tr>
<tr>
<td>NYHA-II</td>
<td>175 (21.1)</td>
</tr>
<tr>
<td>NYHA-III/IV</td>
<td>64 (7.7)</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td></td>
</tr>
<tr>
<td>VSD / ASD / ASD-I / PDA</td>
<td>306 (36.3)</td>
</tr>
<tr>
<td>TOF / PS</td>
<td>162 (19.2)</td>
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<tr>
<td>BAV / AS / SubvAS</td>
<td>121 (14.3)</td>
</tr>
<tr>
<td>CoA</td>
<td>106 (12.6)</td>
</tr>
<tr>
<td>TGA / ccTGA</td>
<td>28 (3.3)</td>
</tr>
<tr>
<td>Other CHD-diagnoses</td>
<td>121 (14.3)</td>
</tr>
</tbody>
</table>

Note: The total sample size ranges from 830 to 845 due to missing values. Numbers are given in frequencies (valid percentages), age in mean years (standard deviation). NYHA = New York Heart Association functional class; VSD = Ventricular Septum Defect; ASD = Atrial Septum Defect; ASD-I = Atrial Septum Defect primum; PDA = Patent Ductus Arteriosus; TOF = Tetralogy of Fallot; PS = Pulmonary Stenosis; BAV = Bicuspid Aortic Valve; AS = Aortic Stenosis; SubvAS = Subvalvar Aorta Stenosis; CoA = Coarctation of the Aorta; TGA = Transposition of the Great Arteries; ccTGA = Congenital corrected Transposition of the Great Arteries; CHD = Congenital heart defect.
Amount of health care use

Little over two-thirds of patients (n=574) reported to have had contact with their cardiologist during the previous year. Nearly 30% of patients (n=247) reported to have had more than one contact (Table 3). Almost 40% of patients (n=324) reported to have had contact with their general practitioner regarding their CHD. Patients reported to have had less contact with additional medical health care providers, ranging from 1.8% for a rheumatologist to 12.4% for a nurse. Little over 10% reported to have been hospitalized (n=87), whereas 10.5% (n=89) had visited the emergency room, and 9.2% (n=78) reported that they were operated upon. Less than 5% reported to have had contact with a psychologist and 2.7% with a social worker.

Table 3: Health care use

<table>
<thead>
<tr>
<th>NUMBER OF CONTACTS</th>
<th>None</th>
<th>Once</th>
<th>More than once</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical health care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary and cardiac outpatient health care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiologist</td>
<td>270 (32.0)</td>
<td>327 (38.7)</td>
<td>247 (29.3)</td>
</tr>
<tr>
<td>General practitioner</td>
<td>518 (61.5)</td>
<td>159 (18.9)</td>
<td>165 (19.6)</td>
</tr>
<tr>
<td>Additional medical outpatient health care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internist</td>
<td>751 (91.3)</td>
<td>46 (5.6)</td>
<td>26 (3.2)</td>
</tr>
<tr>
<td>Nurse</td>
<td>721 (87.6)</td>
<td>42 (5.1)</td>
<td>60 (7.3)</td>
</tr>
<tr>
<td>Pulmonologist</td>
<td>759 (92.4)</td>
<td>36 (4.4)</td>
<td>26 (3.2)</td>
</tr>
<tr>
<td>Genetic counselor</td>
<td>800 (98.3)</td>
<td>9 (1.1)</td>
<td>5 (0.6)</td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>804 (98.3)</td>
<td>7 (0.9)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Surgeon</td>
<td>761 (93.1)</td>
<td>31 (3.8)</td>
<td>25 (3.1)</td>
</tr>
<tr>
<td>Gynecologist</td>
<td>778 (95.3)</td>
<td>22 (2.7)</td>
<td>16 (1.9)</td>
</tr>
<tr>
<td>Pacemaker specialist</td>
<td>728 (88.8)</td>
<td>21 (2.6)</td>
<td>71 (8.7)</td>
</tr>
<tr>
<td>Thrombosis specialist</td>
<td>741 (90.0)</td>
<td>20 (2.4)</td>
<td>62 (7.5)</td>
</tr>
<tr>
<td>Inpatient health care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>758 (89.7)</td>
<td>57 (6.7)</td>
<td>30 (3.6)</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>754 (89.4)</td>
<td>55 (6.5)</td>
<td>34 (4.0)</td>
</tr>
<tr>
<td>Operations</td>
<td>765 (90.7)</td>
<td>61 (7.2)</td>
<td>17 (2.0)</td>
</tr>
<tr>
<td>Psychological health care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychologist</td>
<td>781 (95.5)</td>
<td>8 (1.0)</td>
<td>29 (3.5)</td>
</tr>
<tr>
<td>Social worker</td>
<td>795 (97.3)</td>
<td>4 (0.5)</td>
<td>18 (2.2)</td>
</tr>
</tbody>
</table>

Note: The total sample size ranges from 814 to 844 due to missing values. Amount of health care use per item was categorized according to no contact, one contact, and more than one contact (similar for hospitalization, emergency room visit, and operation). All numbers are given in frequencies (percentages). A time frame of 1 year was used.
Predictors of health care use at two-year follow-up

Demographic and clinical characteristics were independently predictive of health care use two years later (Table 4). More specifically, females reported more additional medical outpatient health care use \((adjusted \ OR=1.70, \ 95\% \ CI=1.17-2.48)\), and older patients reported less psychological health care use \((adjusted \ OR=0.93, \ 95\% \ CI=0.90-0.97)\). The complexity of the defect was independently predictive of additional medical outpatient, inpatient, and psychological health care use (see Table 4 for the specific contrasts). Finally, patients with a poorer functional status (NYHA-II and NYHA-III/IV respectively) reported more primary and cardiac outpatient \((adjusted \ OR=1.45, \ 95\% \ CI=1.02-2.06)\) and inpatient health care use \((adjusted \ OR=5.39, \ 95\% \ CI=1.85-15.73)\).

In addition, patients who were being treated in a regional center reported more inpatient \((adjusted \ OR=2.42, \ 95\% \ CI=1.35-4.36)\) and psychological health care use at follow-up \((adjusted \ OR=6.18, \ 95\% \ CI=2.53-15.08)\).

Type D personality and quality of life

Patients with a Type D personality reported less inpatient \((adjusted \ OR=0.34, \ 95\% \ CI=0.15-0.76)\) and psychological health care use \((adjusted \ OR=0.21, \ 95\% \ CI=0.06-0.81)\) than patients without a Type D personality. A poor QoL was independently predictive of more future clinical health care use (see Table 4 for the specific significant relations).

Negative and positive emotions

High trait-anxiety was predictive of increased psychological health care use two years later \((adjusted \ OR=1.10, \ 95\% \ CI=1.01-1.19)\). Depressive symptoms, happiness and optimism were not related to health care use in the multivariable analyses.

Illness perceptions

Illness perceptions were independently predictive of health care use at two-year follow-up. In more detail, patients who felt their CHD had a severe impact on their life, reported more primary and cardiac outpatient \((adjusted \ OR=1.06, \ 95\% \ CI=1.03-1.09)\), additional medical outpatient \((adjusted \ OR=1.11 \ 95\% \ CI=1.05-1.17)\), and psychological health care use \((adjusted \ OR=1.30, \ 95\% \ CI=1.14-1.48)\). Patients who believed that their CHD could be managed by themselves reported more additional medical outpatient \((adjusted \ OR=1.09, \ 95\% \ CI=1.03-1.16)\) and less inpatient health care use \((adjusted \ OR=0.91, \ 95\% \ CI=0.84-0.97)\). Patients who believed that their CHD could be managed by treatment reported more inpatient health care use \((adjusted \ OR=1.15, \ 95\% \ CI=1.04-1.28)\).
Table 4: Predictors of health care use at two-year follow-up

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>CLINICAL HEALTH CARE</th>
<th>PSYCHOLOGICAL HEALTH CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>1.12(0.91-1.37)</td>
<td>1.36(0.60-3.10)</td>
</tr>
<tr>
<td>Age</td>
<td>1.00(0.99-1.01)</td>
<td>0.93(0.90-0.97)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease complexity°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.12(0.91-1.39)</td>
<td>0.64(0.26-1.55)</td>
</tr>
<tr>
<td>Complex</td>
<td>1.38(1.00-1.92)</td>
<td>0.22(0.06-0.84)</td>
</tr>
<tr>
<td>Functional status†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>1.45(1.02-2.06)</td>
<td>0.54(0.20-1.48)</td>
</tr>
<tr>
<td>NYHA-III/IV</td>
<td>1.39(0.87-2.22)</td>
<td>0.34(0.09-1.34)</td>
</tr>
<tr>
<td>Regional center§</td>
<td>0.95(0.74-1.22)</td>
<td>6.18(2.53-15.08)</td>
</tr>
<tr>
<td>Psychological characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type D personality‡</td>
<td>0.82(0.61-1.11)</td>
<td>0.21(0.06-0.81)</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>1.00(0.99-1.02)</td>
<td>0.95(0.91-1.00)</td>
</tr>
<tr>
<td>MCS</td>
<td>1.00(0.99-1.02)</td>
<td>0.96(0.91-1.01)</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.98(0.97-0.99)</td>
<td>1.00(0.96-1.04)</td>
</tr>
<tr>
<td>Worries</td>
<td>0.98(0.97-1.02)</td>
<td>1.02(0.98-1.06)</td>
</tr>
</tbody>
</table>
Table 4: Predictors of health care use at two-year follow-up (continued)

<table>
<thead>
<tr>
<th></th>
<th>CLINICAL HEALTH CARE</th>
<th></th>
<th>PSYCHOLOGICAL HEALTH CARE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Primary and cardiac outpatient health care (n=803)</strong></td>
<td><strong>Additional medical outpatient health care (n= 773)</strong></td>
<td><strong>Inpatient health care (n=803)</strong></td>
</tr>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>p</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td><strong>Negative and positive emotions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>1.00 (0.95-1.05)</td>
<td>0.92</td>
<td>0.99 (0.86-1.13)</td>
</tr>
<tr>
<td>Trait-anxiety</td>
<td>1.00 (0.98-1.02)</td>
<td>0.92</td>
<td>0.99 (0.96-1.02)</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.09 (0.90-1.32)</td>
<td>0.38</td>
<td>1.07 (0.76-1.52)</td>
</tr>
<tr>
<td>Optimism</td>
<td>0.99 (0.95-1.03)</td>
<td>0.52</td>
<td>0.94 (0.86-1.02)</td>
</tr>
<tr>
<td><strong>Illness perceptions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>1.06 (1.03-1.09)</td>
<td>&lt;0.01**</td>
<td>1.11 (1.05-1.17)</td>
</tr>
<tr>
<td>Personal control</td>
<td>1.00 (0.98-1.03)</td>
<td>0.76</td>
<td>1.09 (1.03-1.16)</td>
</tr>
<tr>
<td>Treatment control</td>
<td>1.02 (0.98-1.06)</td>
<td>0.27</td>
<td>0.95 (0.86-1.04)</td>
</tr>
<tr>
<td>Illness coherence</td>
<td>1.01 (0.98-1.05)</td>
<td>0.43</td>
<td>0.99 (0.93-1.06)</td>
</tr>
<tr>
<td>Timeline – cycle</td>
<td>1.02 (0.97-1.07)</td>
<td>0.43</td>
<td>0.94 (0.87-1.02)</td>
</tr>
<tr>
<td>Emotional representation</td>
<td>1.01 (0.98-1.04)</td>
<td>0.56</td>
<td>0.98 (0.93-1.04)</td>
</tr>
</tbody>
</table>

Note: Primary and cardiac outpatient health care = the number of contacts with a cardiologist and general practitioner; additional medical outpatient health care = the number of contacts with an internist, nurse, pulmonologist, generic counselor, rheumatologist, surgeon, gynecologist, physical therapist, dietician, pacemaker specialist, thrombosis specialist, and home care aid; inpatient health care use = the number of hospitalizations, emergency room visits and operations; psychological health care = the number of contacts with a psychologist and social worker; NYHA = New York Heart Association functional class; * = reference category is simple; † = reference category is NYHA-I; § = reference category is tertiary referral center; ‡ = reference category is a non-Type D personality; Consequences = the impact on patients’ lives; Personal control = self-management; Treatment control = management by treatment; Illness coherence = patients’ understanding; Timeline-cycle = changeability of the illness; Emotional representation = experienced negative feelings; adjusted OR = adjusted odds ratio; 95%CI = 95% confidence interval; p = p-value; * p < 0.05, ** p < 0.01.
DISCUSSION

To our knowledge, this is the first longitudinal study on predictors of future health care use in adults with CHD. Our main result is that health care use is not entirely determined by the complexity of the cardiac defect or functional status, but also for a large part by psychological characteristics. That is, patients without a Type D personality, who have a poor QoL, a strong belief that their CHD has a severe impact on their life, and who believe their CHD can be managed by themselves or treatment, reported more health care use.

More specifically, patients with a Type D personality reported less health care use two years later than patients without such a personality, irrespective of disease complexity and functional status. This is in agreement with the results of our previous cross-sectional study which is part of this larger research project. Our finding is supported by a vast amount of literature indicating that negative emotions are related to a poor prognosis and unhealthy behaviors. Moreover, social inhibition may prevent patients from contacting a health care provider, because they feel insecure and less competent in communicating.

Furthermore, patients with a poor QoL reported more clinical health care use independent of their disease complexity or functional status. This indicates that psychosocial care may be more appropriate for these patients. Nurse practitioners, social workers or psychologists could focus on improving patients’ QoL, which may decrease future clinical health care use. Results show that neither depressive or anxious feelings nor feelings of happiness or the tendency to be optimistic are predictive of clinical health care use. As these emotions partially determine patients’ QoL they may have an indirect impact on their health care use. In addition, patients who feel anxious report more psychological health care use at follow-up. Experimental studies have demonstrated that anxious CHD-patients perceive more cardiac symptoms than non-anxious patients. This patient group may indeed benefit from psychological counseling to reduce their anxiety.

The finding that patients’ illness perceptions were independently predictive of future health care use is consistent with previous studies in a range of chronically ill patients. More specifically, patients who felt that their CHD had a severe impact on their daily life reported more health care use. This relation was independent of disease complexity and functional status. Thus the way patients perceive their CHD and its symptoms is vital for seeking medical help. Moreover, patients’ perception about how their CHD can be managed was also predictive of health care use. In detail, patients who believed that they could manage their CHD themselves reported more additional medical outpatient and less inpatient health care use. It is likely that these patients have a problem-focused coping style and show adequate self-care management, which is probably contributing to more additional medical outpatient health care use. This in turn, may be preventive for using the more costly and possibly invasive inpatient health care. Patients who believed their CHD could be managed by treatment reported more inpatient health care use.

Interestingly, patients who were treated in a regional center reported significantly more inpatient and psychological health care use, independent of demographic, clinical and psychological
characteristics. This is a finding somewhat difficult to explain. It could be related to differences in local organization of health care.

This study has a number of strengths we would like to emphasize. First, 845 patients from eight different centers were included. That is 6.5% of all registered patients in the national database and around 2.5% of the estimated total adult CHD-population in the Netherlands. Thus, a broad spectrum of Dutch adult CHD-patients represents our sample. Second, we studied various types of health care use representing the recommended multidisciplinary care structure. Third, this is the first study in CHD-patients where in addition to demographic and clinical characteristics, psychological characteristics such as QoL and depressive symptoms were included as predictors of future health care use. Fourth, we are the first to employ a longitudinal design in studying the relation between patient characteristics and health care use of adult CHD-patients allowing firmer explanations and the prediction of health care use.

**Study limitations**

The limitations of this study merit attention. First, results might be influenced by patients’ recall bias; the involuntary or voluntary over- or underreporting of health care use. Second, other factors not measured, such as organizational aspects of treatment centers or other parameters of patients’ physical functioning (e.g. cardiac lesions) may also be related to health care use. Nonetheless, information on patients’ disease complexity and functional status was available. Third, this study was conducted in a country with a compulsory insurance health care system. Caution is therefore warranted to extrapolate these results to countries using other insurance and/or health care systems.

**CONCLUSIONS**

Health care use is not entirely determined by disease complexity and functional status but also for a large part by psychological patient characteristics. This indicates that physicians should not only focus on medical care, but they should also be aware that patients may need to be referred to psychosocial health care providers. Nurse practitioners, social workers, or psychologists could then focus on improving patients’ QoL, reducing the negative impact of the CHD, and teaching patients self-management skills. For example, cognitive behavioral therapy to alter (wrong) perceptions can be helpful in improving patients’ QoL and reducing the negative impact. Moreover, nurse practitioners can teach patients coping skills and increase their knowledge about symptoms that warrant contact with a physician. This will probably lead to more timely medical health care use, preventing patients to use more costly inpatient health care. Concluding, providing psychosocial care when needed is not only more appropriate but also more effective and less expensive than medical care.
REFERENCES


Chapter 6

Peri-operative care in adults with congenital heart disease: Room for improvement in after care

Cardiology in the Young, 2012

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ABSTRACT

Background Patient satisfaction with care has received little attention within the field of congenital heart disease (CHD). Our objective was to examine patient satisfaction with the care received when undergoing open-heart surgery in order to identify best and worst aspects of peri-operative care. Moreover, we examined whether having contact with a specialized nurse in addition to usual care is associated with higher patient satisfaction levels.

Methods Patient satisfaction was measured by the Satisfaction with Hospital Care Questionnaire, evaluating nine aspects of care by answering individual items and giving overall grades. A top-10 of best and worst items was selected. Linear regression analyses were used to examine the relation between having contact with a specialized nurse and patient satisfaction (nine grades), independent of patient characteristics (sex, age, educational level, and health status).

Results Data were available for 75 patients. Grades ranged from 6.74 for “discharge and after care” to 8.18 “medical care”. In all, 21% of patients were dissatisfied with the clarity of the information about lifestyle adjustments given by the surgeon. However, patients who had contact with a specialized nurse were more satisfied with the provided information ($B=0.497$, $p=0.038$) independent of patient characteristics.

Conclusions Patients were satisfied with the received care, although there is room for improvement, especially in discharge and after care and the clarity of the information provided by the surgeon. This gap in care can be compensated for by specialized nurses, as patients who were counseled by a specialized nurse were more satisfied with the provided information.
INTRODUCTION

There is increasing awareness of the importance of patient-reported outcomes within the field of congenital cardiology. Although patient-reported outcomes such as quality of life and psychological functioning of patients with CHD have been extensively studied, various other patient-reported outcomes (e.g. patient satisfaction with care) have received little attention. Patient satisfaction is defined as “the individuals’ positive evaluations of distinct dimensions of health care” (p. 580). To our knowledge, only one study researched patients’ satisfaction levels regarding the received care concerning their CHD. In addition, three other studies have been published on closely related patient-reported outcomes. Two studies focused on patients’ experiences with the transfer from pediatric to adult cardiology. The third study examined patients’ perception of the expertise and communication skills of the general practitioner and cardiologist, and patients’ perception of the need for health care improvements. Studying patients’ satisfaction with care is of utmost importance as this information provides insight into the impact of treatment and the quality of the provided care, which can ultimately direct the future organization of care.

Thanks to the improvements in cardiac surgery over the past decades, today more than 90% of patients with a CHD reach adulthood. Many patients require re-operations, as most adult patients have residual lesions that negatively affect daily life. The number of adult patients undergoing re-operation varies with type of cardiac defect, ranging from less than 1% for simple defects such as an atrial septal defect to more than 14% for a transposition of the great arteries. Undergoing open-heart surgery has a high impact; patients are likely to experience stress, feelings of fear, anxiety, uncertainty, loss of control and other emotional problems. Several studies have demonstrated that such feelings of psychological distress have negative effects on recovery. Specialized nurses can have a vital function for patients undergoing open-heart surgery, informing them about the procedure, lifestyle adjustments after surgery, and the recovery trajectory.

Given the complex character and the high impact of open-heart surgery, high quality of care is of paramount importance. To the best of our knowledge, patients’ level of satisfaction with the care provided when undergoing open-heart surgery has never been studied within the field of CHD. Moreover, the relationship between counseling by a specialized nurse and patient satisfaction levels has also never been examined. The objective of this study was to evaluate the care as it is provided in daily clinical practice. Hence, we did not intervene in the peri-operative care processes. Our aims were therefore (1) to examine patient satisfaction levels in order to identify the best and worst evaluated aspects of the currently provided care for patients with CHD undergoing open-heart surgery, and (2) to examine whether the involvement of specialized nurses is associated with higher levels of patient satisfaction.

MATERIALS AND METHODS

Study population and procedure

Patients who were diagnosed with a CHD, 18 years or older, mentally not impaired, literate in Dutch and undergoing open-heart surgery were eligible. All surgeries were performed in a tertiary
hospital located in an urban European city. Between January, 2010 and July, 2011, 132 consecutive eligible patients were invited three to six weeks after their operation to participate in this study. All patients completed a questionnaire at home and returned it via a pre-stamped envelope. Under Dutch law ethical approval is not required for questionnaire studies. Therefore, this study was exempt from approval of the Medical Ethics Committee of the Academic Medical Center in Amsterdam, the Netherlands. This study was conducted in accordance with the principles of the “Declaration of Helsinki”.23

Measurements

Patient characteristics

Patients’ sex, age, and educational level were measured through self-report. Health status was assessed by the first item of the Short Form Health Survey-36: “In general would you say your health is?”.24 Answers were given on a 5-point Likert scale with the options; “excellent”, “very good”, “good”, “fair”, and “poor”. Patients’ diagnoses were obtained from their medical record.

Patient satisfaction levels

Patient satisfaction levels were measured by the Satisfaction with Hospital Care Questionnaire25 consisting of 12 scales addressing different aspects of care – that is, Admission procedure, Nursing care, Medical care, Other disciplines, Information, Patient autonomy, Emotional support, Hotel care, Recreation facilities, Miscellaneous aspects, Ease of access to the hospital, and Discharge and aftercare. Each scale consists of several questions (ranging from two to seven) employing a 5-point Likert scale; “unsatisfied”, “moderately satisfied”, “reasonably satisfied”, “clearly satisfied” and “highly satisfied”, with the added option “not applicable”. Moreover, patients gave overall grades for each scale ranging from zero to ten, with ten indicating the highest level of satisfaction. The Satisfaction with Hospital Care Questionnaire was adapted for this study to lower patient-burden. The questions of the scales “other disciplines” and “patient autonomy” were incorporated into the scales “medical care” and “nursing care” respectively. The questions in the “medical care” scale were targeted at open-heart surgery. For example questions about “the medical specialist” were reformulated into “surgeon”. Based on a study by Kleefstra et al26 examining the structure of the Satisfaction with Hospital Care Questionnaire, the “emotional support” scale was excluded. The Satisfaction with Hospital Care Questionnaire has good psychometric properties and is found to be a valid and reliable instrument.27 The adapted questionnaire thus yields nine scales, assessing patient-satisfaction levels with nine different aspects of care and consists of 57 questions in total. In addition, as a general measure of patient satisfaction, we asked patients (a) to rate the overall experienced care by giving a grade, ranging from one to ten, and (b) whether they would recommend this hospital to others.

Contact with a specialized nurse

Although a uniform definition of a specialized nurse is lacking, Moons et al28 described that nurses are specialized if they have a certain level of specialization in the field of CHD, obtained
by education and experience. Specialized nurses provide important support for patients with a CHD, identifying their needs, screening for psychosocial problems, and educating and counseling patients.\textsuperscript{21,22,29} With regard to having open-heart surgery specialized nurses inform patients about the procedure, lifestyle adjustments after surgery, and the recovery trajectory.

Within the Academic Medical Centre, patients with a CHD are referred to a specialized nurse by their treating cardiologist if they experience psychosocial problems, or have lifestyle issues that need to be addressed – for example, high glucose levels in patients with diabetes. Hence, whether patients were counseled by a specialized nurse was based on the clinical assessment of their treating cardiologist.

Patients answered the following question to assess whether they had contact with a specialized nurse. “Did you have contact with a specialized nurse prior or during your admission in the hospital?” An additional question assessed patients’ satisfaction with the care provided by the specialized nurse, and was rated on a 5-point Likert scale ranging from “unsatisfied” to “highly satisfied”.

Statistical analyses
Patient characteristics were explored by means of descriptive statistics. Characteristics of patients with and without contact with a specialized nurse were compared by means of chi-squared tests for categorical variables and a t-test for the continuous variable age.

Grades for each scale were provided for the total group of patients and specified by contact with a specialized nurse (yes/no). Additionally, the ten items with the best (highest percentage of patients who answered “clearly satisfied” or “highly satisfied”) and worst scores (highest percentage of patients who answered “unsatisfied” or “moderately satisfied”) were provided. Moreover, as a general indicator of patients’ satisfaction, the mean grade for the overall received care and the percentage of patients that would recommend this hospital to others were calculated. Finally, the relationship between contact with a specialized nurse and the level of satisfaction with the nine different aspects of care (the grades for each scale), independent of patient characteristics (sex, age, educational level, and health status), was examined by multivariable linear regression analyses using general linear model. Patients’ diagnosis was not included in the analyses due to the small number of patients within each category. Exploring analyses showed that patients’ diagnosis was unrelated to patients’ level of satisfaction (the grades for all nine scales). All analyses were conducted in SPSS 16.0 and tested at a significance level of 5%.

RESULTS
Of the 132 eligible patients, 75 participated in this study (response rate 56.8%). Of the included 75 patients, 44% (33 patients) indicated to have had contact with a specialized nurse prior or during hospital admission. Patient characteristics for the total group and specified by contact with a specialized nurse are presented in Table 1. Patient characteristics of patients who had contact
with a specialized nurse were not statistically different from patients who did not have contact with a specialized nurse.

Table 1: *Patient characteristics for the total group of patients and specified for the patients with and without contact with a specialized nurse*

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total group (n=75)</th>
<th>Contact with specialized nurse (n=33)</th>
<th>No contact with specialized nurse (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>45 (60.0)</td>
<td>19 (57.6)</td>
<td>26 (61.9)</td>
</tr>
<tr>
<td>Age (mean years; standard deviation)</td>
<td>41 (12.7)</td>
<td>38 (12.1)</td>
<td>40 (12.0)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>9 (12.3)</td>
<td>5 (15.6)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Secondary school</td>
<td>33 (45.2)</td>
<td>16 (50.0)</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Higher education</td>
<td>31 (42.5)</td>
<td>11 (34.4)</td>
<td>20 (48.8)</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrioventricular Septal Defect</td>
<td>24 (32.0)</td>
<td>10 (30.3)</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>16 (21.3)</td>
<td>6 (18.2)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Tetralogy of Fallot/ Pulmonary Stenosis</td>
<td>15 (20.0)</td>
<td>7 (21.2)</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>Bicuspid Aortic Valve/ (Subvalvar) Aorta stenosis</td>
<td>8 (10.7)</td>
<td>4 (12.1)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>(Congenitally corrected) Transposition of the Great Arteries</td>
<td>3 (4.0)</td>
<td>3 (9.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Coarctation of the Aorta</td>
<td>1 (1.3)</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
</tr>
<tr>
<td>Other congenital heart defects</td>
<td>8 (10.7)</td>
<td>3 (9.1)</td>
<td>5 (11.9)</td>
</tr>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>7 (9.5)</td>
<td>4 (12.5)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>More than well</td>
<td>18 (24.3)</td>
<td>8 (25.0)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Well</td>
<td>32 (43.2)</td>
<td>14 (43.8)</td>
<td>18 (42.9)</td>
</tr>
<tr>
<td>Reasonable</td>
<td>14 (18.9)</td>
<td>5 (15.6)</td>
<td>9 (21.4)</td>
</tr>
<tr>
<td>Bad</td>
<td>2 (2.7)</td>
<td>0 (0)</td>
<td>2 (4.8)</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean (standard deviation) or number (percentages).

**Patient satisfaction levels**

Grades for the nine scales are shown in Figure 1. All grades were higher than six. Patients were most satisfied with “medical care” (mean grade is 8.18), and least satisfied with “discharge and after care” (mean grade is 6.74).
Figure 1: Grades on each scale for the total group and specified by patients with and without contact with a specialized nurse

![Graph showing grades on each scale for the total group and specified by patients with and without contact with a specialized nurse.]

Note: *Having contact with a specialized nurse is significantly related to patient satisfaction level, independent of patient characteristics.

More specifically, a top-10 of best and worst valued aspects of care is given in Table 2a and b respectively. Most patients were satisfied with aspects of care directly related to their operation (for example, “The expertise of the surgeon” [93.0%], and “The consultation with the surgeon prior to the surgery” [87.5%]). Patients were most dissatisfied with aspects of “hotel care” (for example, “The hospital meals” [36.0%]) and aspects related to “information” (for example, “The clarity of information about lifestyle adjustments after surgery given by the surgeon” [21.2%]) and “discharge and after care” (for example, “The care provided by the surgeon after surgery” [20.0%]). Notably, 25 patients (33.8%) did not have an exit interview with the surgeon. Of the 49 patients who did have an exit interview with the surgeon, five patients (10.2%) were dissatisfied. Patients rated the received overall care a 7.61, and 84% of patients would recommend this hospital to others, indicating a high general level of satisfaction.

**Contact with a specialized nurse**

Figure 1 shows the grades on the nine scales, specified for the 33 patients with and the 42 patients without contact with a specialized nurse. Descriptive analysis – frequencies and percentages – showed that 80% of the patients who had seen a specialized nurse were satisfied with the care provided by him/her.

Patients who had contact with a specialized nurse were more satisfied with the received information (mean grade is 7.84) than patients who had no contact with a specialized nurse (mean grade is 7.31), independent of patient characteristics ($B=0.497, p=0.038, \text{partial } \eta^2=0.071$). In addition, older patients reported higher grades, reflecting a higher level of satisfaction with the provided care.
Table 2a: Top-10 of the best valued aspects of care by the total group of patients

<table>
<thead>
<tr>
<th>Aspect of care</th>
<th>Percentage satisfied or highly satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The expertise of the surgeon</td>
<td>93.0%</td>
</tr>
<tr>
<td>2. The consultation with the surgeon prior to the operation</td>
<td>87.5%</td>
</tr>
<tr>
<td>3. The clarity of the information given by the surgeon</td>
<td>86.3%</td>
</tr>
<tr>
<td>4. The proceedings in the operating room</td>
<td>86.2%</td>
</tr>
<tr>
<td>5. The clarity of the provided written information</td>
<td>85.1%</td>
</tr>
<tr>
<td>6. The way the anesthesiologist was treating you</td>
<td>83.9%</td>
</tr>
<tr>
<td>7. The way the surgeon was treating you</td>
<td>82.6%</td>
</tr>
<tr>
<td>8. The atmosphere on the ward</td>
<td>82.4%</td>
</tr>
<tr>
<td>9. The facilities at your bedside (e.g. television)</td>
<td>80.0%</td>
</tr>
<tr>
<td>10. The expertise of the nursing staff</td>
<td>79.2%</td>
</tr>
</tbody>
</table>

Table 2b: Top-10 of the worst valued aspects of care by the total group of patients

<table>
<thead>
<tr>
<th>Aspect of care</th>
<th>Percentage satisfied or highly satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The hospital meals</td>
<td>36.0%</td>
</tr>
<tr>
<td>2. The temperature on the ward</td>
<td>30.7%</td>
</tr>
<tr>
<td>3. The hygiene and cleanliness</td>
<td>26.7%</td>
</tr>
<tr>
<td>4. The clarity of the information about lifestyle adjustments after surgery given by the surgeon</td>
<td>21.2%</td>
</tr>
<tr>
<td>5. The availability of plumbing</td>
<td>20.0%</td>
</tr>
<tr>
<td>6. The care provided by the surgeon after discharge from the hospital</td>
<td>20.0%</td>
</tr>
<tr>
<td>7. The clarity of the information about lifestyle adjustments after surgery given by the nurses</td>
<td>19.4%</td>
</tr>
<tr>
<td>8. The timing of your discharge from the hospital</td>
<td>18.7%</td>
</tr>
<tr>
<td>9. Consultation with the anesthesiologist</td>
<td>17.6%</td>
</tr>
<tr>
<td>10. The exit interview by the nurse</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

DISCUSSION

Overall, patients were satisfied with the provided care, with grades ranging from 6.74 for “discharge and after care” to 8.18 for “medical care”, as is the case in most satisfaction studies. The lowest grades were for “discharge and after care” indicating that there is room for improvement. More specifically, 20.0% of patients were dissatisfied with the after care provided by the surgeon, whereas 21.2% of patients were dissatisfied with the clarity of the information about lifestyle adjustments provided by the surgeon. Having contact with a specialized nurse is associated with a higher level of satisfaction with the provided information. Additionally, patient satisfaction levels were associated with higher age which is a common finding in satisfaction studies.
The following limitations merit attention. First, we have no information on non-respondents. It is for example fair to assume that extremely (dis)satisfied patients participated in this study. Second, this study focused solely on patient satisfaction. Additional information is needed to further identify aspects of care that need to be improved. For example, future studies should also address the relative importance that patients attach to certain aspects of care. Moreover, one can debate on whether the high satisfaction scores enable the identification of targets for improvement. Nevertheless, variation in the level of satisfaction with different aspects of care is detected, with grades ranging from 6.74 to 8.18. Third, this is a single center study; therefore, results can not be automatically extrapolated to other hospitals. Fourth, we evaluated current clinical practice; patients were thus not randomly assigned to one of two conditions (i.e. contact versus no contact with a specialized nurse). This implies a selection bias and may have affected the found association between having contact with a specialized nurse and patient satisfaction levels. Given that patients who were counseled by a specialized nurse, were referred by their treating cardiologist based on their complex situation – for example, having psychosocial problems – one would expect lower satisfaction levels for this group. Yet, patients who were counseled by the specialized nurse reported even higher satisfaction levels than the patients who were not referred. This suggests that if patients were randomly assigned to one of the two groups the association between having contact with a specialized nurse and patient satisfaction levels may be even higher. Finally, information about the frequency of visits to the specialized nurse is lacking. It can be hypothesized that patients’ satisfaction levels may be related to the number of contacts with a specialized nurse.

To our knowledge this is the first study that examined satisfaction levels of patients with CHD undergoing open-heart surgery. Moreover, we are the first to examine the association between having contact with a specialized nurse and patients’ satisfaction levels.

In conclusion, CHD-patients are satisfied with the provided care, although results indicate that there is room for improvement in the discharge and after care procedure. In addition, information provided by the surgeon may be improved, as on average 20% of patients were dissatisfied with the clarity of the information and the after care provided by their surgeon. This gap in the current care for CHD-patients undergoing open-heart surgery may be compensated for by specialized nurses. For example, informing patients on lifestyle issues can be easily performed by specialized nurses, likely resulting in increased satisfaction levels and quality of care. It is important to note however, that our results have to be replicated in a larger multi-center study.

ACKNOWLEDGEMENTS
We are very grateful to all patients. Moreover, we thank Mrs. A.Y. Schotanus for her help with the data collection.
REFERENCES

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PART II

Quality of Life
Chapter 7

New York Heart Association class assessment by cardiologists and outpatients with congenital heart disease: A head-to-head comparison of three patient-based versions

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Yuma L Mager
Frans J Oort
Mirjam AG Sprangers
Barbara JM Mulder
ABSTRACT

Background The objective of this study was to compare three patient-based New York Heart Association (NYHA) class assessments with cardiologist assessments in outpatients with congenital heart disease (CHD).

Methods Consecutive adult outpatients completed three questionnaires in a random order: a patient-based translation of the NYHA classes, a self-constructed questionnaire based on the NYHA classes, and the Specific Activity Scale (SAS). The treating cardiologist assessed the NYHA class on the same day. Patient-cardiologist agreement was assessed by calculating percent agreement and weighted kappa. We also explored the level of agreement for patients without co-morbidity.

Results In all, 86 adults with a median age of 35.8 years – including 46 women participated. An agreement of 75.6% (weighted kappa is 0.43; p<0.01), 70.6% (weighted kappa is 0.44; p<0.01), and 74.4% (weighted kappa is 0.28; p<0.01) was found between the cardiologist assessment and the patient-based translation, self-constructed questionnaire, and SAS respectively. The patient-based translation equally over- and underestimated the NYHA class, whereas the self-constructed questionnaire overestimated and the SAS underestimated the NYHA class. Agreement levels for patients without co-morbidity were higher than agreement levels for the total group.

Conclusion The patient-based translation yielded adequate agreement with cardiologist-assessed NYHA class, showed equal over- and underestimation, and was easy to complete. The patient-based translation with the instruction to only consider functional impairments caused by the CHD, is recommended in future studies of outpatients with CHD.
INTRODUCTION

The mean prevalence of congenital heart disease (CHD) at birth is 7.7 per 1000 live births.\(^1\) CHD is a generic term for malformations of the heart present at birth. Three of the most common malformations are (a) the narrowing of the aorta (aortic coarctation); (b) an opening in the wall dividing the left and right heart chambers (ventricular septum defect); and (c) an opening in the wall dividing the left and right atrium (atrial septum defect). In the Netherlands, approximately 1600 children with CHD are born each year.\(^2\) At least 85% of these patients reach adulthood owing to the successes of cardiac surgery.\(^2\) Even after corrective surgery, however, most patients have residual lesions with varying effects on daily functioning, for example exercise capacity and quality of life (QoL).\(^3,4\)

In daily clinical practice, many treating cardiologists assess the exercise capacity or functional status of patients with CHD following the four New York Heart Association (NYHA) classes (Table 1). These four classes were originally developed to help physicians evaluate the effect of cardiac symptoms on patients’ daily activities, but are also increasingly used to estimate patients’ functional status in clinical trials.\(^5\) The NYHA classification has been found to be clinically useful, as it is associated with survival and QoL.\(^2,6,7\)

In large scale medical research where patients cannot be seen by a physician at each time point, it is advantageous if functional status could be assessed by patients themselves. However, the usefulness of such patient-based NYHA class assessment critically depends on its agreement with the cardiologist-based score. Since the NYHA classification is a physician-based score, the cardiologist can be seen as the gold standard.

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

To our knowledge, only four studies explicitly compared patient-cardiologist assessed NYHA class.\(^8-11\) These studies included patients with heart failure. In these four studies, only Goode et al\(^9\) made a direct comparison between patient-assessment and physician-assessed NYHA class. The remaining three studies\(^8,10,11\) inferred the NYHA class from patient-reported functional class scales\(^8,10,11\) or a QoL questionnaire\(^11\). In these four studies different levels of agreement were found. Contrary to heart failure patients, CHD-patients are born with impairments. Therefore,
these patients may be more used to their limitations, which might result in a different perspective of their functional status. The objective of this study is to compare three patient-based NYHA class assessments with cardiologist-assessed NYHA class in outpatients with CHD to enable “best choice”.

MATERIALS AND METHODS

Study population and procedure
Consecutive patients, who attended one of four cardiologists of the congenital heart outpatient clinic of the Academic Medical Center from March to June, 2007, were asked to participate in this study. Patients who were not literate in Dutch were excluded.

Patients with various confirmed CHD completed three questionnaires assessing the NYHA class preceding their visit to the cardiologist. The treating cardiologist completed the NYHA class assessment on the same day as the patient-assessments and was blinded to the patients’ responses. Since no ethical approval is required for completion of the self-report questionnaires under Dutch law, the medical ethics committee exempted this study from ethical approval. This study is conducted in full accordance with the principles of the “Declaration of Helsinki” as amended in Tokyo, Venice, and Johannesburg.

Measures

Socio-demographic and clinical data
Sex, birth date, employment status and presence of co-morbidity – such as diabetes, renal diseases, hypertension, chronic obstructive pulmonary diseases, rheumatoid arthritis, chronic allergies, chronic back pain, limitation in the use of arm or leg, or “other illnesses” – were measured through self-report. Primary diagnosis was extracted from the CONCOR database, a nationwide registry for patients with CHD.\textsuperscript{12}

New York Heart Association class assessment

Patient-based translation
We directly translated the four classes into patient-based statements (see Appendix). Class II, for example, was formulated as “I am slightly limited in performing physical activities. I do not experience any symptoms at rest, but ordinary physical activities cause extraordinary fatigue, palpitation or dyspnea”. Patients were asked to choose the statement that was most applicable to him or her. The NYHA classes were directly derived from the answers.

Self-constructed questionnaire
The self-constructed questionnaire was devised with the help of four expert cardiologists and consisted of 11 questions concerning possible physical limitations as a result of the following cardiac symptoms: fatigue, dyspnea and palpitation. We queried the presence of each of the symptoms separately at three different levels of exertion: heavy (exemplified by running, doing
sports, biking with adverse wind, climbing a flight of 20 steps), ordinary (exemplified by climbing a flight of three steps, walking, dressing) and at rest or when performing the slightest exertion (exemplified by standing up, reading a book, talking). For example, “Do you experience palpitations during regular physical activities (walking, climbing three steps, showering, getting (un)dressed)?”. For all questions a “yes” or “no” response option was used. The final question assessed whether discomfort of possible symptoms at rest increased when any physical activity was undertaken.

Specific Activity Scale
The Specific Activity Scale (SAS) consists of five stem questions, of which three have a different number of sub questions (4-8), each addressing a different number of example activities (1-5). The SAS is based on the metabolic expenditure values of activities that a patient reports he or she can or cannot do, and classifies patients into one of the four functional classes. The SAS is available in the original article by Goldman et al. The SAS functional classification system is comparable to the NYHA classification system. The SAS was translated into Dutch. Minor cultural adaptations that left the structure intact and that did not affect the NYHA scoring included the deletion of four examples that are inapplicable to or too specific for Dutch adults (i.e., roller skating, hang washed clothes, bowl, and push power lawn mower); and the transformation of weight (pounds) and speed (miles) into the international system of unit (i.e., kilograms and kilometers).

Pilot, order and debriefing questions
Two pilot studies were conducted to test the appropriateness of the wording of the three questionnaires. Improvements were made to the questionnaires, wherever needed.

The order of the three questionnaires was counterbalanced to avoid order effects. Thus, there were six different sets of questionnaires, which were alternately administered to the participating patients.

After completing the three questionnaires, the patients were asked two additional debriefing questions: “In your opinion, which questionnaire describes your physical functioning best?” and “Which questionnaire did you find easiest to answer?”.

Cardiologist-assessed New York Heart Association class
The standard definition of the NYHA classification (Table 1) was used by the treating cardiologists to assess patients’ NYHA class following regular clinical guidelines.

Statistical analysis
For the patient-based translation of the NYHA class, the scores were mapped directly to a NYHA class. For the self-constructed questionnaire, the NYHA classes were calculated by following an algorithm designed after consulting an expert cardiologist and following clinical guidelines in assessing NYHA class. Patients were categorized as NYHA class I if they answered negatively to all questions, indicating that they were not at all physically limited. Patients who indicated to be physically limited at heavy exertion were rated as NYHA class II. Patients limited at ordinary
exertion were rated as NYHA class III. Patients were categorized in NYHA class IV, if they indicated to experience at least one of the three cardiac symptoms at rest, and the experienced discomfort at rest increased when any physical activity was undertaken. In all, 38 patients (44.2%) completed the self-constructed questionnaire inconsistently. For example, patients rated that they experienced cardiac symptoms at ordinary, but not at heavy exertion. For these 38 patients, NYHA class was blindly assessed by one of the cardiologists (BJMM) by manually rating the answers. For the SAS we followed the original scoring procedure as developed by Goldman et al.13

The association between patient- and cardiologist-assessed NYHA class was calculated by the Spearman rank correlation coefficient and was interpreted as small (if smaller than 0.30), medium (if ranging from 0.30 to 0.50), or large (if bigger than 0.50).14 To assess agreement between patient- and cardiologist-assessed NYHA class, we calculated percent agreement and weighted kappa, which was interpreted as slight (if smaller than 0.20), fair (if ranging from 0.21 to 0.40), moderate (if ranging from 0.41 to 0.60), or substantial (if bigger than 0.61).15,16 Weighted kappa was used, as the inclusion of a weight variable enabled the calculation of kappa in SPSS, despite the unequal range of scores across types of raters (i.e. cardiologists and patients).17 Since comorbidity is known to affect self-reported health, we also explored the level of agreement for patients without co-morbidity.

**RESULTS**

**Patients**

A total of 86 adult outpatients with a congenital malformation of the heart participated. The median age was 35.8 years, and more than half of the patients were women (53.5%). Most patients worked at least part-time (74.4%). Patients were primarily diagnosed with Marfan syndrome (26.7%), aortic coarctation (16.3%), valve malformation (15.1%), or Tetralogy of Fallot (12.8%) (see Table 2). Fifteen patients (17.4%) categorized into “other congenital heart defects”, including 11 different diagnoses, for example, Eisenmenger’s syndrome, Ebstein’s syndrome, and atrium septum defect. A total of 56 patients (65.1%) reported to have no co-morbidity, whereas 23 patients (26.7%) reported one co-morbidity. The most common co-morbidities were hypertension (9.3%), chronic back pain (5.8%), chronic obstructive pulmonary diseases (2.3%), and rheumatoid arthritis (2.3%). The number of co-morbidities were distributed across the NYHA classes as follows: class I included 27.9% (17 patients), class II included 54.5 % (12 patients), and class III included 33.3% of the patients (one patient) who had one or more co-morbidities.

**Comparison of patient- and cardiologist-assessed New York Heart Association class**

Patient-cardiologist agreement and association for each questionnaire are presented in Table 3. The agreement between the patient-based translation and the cardiologist assessment was 75.6%. The patient-based translation correlated highly (Spearman rank correlation coefficient is 0.54), and agreed moderately (weighted kappa is 0.43) with the cardiologist-assessed NYHA class. In 11 cases, NYHA class assessed by the patient-based translation was overestimated, as patients
reported a higher NYHA class compared with the cardiologist assessment, whereas in ten cases NYHA class was underestimated by patients. When calculating agreement, including only patients without co-morbidity (56 patients), the percentage agreement increased from 75.6% to 82.1%, and weighted kappa from 0.43 to 0.51.

Table 2: Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (86 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median; range)</td>
<td>35.8 (19-64)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>53.5 (46)</td>
</tr>
<tr>
<td>Work</td>
<td></td>
</tr>
<tr>
<td>Full time</td>
<td>40.7 (35)</td>
</tr>
<tr>
<td>Part time</td>
<td>33.7 (29)</td>
</tr>
<tr>
<td>Inability to work</td>
<td>5.8 (5)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Retired</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>12.8 (11)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>26.7 (23)</td>
</tr>
<tr>
<td>Other congenital heart defects</td>
<td>17.4 (15)</td>
</tr>
<tr>
<td>Aorta coarctation</td>
<td>16.3 (14)</td>
</tr>
<tr>
<td>Valve malformation</td>
<td>15.1 (13)</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>12.8 (11)</td>
</tr>
<tr>
<td>Transposition of the Great Arteries</td>
<td>7.0 (6)</td>
</tr>
<tr>
<td>Ventricle Septum Defect</td>
<td>4.7 (4)</td>
</tr>
<tr>
<td>Number of co-morbidities</td>
<td></td>
</tr>
<tr>
<td>No co-morbidity</td>
<td>65.1 (56)</td>
</tr>
<tr>
<td>One co-morbidity</td>
<td>26.7 (23)</td>
</tr>
<tr>
<td>Two co-morbidities</td>
<td>5.8 (5)</td>
</tr>
<tr>
<td>Three or more co-morbidities</td>
<td>2.3 (2)</td>
</tr>
<tr>
<td>Cardiologist-assessed NYHA class</td>
<td></td>
</tr>
<tr>
<td>Class-I</td>
<td>70.9 (61)</td>
</tr>
<tr>
<td>Class-II</td>
<td>25.6 (22)</td>
</tr>
<tr>
<td>Class-III</td>
<td>3.5 (3)</td>
</tr>
<tr>
<td>Class-IV</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

Note: Data is presented in percentage (numbers). NYHA = New York Heart Association. Other congenital heart defects = including for example Eisenmenger’s syndrome, Ebstein’s syndrome, and atrium septum defect.

The agreement between the self-constructed questionnaire and cardiologist assessment was 70.6%, with a high correlation (Spearman rank correlation coefficient is 0.59) and moderate agreement.
(weighted kappa is 0.44). The self-constructed questionnaire led primarily to overestimation of patient-assessed NYHA class (22 overestimations versus three underestimations). A similar increase in agreement levels was seen when agreement was calculated for only those patients without co-morbidity (from 70.6% to 78.2% and weighted kappa from 0.44 to 0.53).

The SAS agreed in 74.4% of the cases with the cardiologist assessment. There was a moderate correlation (Spearman rank correlation coefficient is 0.40) and a fair agreement (weighted kappa is 0.28). The SAS led to underestimation in 18 cases, and in only four cases to overestimation compared with the cardiologist-assessed NYHA class. Again, agreement levels between the SAS and the cardiologist were calculated for patients without co-morbidity, showing a small increase in agreement percentages (from 74.4% to 78.6%) and a decrease in weighted kappa (0.28 to 0.18).

As shown in Table 3, in two occurrences there was maximal discrepancy between the patient and cardiologist, that is, a patient rated himself/herself in class IV, whereas the physician rated the patient in class I. Inspection of the data identified that the same patient was involved in both occurrences. Additional analyses showed that this patient reported to have one co-morbidity, that is, “other illness”.

Table 3: Patient-cardiologist agreement and association per questionnaire

<table>
<thead>
<tr>
<th>Cardiologist-assessed NYHA class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient-based translation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>53</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>11</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Agreement</td>
<td>75.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-constructed questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>42</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>17</td>
<td>17</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Agreement</td>
<td>70.6%</td>
<td>Spearman rank correlation coefficient is 0.54</td>
<td>Weighted kappa is 0.43</td>
<td></td>
</tr>
<tr>
<td><strong>Specific Activity Scale</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>58</td>
<td>16</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Agreement</td>
<td>74.4%</td>
<td>Spearman rank correlation coefficient is 0.40</td>
<td>Weighted kappa is 0.28</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data is presented as frequencies, unless stated otherwise.
Debriefing questions

Eighteen (20.9%) and eight (9.3%) patients did not answer the two debriefing questions, respectively. Four (4.7%) and one (1.2%) patient(s), chose all three questionnaires. The two debriefing questions were thus completed following the instruction by 89.5% and 74.4% of the patients, respectively. The distribution of their preference is given in Table 4. Patients reported the SAS as the questionnaire best describing their functional status followed by the self-constructed questionnaire, and patient-based translation, respectively. Both the patient-based translation and SAS were reported as easiest to complete, followed by the self-constructed questionnaire.

Table 4: Answers to the debriefing questions for each questionnaire

<table>
<thead>
<tr>
<th>Best describing (77 patients)</th>
<th>Easiest to complete (64 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-based translation</td>
<td>23.4 (18)</td>
</tr>
<tr>
<td>Self-constructed questionnaire</td>
<td>26.0 (20)</td>
</tr>
<tr>
<td>Specific Activity Scale</td>
<td>50.6 (39)</td>
</tr>
</tbody>
</table>

Note: Data is presented in percentage (numbers).

DISCUSSION

This study was conducted to explore which patient-based NYHA class assessment agrees best with cardiologist-assessed NYHA class and can be used in future research contexts. The patient-based translation was found to be the best choice in assessing the NYHA class in CHD-patients given its adequate agreement, its equal over- and underestimation, and its ease of completion. The patient-based translation can be used for research purposes; however, its 75.6% agreement with the cardiologist precludes its use in the individual case. The self-constructed questionnaire also showed adequate agreement, but led primarily to overestimation of the NYHA class, whereas the SAS showed only fair agreement, and led primarily to underestimation of the NYHA class. Interestingly, for all three questionnaires agreement levels for patients without co-morbidity were higher than agreement levels for the total group.

In general, the agreement levels found in our study are higher than the agreement levels found in the four previous studies. Goode et al. used a direct comparison that is comparable to the patient-based translation and found an agreement of kappa is 0.28. Similar to our study, there was equal over- as underestimation of patient-assessed NYHA class. In the study by Goode et al patients were referred to the cardiologist for the first time, whereas in our study the NYHA class was assessed by the regularly treating cardiologist. Perhaps the latter cardiologists have more clinical data – for example, electrocardiography or echography – about the patient to base their rating on. Moreover, they may be better informed about possible co-morbidity and therefore might be more accurate. In addition, patients may also be better aligned to the physician owing
to experience ("training effect"). These factors may have resulted in a higher level of agreement between patient- and cardiologist-assessed NYHA class in our study.

Subramanian et al assessed patient-based NYHA class by means of the Kansas City Cardiomyopathy Questionnaire. A general nurse or a project coordinator assessed the NYHA class on average 20 days after the patient-assessment. An agreement level of 43%, with a weighted kappa of 0.28, was found. Factors likely to have contributed to this greater discrepancy between patient-based and cardiologist-assessed NYHA class include a lower health literacy of the patients, assessment by a nurse or project coordinator instead of a cardiologist, and a time lapse of 20 days between assessments.

In the study by Kubo et al, patients with heart failure were interviewed by a physician assistant or nurse, who recorded their answers on a questionnaire. These answers were then categorized into the NYHA classes by one of three independent raters. The NYHA class assessed by the cardiologist was subsequently compared with the NYHA class scored by each of these independent raters. Results showed agreement levels ranging from 57% to 65%, with weighted kappa scores ranging from 0.55 to 0.63. Contrary to our study, rater-based patient assessment underestimated the NYHA class compared with cardiologist-assessed NYHA class. The agreement levels found by Kubo et al were lower, whereas, slightly higher kappa levels were reported compared to those found in our study. The raters of the patient-based assessments are health care professionals, they are likely more closely aligned to the cardiologists.

Ekman et al found an agreement of 32% between the SAS and cardiologist-assessed NYHA class. Kappa was not calculated. Similar to our study, the SAS scores primarily underestimated the NYHA class compared with cardiologist assessment. Similar to the study conducted by Goode et al, patients were referred to an outpatient heart failure clinic for the first time. The discrepancy between the SAS and cardiologist-assessed NYHA class might be explained by similar reasons formulated to explain the results of Goode et al.

On a general note, CHD-patients are born with their impairments, and as a consequence have visited a cardiologist their entire life, contrary to heart failure patients. This might result in better alignment with their cardiologist in the interpretation of their symptoms and the assessment of the NYHA class. Moreover, both the patient and the cardiologist assessed the NYHA class on the same day, possibly further increasing agreement levels. In addition, in all four studies the presence of co-morbidity was not assessed and its influence on the level of agreement was therefore not explored. Co-morbidity is relevant for heart failure patients as they are generally in the higher age ranges.

The finding that co-morbidity affects patient-cardiologist agreement in assessing the NYHA class deserves further attention, especially since co-morbidity is common in CHD-patients. It might be hypothesized that the cardiologists filter out the impact of co-morbidity in assessing the NYHA class, whereas patients do not. The maximal discrepancy in patient and cardiologist assessment found in this study, might also be explained by the ability of the cardiologist to discriminate between the CHD and co-morbidities, since the patient involved reported to have one co-morbidity. On the
basis of the results of this study we added an instruction to the patient-based translation (see Appendix) in which we ask patients to only consider functional impairments caused by their CHD.

The results of this study raise the following question: who should be the gold standard in assessing the NYHA class, the cardiologist or the patient? Since the NYHA class is based on the patient’s subjective perceptions of disease-related restrictions in physical activity, and the patient is by definition the expert on these subjective perceptions, the patient can be considered the gold standard. In contrast, the ability of the cardiologists to filter out the impact of co-morbidity when assessing the NYHA class pleads for the cardiologist as the gold standard. One can also choose an empirical approach to this question. Future studies should examine whose subjective assessment (i.e. cardiologist or patient) is most closely aligned with an objective measure of patients’ functional status such as an exercise test (e.g. the six minute walking test). The most closely related measure can be considered the gold standard.

The limitations of this study merit attention. First, the sample size was too small to explore patient characteristics affecting the patient-cardiologist agreement. For example, it would have been interesting to compare the patients who underestimated versus overestimated their NYHA class with regard to a number of background characteristics. However, the sample size was sufficiently large to explore whether co-morbidity affects patient-cardiologist agreement levels, by examining the group of patients without co-morbidity separately. Second, the focus of this study was on outpatients. As a consequence, the distribution of NYHA classes was skewed, with most patients being categorized in physician-based NYHA class I and II and none in class IV. This may have resulted in lower Kappa levels. More importantly, the results are only generalizable to patients with NYHA classes I and II. Despite the fact that it may not be too far-fetched to expect that the simple, direct translation of the NYHA classes would also work for the two higher classes, this needs to be confirmed in future studies with patients who have poorer function, such as hospitalized patients. Third, it is important to note that the distribution of CHD was not representative for adults with CHD, since patients with the Marfan syndrome constituted the largest group. Our patient sample was therefore not representative of the population of adults with CHD. Fourth, we were unable to describe the patient sample with respect to a number of clinical characteristics, such as cardiac functioning and type of treatment. However, we did present data on type of CHD, physician-based functional class and co-morbidity, allowing for characterization of the patient sample in clinical terms.

We would also like to highlight the strengths of this study. It is the first study that addresses outpatients with CHD, compares three patient-based questionnaires in a counterbalanced way, and explores whether co-morbidity affects patient-cardiologist agreement in NYHA class assessment. A final strength of this paper is that patients and their treating cardiologists completed the NYHA assessment on the same day. This study shows that the simple and direct translation of the NYHA class, as provided in the Appendix, is a valuable patient-based tool that can be used in future studies of outpatients with CHD.

In summary, the patient-based translation with the instruction to only consider functional impairments caused by the CHD, is recommended in future studies of outpatients with CHD,
given its adequate agreement with cardiologist-assessed NYHA class, its equally over- and underestimation, and its ease of completion.

ACKNOWLEDGEMENTS
We are very grateful to all participants. Moreover, we thank all participating congenital cardiologists from the Academic Medical Centre in Amsterdam. This study is partly financed by the Interuniversity Cardiology Institute of the Netherlands.
REFERENCES


APPENDIX

Patient-based translation

Below you find four descriptions that describe different degrees in which individuals are limited in their physical functioning. Which description is most applicable to you? Please only consider the limitations that you believe are caused by your congenital heart defect.†

☐ A I am not limited during physical activities. Ordinary physical activities do not cause extraordinary fatigue, palpitations or shortness of breath.

☐ B I am slightly limited during physical activities. I do not experience any symptoms at rest, but ordinary physical activities cause extraordinary fatigue, palpitations or shortness of breath.

☐ C I am considerably limited during physical activities. I do not experience any symptoms at rest, but less than ordinary physical activities cause extraordinary fatigue, palpitations or shortness of breath.

☐ D I am unable to be physically active without experiencing discomfort. I experience one or more of the following complaints at rest; fatigue, palpitations or shortness of breath. When I am physically active, the discomfort increases.

Note: † = this instruction was adapted on the basis of this study.
Chapter 8

Perceived health is partially associated with the symptomatological profile in patients with benign and severe conditions: The case of congenital heart disease

Quality of Life Research, 2012

Dounya Schoormans
Mirjam AG Sprangers
Werner Budts
Barbara JM Mulder
Silke Apers
Philip Moons
ABSTRACT

Purpose Individuals with serious medical conditions can perceive their health status as good. This might be explained by the symptomatology inherent to the condition. Research in this respect is scarce. Congenital heart disease (CHD) is a spectrum of mild, moderate and complex heart defects, representing more benign and severe chronic conditions. We investigated (1) symptomatology (i.e., symptom frequency and symptom distress) of CHD-patients; (2) the extent to which symptomatology was independently related to perceived health; and (3) the relative importance of individual symptoms for perceived health.

Methods A secondary data analysis on two separate patient samples (629 Belgian and 1109 Dutch patients) was conducted. Patients’ symptomatology was measured with the TAAQOL-CHD. Perceived health was measured by the EQ-5D in Belgian patients, and by a single item (EVGFP rating) of the SF-36 in Dutch patients. Linear regression analyses were performed to investigate the relationship between symptoms and perceived health, while controlling for sex, age, disease complexity, and functional status.

Results The most frequently occurring symptoms were dizziness, palpitations and nycturia. Symptom distress was associated with perceived health, independent of confounders. Symptom distress with respect to shortness of breath while walking; palpitations; and dizziness were independently related to perceived health.

Conclusions Perceived health in CHD-patients is partially associated with their symptomatology. This finding underscores the possibility that differences in perceived health across patient groups with more benign and severe conditions may be caused by the different impact conditions have – in terms of symptoms – on the day-to-day life.
INTRODUCTION

Perceived health is the subjective rating of one's general health status. This rating is based on various aspects including patients’ knowledge about their medical condition and symptoms. Patients’ perceived health is frequently measured in research and clinical practice, because it can be easily assessed and gives a general idea about how individuals appraise their condition. In addition, it is a very powerful variable, because studies have found that it is predictive for mortality, and poor health outcomes such as morbidity, self-management and health care use. Hence, it can guide health care providers’ decision-making.

Research findings on perceived health show sometimes paradoxal and counterintuitive results. For instance, patients with a transposition of the great arteries or single ventricle physiology, which are obviously complex congenital heart defects (CHD), had a median score of 75-90 on the EQ-5D vas that ranged from zero to 100 (higher scores represent a better perceived health). Patients with an unruptured cerebral or an abdominal aortic aneurysm also perceived their health to be good (EQ-5D vas=80). In contrast, patients with irritable bowel syndrome (EQ-5D vas=66), psoriasis (EQ-5D vas=64), or asthma (EQ-5D vas=61) reported substantially lowers scores. In sum, patients with a severe condition such as a transposition of the great arteries, single ventricle physiology or cerebral/aortic aneurysm perceive their health as good, whereas the other patients with a more benign condition perceive their health as poorer.

It is well-known that within-group variations in perceived health are partially due to differences in experienced symptoms. The question then emerges whether the symptomatology is also responsible for differences in perceived health of individuals with different chronic conditions. It can be hypothesized that differences in the symptomatological profile inherent to a condition is the reason why patients with more benign conditions perceive their health as poorer than individuals with obviously serious medical conditions.

A study on the direct relationship of perceived health and symptoms is not self-evident. Symptoms are often disease-specific, hampering comparisons of the symptoms across patients with different disorders. Furthermore, prior studies were mainly undertaken in patient populations with a prominent symptomatological profile, such as asthma or eczema. Therefore, there is a need for studies conducted in patients with a more subtle symptom experience, and in disorders that represent the spectrum of benign to severe conditions.

In the present study, we assessed the relation between symptomatology and perceived health in CHD-patients. Indeed, CHD is an appropriate patient population to test this relationship because CHD comprises a broad spectrum of defects (ranging from mild to complex defects) representing more benign and serious chronic conditions. Moreover, in contrast to other conditions where severity is often based on the symptoms displayed (e.g., eczema), the complexity of a CHD is objectively assessed based on the type of defect. Furthermore, the complexity of a CHD is found to be (largely) unrelated to perceived health. Thus, variation in perceived health across CHD-patients is automatically the result of other factors than disease severity, such as symptom experience. It may be the case that a patient with a complex defect who experiences few symptoms consequently reports a better perceived health, than a patient with a simple defect.
who experiences many symptoms. Hence, our specific aims were (1) to examine which symptoms are most frequent and distressing in patients with CHD; (2) to examine the extent to which symptomatology (i.e., symptom frequency and symptom distress) was independently related to perceived health; and (3) to examine the relative importance for individual symptoms on patients’ perceived health.

METHODS

We undertook a secondary analysis on data from two prior studies (i.e., a Belgian and a Dutch patient sample) that used similar methods.\textsuperscript{14,17}

Study population and procedure

Belgian patient sample
Seven hundred and sixteen adult patients with CHD attending the outpatient clinic of the Adult Congenital Heart Disease Program of the University Hospitals Leuven were eligible for inclusion in this study.\textsuperscript{14} Patients were excluded if they were mentally impaired, illiterate in Dutch, visited the outpatient clinic for the first time, referred for or in follow-up after percutaneous closure of an atrial septal defect (ASD), or a patent foramen ovale.\textsuperscript{14} Institutional Review Board approval was provided by the Medical Ethics Committee of the University Hospital Leuven. Verbal informed consent was provided by all included patients.

Dutch patient sample
Sixteen hundred and seventy adult patients with CHD from five tertiary referral and three regional Dutch centers were randomly selected from the CONCOR database, a Dutch registry for patients with CHD.\textsuperscript{18} Exclusion criteria were: being diagnosed with Marfan syndrome, being mentally impaired, or illiterate in Dutch.\textsuperscript{17} Under Dutch law, ethical approval is not required for questionnaire studies. Therefore, the study was exempted from approval of the Medical Ethics Committee of the Academic Medical Center in Amsterdam.

Measurements

Demographics and clinical variables

Belgian patient sample
Sex, age, and type of CHD were obtained from patients’ medical records. Based on the type of CHD, we have categorized patients into three classes of disease complexity (i.e. mild, moderate, and complex) according to the Task Force 1 of the 32\textsuperscript{nd} Bethesda conference of the American College of Cardiology (ACC).	extsuperscript{19} Functional status was assessed by the New York Heart Association (NYHA) classification\textsuperscript{20} and was scored by one cardiologist.\textsuperscript{14}
**Dutch patient sample**

Sex and age were both measured through self-report. Type of CHD was subtracted from the CONCOR database and categorized into classes of disease complexity, according to the Task Force 1 of the 32nd Bethesda conference of the ACC. Functional status was measured by one patient-based question assessing the NYHA classification.

**Symptomatology**

**Belgian and Dutch patient sample**

Somatic symptoms as experienced by the patients were measured by the 9-item Symptoms subscale of the TNO/AZL Adult Quality Of Life-CHD (TAAQOL-CHD) in both patient samples. For each item, both the frequency and perceived level of distress were scored. First, the frequency of each symptom during the past month is scored on a 3-point scale (0=never; 1=occasionally; 2=often). If a symptom occurred (i.e., score one or two on frequency), the level of the associated distress is assessed on a 4-point scale, ranging from one (“not at all”) to four (“very much”). Consistent with the TAAQOL-CHD algorithm, the scores on both frequency and distress were combined into one score ranging from zero to four, with a zero if the symptom did not occur, and the one to four distress-scores if the symptom did occur. For the purpose of this study, we calculated two sum scores. First, after dichotomizing the frequency score according to the presence of the symptom (no=0; yes=1), a total symptom frequency score was computed by summing the scores over all nine items, yielding a total score ranging from zero to nine. Second, we calculated symptom distress, based on the combined item scores. The total symptom distress score could range from zero to 36, with higher scores reflecting a higher level of symptom distress.

**Perceived health**

**Belgian study sample**

Perceived health was measured by the EQ-5D_vas, a vertically oriented 10-cm line. The line was graded with indicators that ranged from zero (worst perceived health) to 100 (best perceived health). Patients were asked to mark the place on the line indicating their perceived health. The EQ-5D_vas has good validity, reliability, and responsiveness when used in patients with CHD.

**Dutch patient sample**

Perceived health was assessed by the first item of the Short Form Survey-36 (SF-36): “In general would you say your health is?”, also known as the EVGFP rating. Answers were given on a 5-point Likert scale with the options; “excellent”, “very good”, “good”, “fair”, and “poor”. To facilitate easy interpretation, the response options were recoded, so that a higher score indicated better perceived health.

**Statistical analyses**

Exploratory analyses showed that there were missing values for both symptomatology variables (symptom frequency and symptoms distress). For both variables, missing values were imputed with
a mean-value if more than 75% of the data was available for that person. Given this imputation of missings, we ran our analyses with missings imputed and by excluding all missings. Results were compared via a sensitivity analysis and showed stable results. We therefore chose the options were missings were imputed.

First, to establish the rank order of the most frequently occurring symptoms (symptom frequency) and the most distressing ones (symptom distress), we calculated frequencies and means, respectively.

Both samples were tested in a different way given the measurement differences in assessing perceived health. The EQ-5D_vas is a continuous variable and was used in the Belgian sample, whereas the categorical EVGFP rating was employed in the Dutch patient sample. Therefore, linear regression analyses were used for the Belgian patient sample, and ordinal regression analyses for the Dutch patient sample. As part of the ordinal regression analyses an indicator for goodness-of-fit for each model was provided as the Akaike information criterion (AIC). A lower score on the AIC indicates a better fitting model.

The assumption that disease complexity is not related to perceived health was tested by means of a regression analysis. Subsequently, we examined the extent to which symptomatology (i.e., symptom frequency and symptom distress) was independently related to perceived health, while adjusting for the four confounders: sex, age, disease complexity, and functional status. As there was multicollinearity between the two symptomatology variables, we employed two separate regression analyses for each symptomatology variable. Thus, the confounders and (a) symptom frequency and (b) symptom distress were associated with perceived health. Given that data from the Dutch sample came from multiple centers, we correcting for clustering by adding a categorical variable representing these centers.

Third, to explore the relevant importance of each symptom for perceived health, an additional regression analysis was employed. Symptom distress of all nine symptoms were simultaneously entered as independent variables together with the confounders (i.e., sex, age, disease complexity, and functional status). In the Belgian study, over 50% of patients had missing values on the item “shortness of breath walking 1-5 km” due to misinterpretation by patients. Therefore, this item was excluded from the analysis in the Belgian study. In analyzing the data from the Dutch sample, we again corrected for clustering within the centers.

All analyses were done with SPSS 16.0. We used two-sided tests, and a significance level of 5% was employed.

RESULTS

Patient characteristics

Belgian patient sample

Of the 716 eligible Belgian patients, 629 participated in this study (response rate 87.8%). Approximately 60% of patients were male, with a mean age of 40 years (Table 1). Twenty-six percent of patients had a mild congenital heart malformation, whereas 58.0% had a moderate
malformation. Most patients (81.5%) were categorized in NYHA-I. The most common types of congenital heart malformations were Tetralogy of Fallot (TOF) and pulmonary stenosis (PS) (n=160, 25.4%).

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Belgian patient sample (n=629)</th>
<th>Dutch patient sample (n=1109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>378 (60.1)</td>
<td>502 (45.8)</td>
</tr>
<tr>
<td>Age in mean years (SD)</td>
<td>39.5 (13.4)</td>
<td>40.7 (14.4)</td>
</tr>
<tr>
<td>Disease complexity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>164 (26.1)</td>
<td>644 (58.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>365 (58.0)</td>
<td>366 (33.0)</td>
</tr>
<tr>
<td>Complex</td>
<td>100 (15.9)</td>
<td>99 (8.9)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-I</td>
<td>511 (81.5)</td>
<td>754 (69.9)</td>
</tr>
<tr>
<td>NYHA-II</td>
<td>85 (13.6)</td>
<td>232 (21.5)</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>26 (4.1)</td>
<td>62 (5.8)</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>5 (0.8)</td>
<td>30 (2.8)</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD / ASD / ASD-I / PDA</td>
<td>140 (22.3)</td>
<td>397 (35.8)</td>
</tr>
<tr>
<td>TOF / PS</td>
<td>160 (25.4)</td>
<td>218 (19.7)</td>
</tr>
<tr>
<td>BAV / AS / SubvAS</td>
<td>93 (14.8)</td>
<td>151 (13.6)</td>
</tr>
<tr>
<td>CoA</td>
<td>89 (14.1)</td>
<td>137 (12.4)</td>
</tr>
<tr>
<td>TGA / ccTGA</td>
<td>46 (7.3)</td>
<td>42 (3.8)</td>
</tr>
<tr>
<td>Other CHD-diagnoses</td>
<td>101 (16.1)</td>
<td>164 (14.8)</td>
</tr>
</tbody>
</table>

Note: Numbers are given in frequencies (percentages), age in mean years (standard deviation). n = numbers; SD = standard deviation; NYHA = New York Heart Association functional class; VSD = Ventricular Septum Defect; ASD = Atrial Septum Defect; ASD-I = Atrial Septum Defect primium; PDA = Patent Ductus Arteriosus; TOF = Tetralogy of Fallot; PS = pulmonary stenosis; BAV = Bicuspid Aortic Valve; AS = Aortic Stenosis; SubvAS = Subvalvar Aorta Stenosis; CoA = Coarctation of the Aorta; TGA = Transposition of the Great Arteries; ccTGA = Congenital corrected Transposition of the Great Arteries; CHD = Congenital heart defect.

**Dutch patient sample**

Of the 1670 eligible Dutch patients, 1109 participated in this study (response rate 66.4%). Almost half of the patients (45.8%) were male. The average age for the total group was 41 years (Table 1). More than half of the patients (58.1%) were diagnosed with a mild heart malformation, whereas 33.0% had a moderate malformation. Almost 70% was classified in NYHA-I. The most common types of congenital heart malformations were Ventricular Septum Defect (VSD), (ASD) or Patent Ductus Arteriosus (PDA) (n=397, 35.8%).
Table 2: Rank order of most frequently occurring and distressing symptoms

<table>
<thead>
<tr>
<th>SYMPTOM FREQUENCY (yes)</th>
<th>SYMPTOM DISTRESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgian patient sample</td>
<td>Dutch patient sample</td>
<td>N (%)</td>
</tr>
<tr>
<td>1. Dizziness</td>
<td>1. Nycturia</td>
<td>265 (42.4)</td>
</tr>
<tr>
<td>2. Palpitations</td>
<td>2. Palpitations</td>
<td>251 (40.0)</td>
</tr>
<tr>
<td>3. Nycturia</td>
<td>3. Dizziness</td>
<td>235 (37.5)</td>
</tr>
<tr>
<td>4. Pale</td>
<td>4. Short of breath walking 1-5km</td>
<td>214 (34.3)</td>
</tr>
<tr>
<td>5. Short of breath walking &lt;100m</td>
<td>5. Pale</td>
<td>168 (31.8)</td>
</tr>
<tr>
<td>6. Orthopnea</td>
<td>6. Oedema</td>
<td>108 (17.3)</td>
</tr>
<tr>
<td>7. Cyanosis during exercise</td>
<td>7. Orthopnea</td>
<td>51 (8.2)</td>
</tr>
<tr>
<td>8. Oedema</td>
<td>8. Short of breath walking &lt;100m</td>
<td>43 (7.0)</td>
</tr>
<tr>
<td>9. Cyanosis during exercise</td>
<td>8. Nycturia</td>
<td>88 (8.0)</td>
</tr>
</tbody>
</table>

Note: n = number; % = percentage; SD = standard deviation.
Symptomatology and perceived health

**Belgian patient sample**

Table 2 shows the rank order of the most frequently occurring (symptom frequency) and distressing symptoms. The three most frequently occurring symptoms in Belgian patients were dizziness, palpitations, and nycturia. The three most distressing symptoms were orthopnea, oedema, and shortness of breath walking <100m. Patients experienced on average 2.57 symptoms (SD=1.93) and reported an average symptom distress score of 4.76 (SD=4.64). Patients perceived their health to be good (median EQ-5D value=80, SD=14.38).

**Dutch patient sample**

In the Dutch patient sample, nycturia, palpitations and dizziness were the most frequently occurring symptoms (Table 2). Patients were mostly distressed about orthopnea and shortness of breath when walking (Table 2). Patients had a mean symptom frequency score of 2.66 (SD=2.22) and a mean symptom distress score of 5.50 (SD=5.84). Around 80% of patients rated their perceived health either as “good” (9.9%), “very good” (18.4) or “excellent” (52.9%).

Symptom perception as an associate of perceived health

The assumption that disease complexity was not related to perceived health was confirmed in both patient samples (data not shown).

**Belgian patient sample**

Results of the multivariable linear regression analysis revealed that symptom distress was significantly associated with perceived health ($b=-1.301; p<0.001$), even when adjusted for sex, age, disease complexity, and functional status (Table 3). More specifically, patients with a high level of symptom distress rated their health as poor. Other factors that contributed to a worse perceived health were male gender or poor functional status (i.e., higher NYHA score). Nearly 24% of the variance in perceived health was explained by this model. Symptom distress was the strongest explanatory factor in this model, as illustrated by the highest absolute $b$-value: -0.420 (Table 3). Result of the model including symptom frequency instead of symptom distress were similar, with symptom frequency as the strongest explanatory factor ($b$-value was -0.326).

**Dutch patient sample**

Results of the ordinal regression show that also in the sample of Dutch patients, symptom distress was related to perceived health (OR=0.906, 95% CI=0.890-0.922; $p<0.001$), while adjusting for the confounders sex, age, disease complexity, and functional status. In addition to a higher level of symptom distress, being male, older age and a poorer functional status were significantly associated with worse perceived health. Symptom distress was the variable that contributed the most (highest Wald statistic, Wald Chi$^2=118.143$) (Table 4). The AIC was 2035.989. Similar results were found in the model including symptom frequency instead of symptom distress. Here
symptom frequency (Wald $\chi^2$ was 96.318) was the strongest explanatory factors. The AIC was 2071.508.

Table 3: Relationship between symptom distress and perceived health, adjusted for potentially confounding factors for the Belgian patient sample

<table>
<thead>
<tr>
<th>Perceived health</th>
<th>B</th>
<th>Standard error</th>
<th>Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>-2.508</td>
<td>1.074</td>
<td>-0.085</td>
<td>0.020*</td>
</tr>
<tr>
<td>Age</td>
<td>-0.073</td>
<td>0.064</td>
<td>-0.041</td>
<td>0.259</td>
</tr>
<tr>
<td>Disease complexity$^a$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.313</td>
<td>1.214</td>
<td>0.014</td>
<td>0.796</td>
</tr>
<tr>
<td>Severe</td>
<td>2.687</td>
<td>1.727</td>
<td>0.012</td>
<td>0.120</td>
</tr>
<tr>
<td>Functional status$^b$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>-6.871</td>
<td>1.583</td>
<td>-0.268</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>-8.833</td>
<td>2.744</td>
<td>-0.345</td>
<td>0.001*</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>-1.296</td>
<td>5.724</td>
<td>-0.051</td>
<td>0.821</td>
</tr>
<tr>
<td>Symptom distress</td>
<td>-1.301</td>
<td>0.119</td>
<td>-0.420</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Note: NYHA = New York Heart Association functional class; $^a$ = reference category is mild complexity; $^b$ = reference category for functional status is NYHA-I; * $p < 0.05$.

Table 4: Relationship between symptom distress and perceived health, adjusted for potentially confounding factors for the Dutch patient sample

<table>
<thead>
<tr>
<th>Perceived health</th>
<th>Wald Chi$^2$</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>5.441</td>
<td>0.841 (0.727-0.973)</td>
<td>0.020*</td>
</tr>
<tr>
<td>Age</td>
<td>12.052</td>
<td>0.990 (0.984-0.996)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Disease complexity$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.437</td>
<td>1.055 (0.901-1.234)</td>
<td>0.509</td>
</tr>
<tr>
<td>Severe</td>
<td>0.825</td>
<td>0.887 (0.685-1.149)</td>
<td>0.364</td>
</tr>
<tr>
<td>Functional status$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>33.413</td>
<td>0.544 (0.443-0.669)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>38.379</td>
<td>0.323 (0.226-0.462)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>20.024</td>
<td>0.293 (0.171-0.502)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Symptom distress</td>
<td>118.143</td>
<td>0.906 (0.890-0.922)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Center$^c$ (overall effect)</td>
<td>9.721</td>
<td>Not available</td>
<td>0.205</td>
</tr>
</tbody>
</table>

Note: Adjusted OR = adjusted odds ratio; 95% CI = 95% confidence interval; NYHA = New York Heart Association functional class; $^a$ = reference category is mild complexity; $^b$ = reference category for functional status is NYHA-I; $^c$ = the overall effect for the categorical variable center and is provided by the Wald Chi-Square test and its p-value; * $p < 0.05$.  

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The relative impact of each symptom on perceived health

**Belgian patient sample**

Adjusted for potentially confounding factors, we found six symptoms to be associated with worse perceived health: shortness of breath walking <100m; orthopnea; oedema; palpitations; dizziness; and cyanosis during exercise (Table 5). Moreover, male sex and a poor functional status were independently related to a poor perceived health. In total, 27.5% of the variance in perceived health was explained.

Table 5: Relative importance of individual symptom to perceived health, while controlling for confounders for the Belgian patient sample

<table>
<thead>
<tr>
<th>Perceived health</th>
<th>B</th>
<th>Standard error</th>
<th>Beta</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>-1.865</td>
<td>1.111</td>
<td>0.063</td>
<td>0.094</td>
</tr>
<tr>
<td>Age</td>
<td>-0.092</td>
<td>0.067</td>
<td>-0.051</td>
<td>0.169</td>
</tr>
<tr>
<td>Disease complexity(^a)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>-0.019</td>
<td>1.233</td>
<td>0.001</td>
<td>0.988</td>
</tr>
<tr>
<td>Severe</td>
<td>2.239</td>
<td>1.758</td>
<td>0.100</td>
<td>0.203</td>
</tr>
<tr>
<td>Functional status(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>-6.675</td>
<td>1.631</td>
<td>-0.261</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>-6.690</td>
<td>2.905</td>
<td>-0.261</td>
<td>0.022*</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>1.639</td>
<td>5.817</td>
<td>0.064</td>
<td>0.778</td>
</tr>
<tr>
<td>Shortness of breath walking &lt;100m</td>
<td>-2.295</td>
<td>0.520</td>
<td>-0.176</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>-1.606</td>
<td>0.677</td>
<td>-0.104</td>
<td>0.018*</td>
</tr>
<tr>
<td>Nycturia</td>
<td>-0.679</td>
<td>0.616</td>
<td>-0.041</td>
<td>0.271</td>
</tr>
<tr>
<td>Oedema</td>
<td>2.174</td>
<td>0.933</td>
<td>0.089</td>
<td>0.020*</td>
</tr>
<tr>
<td>Palpitations</td>
<td>-1.620</td>
<td>0.564</td>
<td>-0.130</td>
<td>0.004*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-2.835</td>
<td>0.570</td>
<td>-0.210</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Cyanosis during exercise</td>
<td>-2.301</td>
<td>0.969</td>
<td>-0.096</td>
<td>0.018*</td>
</tr>
<tr>
<td>Looking pale</td>
<td>0.038</td>
<td>0.710</td>
<td>0.002</td>
<td>0.957</td>
</tr>
</tbody>
</table>

Note: NYHA = New York Heart Association functional class; \(^a\) = reference category is mild complexity; \(^b\) = reference category for functional status is NYHA-I; * \(p < 0.05\).

**Dutch patient sample**

In the Dutch sample, the following symptoms were related to a lower level of perceived health when adjusted for confounders: shortness of breath walking 1-5km; orthopnea, nycturia, palpitations; and dizziness (Table 6). Additionally, being male, older age and poor functional status were independently related to a poor perceived health. The AIC was 1923.721.
### Table 6: Relative importance of individual symptom to perceived health, while controlling for confounders for the Dutch patient sample

<table>
<thead>
<tr>
<th></th>
<th>Perceived health</th>
<th>Wald Chi²</th>
<th>Adjusted OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td></td>
<td>4.677</td>
<td>0.845 (0.726-0.984)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>8.899</td>
<td>0.990 (0.984-0.997)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Disease complexity[^a]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td>0.385</td>
<td>1.053 (0.894-1.240)</td>
<td>0.535</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>0.794</td>
<td>0.884 (0.674-1.159)</td>
<td>0.373</td>
</tr>
<tr>
<td>Functional status[^b]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td></td>
<td>30.402</td>
<td>0.547 (0.441-0.678)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-III</td>
<td></td>
<td>35.145</td>
<td>0.302 (0.203-0.449)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td></td>
<td>21.550</td>
<td>0.246 (0.136-0.445)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Shortness of breath walking &lt;100m</td>
<td></td>
<td>0.007</td>
<td>1.006 (0.884-1.143)</td>
<td>0.933</td>
</tr>
<tr>
<td>Shortness of breath walking 1-5km</td>
<td></td>
<td>13.147</td>
<td>0.829 (0.749-0.917)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Orthopnea</td>
<td></td>
<td>4.202</td>
<td>0.905 (0.822-0.996)</td>
<td>0.040*</td>
</tr>
<tr>
<td>Nycturia</td>
<td></td>
<td>4.349</td>
<td>0.918 (0.847-0.995)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Oedema</td>
<td></td>
<td>2.877</td>
<td>0.926 (0.846-1.012)</td>
<td>0.090</td>
</tr>
<tr>
<td>Palpitations</td>
<td></td>
<td>12.312</td>
<td>0.881 (0.820-0.946)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>8.866</td>
<td>0.893 (0.829-0.962)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Cyanosis during exercise</td>
<td></td>
<td>0.542</td>
<td>1.064 (0.902-1.254)</td>
<td>0.462</td>
</tr>
<tr>
<td>Looking pale</td>
<td></td>
<td>0.711</td>
<td>0.958 (0.686-1.058)</td>
<td>0.399</td>
</tr>
<tr>
<td>Center[^c] (overall effect)</td>
<td></td>
<td>10.647</td>
<td>Not available</td>
<td>0.155</td>
</tr>
</tbody>
</table>

Note: Adjusted OR = adjusted odds ratio; 95% CI = 95% confidence interval; NYHA = New York Heart Association functional class; ^a = reference category is mild complexity; ^b = reference category for functional status is NYHA-I; ^c = the overall effect for the categorical variable center is provided by the Wald Chi-Square test and its p-value; * p < 0.05.

### DISCUSSION

To our knowledge, this is the first study examining the direct relation between symptomatology and perceived health in a population with a subtle symptom experience profile that represents a broad spectrum of benign to severe conditions. We tested this relation in two large samples of patients with CHD, an appropriate population, because CHD comprises a broad range of defects (mild to complex) representing benign to severe chronic conditions. We found that perceived health in patients with CHD is associated with their symptomatology, in particular symptom distress, rather than disease severity. Indeed, in both samples, symptom distress was the strongest predictor (highest absolute beta coefficient in the Belgian patient sample and the highest Wald Chi² in the Dutch patient sample).

Comparison of the analyses including either symptom frequency or symptom distress showed that the model including symptom distress explained the highest proportion of variance in the
Belgian sample and the lowest AIC score in the Dutch sample. This indicates that symptom distress is a stronger correlate of perceived health than symptom frequency.

The most frequently experienced symptoms in patients with CHD were dizziness, palpitations, and nycturia. The most distressing symptoms, however, were orthopnea and shortness of breath walking <100m. This finding is in line with prior studies in various patient groups, showing that the most frequently occurring symptoms are not necessarily the most distressing ones. In relation to patients’ perceived health, distress about shortness of breath when walking, palpitations, and dizziness were important in both patient samples. In addition, for the Belgian patients, distress about oedema and cyanosis during exercise were independently related to their perceived health. A potential explanation for the difference in the relation between specific symptoms and perceived health across samples may be the different measurement instruments for perceived health.

The findings of our study seem to be robust. The relationship between symptoms and perceived health was confirmed in the two independent studies that we report in this article. Furthermore, it was corroborated in a recent article by Berghammer et al that was published online at the time of this writing. Berghammer et al. concluded that symptomatic patients with CHD rate their health as poorer than asymptomatic patients. This relation remained significant after controlling for age, sex, functional status, and diagnosis. An important difference between our studies and the Berghammer study is that in the latter, symptoms were rated by cardiologists, whereas in our studies symptoms were measured using a structured self-report questionnaire. Patients’ symptomatology is based on patients’ subjective perceptions. The patient is therefore by definition the expert on these subjective perceptions, and can thus be considered the gold standard. It is known that physicians’ report of symptoms is underestimating the symptomatological profile of patients, when compared with standardized assessment through self-report questionnaires (the gold standard). Hence, it is likely that symptoms are underrated in the Berghammer study. Indeed, only 30% of their patients were considered to be symptomatic, whereas this proportion was 82.7% and 80.6% in our studies. Furthermore, the Berghammer study only included the presence of symptoms, whereas we have assessed both symptom frequency and symptom distress. Irrespective of these differences, their findings are in keeping with our results.

**Clinical implications**

In general, it is recommended that physicians assess patients’ perceived health, since it gives the physician a general sense of how patients rate their health. In addition, we advise that next to clinical objective data, patients’ perceived health is taken into consideration when physicians discuss treatment planning. Information on why patients rate their perceived health the way they do is inevitable, particularly in the case where there is a discrepancy between patients’ perceived health and physicians’ evaluation. This knowledge may help clinicians in deciding which perspective preponderates in the decision-making. The results of our study moreover suggest that a systematic appraisal of symptoms, with in particular symptom distress, is essential in the assessment of perceived health, irrespective of disease complexity. Indeed, one of the included Dutch patients was a 39-year-old male with a complex defect (i.e., transposition of the great
arteries) who reported no symptoms or symptom distress and perceived his health to be excellent. In contrast, a Dutch female 25-year-old patient with a mild defect (i.e., atrial septum defect) who reported seven symptoms and experienced severe symptom distress perceived her health to be only fair. It is advocated to use standardized assessments to appraise symptoms, because spontaneous reports of symptoms by patients during clinical interview only give a partial view on the symptomatological profile of patients. This would give clinicians better insight in the illness perception of patients, and allow them to better understand why patients consider their health status as good or bad, irrespective of the objective condition.

Methodological issues
The strengths of this study are worth mentioning. First, data of two large patient samples (total number of patients is 1738), recruited at nine different centers and across two countries were included. Second, not only symptom frequency, but also perceived distress regarding symptoms was measured.

However, our study also has some limitations. First, although the study designs were quite similar across both patient samples, data could not be pooled due to differences in measurements. Primarily, perceived health was measured by the EQ-5D in Belgian patients and by the EVGFP in Dutch patients. Moreover, functional status was appraised by a cardiologist in the Belgian sample, but was assessed by patients themselves in the Dutch sample. Furthermore, one item of the TAAQOL-CHD symptoms subscale was missing in the Belgian sample. Second, the Belgian and Dutch sample differed with respect to disease complexity; the number of patients with mild congenital malformations was larger in the Dutch study. This might be a result of the selection procedure. Belgian patients were recruited at the outpatient clinic, whereas Dutch patients were randomly selected from a national database. This difference in distribution of disease complexity was controlled for in the multivariable statistical analyses. Although some further baseline characteristics of the patient groups were slightly different, the relationship between symptomatology and perceived health was confirmed in both patient samples. Third, it is important to note that both studies were conducted in Western Europe. It is well known that studies in other countries or continents conclude that patients with CHD are more negatively affected by their condition than Belgian or Dutch patients. Therefore, results from this study cannot be automatically generalized to populations of persons with CHD. Fourth, other factors that are not measured in our study, are likely to be involved as well. For example, illness perceptions, depression, anxiety, and Type D personality are also found to be related to patients’ perceived health and symptom perception. Indeed, our multivariable model explained only 23.6% of the variance in perceived health. Fifth, although the SF-36 is a well validated questionnaire, we were faced with the asymmetric nature of the EVGFP rating. More specifically, the five response categories for the question “In general, would you say your health is” are as follows: “excellent”; “very good”; “good”; “fair”; and “poor”. The middle category represents a good health status, which has a positive instead of a neutral connotation. Therefore, direct comparison with the EQ-5D is not possible, even if the EVGFP rating is transformed into a 100-point scale. However,
we believe that the inclination of our regression analyses is not affected by these differences in measurements of perceived health, although it may have affected the strength of our relations and model fit.

CONCLUSION
In a heterogeneous group of adult patients with CHD, symptomatology and in particular symptom distress, is related to perceived health. Confirmation that symptoms are related to perceived health in a patient population comprising more benign and severe conditions and experiencing a low symptom burden underscores the possibility that the differences in perceived health across patient groups are caused by the different impact that conditions have – in terms of symptoms – on the day-to-day life. Studies examining perceived health should be interpreted in light of our conclusions, as paradoxal results (e.g., good perceived health in seriously ill patients) could be explained by the symptomatological profile.

ACKNOWLEDGMENT
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Chapter 9

Quality of life in adults with congenital heart disease: Happiness as a buffer for the negative effect of depressive symptoms

Submitted

Dounya Schoormans
Miriam C Kuilman
Barbara JM Mulder
Pythia T Nieuwkerk
Mirjam AG Sprangers
ABSTRACT

Purpose To improve patients’ quality of life (QoL) we need to identify modifiable determinants. Positive affect may be an important factor for the maintenance of QoL, but is largely unstudied. Our objectives were: (1) to assess the relationship between negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) in patients with congenital heart disease (CHD), (2) to examine to what extent negative and positive affect are independently predictive of QoL at two year follow-up, and (3) to examine whether positive affect serves as a buffer for the detrimental consequence of negative affect on patients’ QoL.

Methods At baseline, 845 adult CHD-patients completed questionnaires assessing depressive symptoms, trait-anxiety, happiness, and optimism. At two-year follow-up, QoL was assessed.

Results Many depressive symptoms and high trait-anxiety scores were related to a poor mental and physical QoL. Happiness was predictive of a better mental but poorer physical QoL. Patients with many depressive symptoms and high happiness scores reported a better mental QoL than patients with many depressive symptoms but low happiness scores. Patients with low trait-anxiety and high optimism scores reported a better physical QoL than patients with low trait-anxiety and low optimism scores. Yet, patients with high trait-anxiety scores and high optimism scores reported a poorer physical QoL than patients with high trait-anxiety but low optimism scores.

Conclusions Happiness functions as a buffer for the negative effect of depressive symptoms on mental QoL. Mental QoL may therefore be improved by a dual policy of decreasing negative affect and simultaneously enhancing positive affect.
INTRODUCTION

Nowadays, over 90% of infants born with congenital heart disease (CHD) reach adulthood thanks to the success of cardiac surgery. CHD is defined as a malformation of the heart or the large blood vessels that develops during the fetal period. Despite cardiac surgery, CHD-patients experience residual lesions, sometimes resulting in impairments in daily life. For this reason there has been increasing awareness for patients’ quality of life (QoL). To improve their QoL, modifiable predictors need to be identified. Only few studies have examined correlates of QoL in CHD. Literature shows that patients’ disease complexity, disease course, sex, age, educational status, depressive predisposition and social support are associated with QoL. Most of these correlates are not amenable to intervention. Research on modifiable predictors of QoL may provide targets for interventions to improve QoL.

In general, it is well known that psychological well-being is an important component of persons’ QoL. During the last few decades the primary focus has been on negative affect (e.g. depression and anxiety) and its relation to QoL. Positive affect may represent a potential target for intervention to improve CHD-patients’ QoL. Recently, a growing number of studies and theories suggest that addressing psychological well-being in terms of positive affect may play a critical part in the maintenance of psychological well-being. It has been suggested that negative and positive affect are independent, in that positive affect is neither simply the opposite nor the absence of negative affect, and that individuals are capable of experiencing low or high levels of both dimensions simultaneously across time. Positive affect can function as a ‘buffer’ for negative affect and both can co-occur. Consequently, we hypothesize that positive affect compensates for the detrimental consequences of negative affect on mental QoL. For physical QoL we have no a priori expectations, this analysis was therefore exploratory.

The overall aim of this study was to predict patients’ QoL by means of negative and positive affect. The specific objectives of this study were (1) to assess the relationship between negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) in patients with CHD, (2) to examine to what extent negative and positive affect are independently predictive of QoL at two year follow-up and (3) to examine whether positive affect serves as a buffer for the detrimental consequences of negative affect on patients’ QoL.

METHODS

Study population and procedure

This longitudinal study used data from a larger research project on patient-reported outcomes of adult CHD-patients. In March, 2009, 1670 adult CHD-patients from five tertiary referral and three regional centers, were randomly selected from the CONCOR database, a nationwide registry for CHD-patients. Selected patients were literate in Dutch, 18 years or older and diagnosed with a CHD (patients with Marfan syndrome were excluded). Patients were invited by letter to complete a set of questionnaires. In March, 2011, first-time respondents were asked to participate again. Ethical approval is not required for questionnaire studies in the Netherlands; therefore this study
was exempted from approval by the Medical Ethics Committee of the Amsterdam Academic Medical Center.

**Measurements**

*Patient characteristics*

Patients’ sex, age, and type of heart defect were extracted from the CONCOR database. Disease complexity was based on type of heart defect and categorized as simple, moderate or complex according to Warnes and colleagues.\(^{20}\) New York Heart Association (NYHA) functional class was determined by one patient-based question.\(^{21}\)

**Negative affect**

Negative affect was defined as: “a broad range of aversive mood states that form a general distress factor which can be measured either as a transient fluctuation in mood (state) or as a stable individual difference in affective level (trait)” (p.159).\(^{22}\) In this study depressive symptoms (state) and trait-anxiety were assessed as measures of negative affect.

Depressive symptoms were measured with the seven-item depression subscale of the Hospital Anxiety and Depression scale (HADS).\(^{23}\) All items are answered on a 4-point (0-3) Likert scale. A sum score is calculated ranging from zero to 21 with a higher score reflecting more depressive symptoms. Studies have shown that the HADS depression subscale is reliable and valid.\(^{23,24}\)

Trait-anxiety was measured using the 20-item Trait-subscale of the State-Trait Anxiety Inventory (STAI-trait).\(^{25}\) A 4-point Likert scale is used to answer all items. Sum scores range from 20 to 80, with higher scores reflecting higher trait-anxiety levels. Both the reliability and validity of the STAI-trait are considered to be sufficient.\(^{26}\)

**Positive affect**

We used the following definition of positive affect: “the feelings that reflect a level of pleasurable engagement with the environment such as happiness, joy, excitement, enthusiasm and contentment” (p.925).\(^{27}\) These feelings can be brief, longer lasting, or more stable trait like feelings. We measured positive affect in terms of feelings of happiness and the tendency to be optimistic.

Happiness was assessed by the four-item Subjective Happiness Scale (SHS).\(^{28}\) All items are answered on a 7-point Likert scale. A sum score is calculated ranging from one to seven, with higher scores reflecting greater happiness. Both the validity and reliability of the SHS were found to be sufficient.\(^{28}\)

The Life Orientation Test (LOT) was used to measure optimism.\(^{29}\) The test consists of 12 items; which are answered on a 5-point Likert scale. The total sum score ranges from two to 24, with higher scores reflecting higher optimism levels. Studies have shown that the LOT is both reliable and valid.\(^{30}\)
Quality of life

QoL can be defined in many ways, at large there is consensus that it is a multidimensional concept including physical, psychological and social functioning. General QoL was assessed by the Short Form Health Survey-36 (SF-36), yielding a mental (MCS) and physical component summary (PCS). The MCS and PCS have a standardized mean of 50. The SF-36 was found to be amply validated.

Disease-specific QoL was measured by the TNO/AZL Adult Quality Of Life-CHD (TAAQOL-CHD). This questionnaire consists of three subscales: symptoms, worries and impact. For each subscale higher scores reflect a better QoL. There has been only one study that validated the TAAQOL-CHD.

Statistical analysis

We calculated mean scores and standard deviations for the depressive symptoms, trait-anxiety, happiness and optimism scales using descriptive statistics.

The relationship between negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) was calculated by a Pearson Product Moment correlation coefficient and interpreted as small ($r < 0.10$), medium ($r 0.30-0.50$) or large ($r > 0.50$).

In addition, we examined (1) to what extent negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) independently predict QoL, and (2) whether positive affect functions as a buffer for the detrimental consequences of negative affect on QoL. Therefore, multiple linear regression analyses using general linear models (GLM) were performed entering depressive symptoms, trait-anxiety, happiness, optimism, their four interaction effects (depressive symptoms x happiness, depressive symptoms x optimism, trait-anxiety x happiness, trait-anxiety x optimism) and patient characteristics simultaneously. To avoid multicollinearity between the main effects and the interaction terms, individual scores were centered before calculating interaction terms. These analyses were performed for each QoL-scale (MCS, PCS, symptoms, worries) separately. The impact subscale was not included, because it primary focuses on the physical load of cardiac examination. All analyses were conducted in SPSS 16.0 and results were tested at the significance level of 5%.

RESULTS

Response, patient characteristics and mean scores for negative and positive affect

Of the 1670 patients, 1109 responded the first time (response rate 66.4%). At follow-up 1100 patients (nine patients died during the two year follow-up period) were sent a second questionnaire. Of the 1100 eligible patients, 845 participated the second time (response rate 76.8%).

Patient characteristics of the 845 CHD-patients are shown in Table 1. More than half of the patients were female, with a mean age of 41.3 years (Table 1). Almost 60% was diagnosed with a simple congenital heart defect. Only 8.5% had a complex defect. A majority of the patients had a NYHA-I classification (71.2%). The most common diagnoses were ventricular septal defect,
atrial septal defect and aortic coarctation (together 36.3%). The distribution of diagnoses is in concordance with the distribution of diagnoses in the CONCOR database.

Table 1: Patient characteristics and scores on negative and positive affect

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (n=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>457 (54.7)</td>
</tr>
<tr>
<td>Age</td>
<td>41.3 (14.4)</td>
</tr>
<tr>
<td>Disease complexity</td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>502 (59.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>270 (32.0)</td>
</tr>
<tr>
<td>Complex</td>
<td>72 (8.5)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
</tr>
<tr>
<td>NYHA-I</td>
<td>591 (71.2)</td>
</tr>
<tr>
<td>NYHA-II</td>
<td>175 (21.1)</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>45 (5.4)</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td></td>
</tr>
<tr>
<td>VSD / ASD / ASD-I / PDA</td>
<td>306 (36.3)</td>
</tr>
<tr>
<td>TOF / PS</td>
<td>162 (19.2)</td>
</tr>
<tr>
<td>BAV / AS / SubvAS</td>
<td>121 (14.3)</td>
</tr>
<tr>
<td>CoA</td>
<td>106 (12.6)</td>
</tr>
<tr>
<td>TGA / ccTGA</td>
<td>28 (3.3)</td>
</tr>
<tr>
<td>Other CHD-diagnoses</td>
<td>107 (12.7)</td>
</tr>
</tbody>
</table>

| Negative and positive affect            |              |
| Depressive symptoms                    | 2.4 (2.8)    |
| Trait-anxiety                           | 35.7 (10.0)  |
| Happiness                               | 4.8 (0.7)    |
| Optimism                                | 16.2 (3.5)   |

Note: Numbers are given in frequencies (valid percentages), and age in mean years (standard deviation). Mean scores (standard deviation) for depressive symptoms (range 0-20), trait-anxiety (range 20-80), happiness (range 1-7), and optimism (range 2-24) are provided. NYHA = New York Heart Association functional class; VSD = Ventricular Septum Defect; ASD = Atrial Septum Defect; ASD-I = Atrial Septum Defect primum; PDA = Patent Ductus Arteriosus; TOF = Tetralogy of Fallot; PS = Pulmonary Stenosis; BAV = Bicuspid Aortic Valve; AS = Aortic Stenosis; SubvAS = Subvalvar Aorta Stenosis; CoA = Coarctation of the Aorta; TGA = Transposition of the Great Arteries; ccTGA = Congenital corrected Transposition of the Great Arteries; CHD = Congenital heart defect.

Patients’ mean scores for negative and positive affect are also provided in Table 1. In comparison to healthy Dutch reference populations, CHD-patients reported significantly higher levels of trait-anxiety (mean=34.0 versus mean=35.7, $p<0.01$), but significantly lower levels of depressive
symptoms (mean=3.4 versus mean=2.8, p<0.01), happiness (mean=5.6 versus mean=4.8, p<0.01) and optimism (mean=25.4 versus mean=16.2, p<0.01). CHD-patients scored average on both the MCS and PCS (means were 50) measuring general QoL, which is comparable to the general population (p>0.05).

**Relationship between negative and positive affect**

As expected, negative affect was inversely related to positive affect (see Table 2). All correlations were large according to Cohen’s guidelines. The largest inverse correlation was between trait-anxiety and optimism (r=-0.69, p<0.01), that is, high levels of trait-anxiety were associated with low levels of optimism.

**Table 2: Correlations between negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism)**

<table>
<thead>
<tr>
<th>Negative affect</th>
<th>Positive affect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressive symptoms</td>
<td>Trait-anxiety</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>--</td>
</tr>
<tr>
<td>Trait-anxiety</td>
<td>0.71*</td>
</tr>
<tr>
<td>Happiness</td>
<td>-0.57*</td>
</tr>
<tr>
<td>Optimism</td>
<td>-0.53*</td>
</tr>
</tbody>
</table>

Note: Pearson Product Moment correlation coefficients are provided; * p < 0.05.

**Predictors of quality of life and positive affect as a buffer for negative affect**

In general, older patients reported a better mental QoL (MCS: B=0.05, p<0.05; Worries: B=0.16, p<0.01), but poorer physical QoL (PCS: B=-0.13, p<0.01; Symptoms: B=-0.15, p<0.01). Males reported a better physical QoL (PCS: B=2.58, p<0.01; Symptoms: B=5.14, p<0.01). Moreover, a complex defect was independently predictive of a poorer physical QoL (PCS: B=-3.36, p<0.01). A poorer functional status was independently predictive of a poorer mental and physical QoL (p<0.05, see table 3 for specific contrasts).

**Mental quality of life**

In the model for the MCS scale, the only significant interaction term was depressive symptoms x happiness. Therefore we reran the analysis excluding the three non-significant interaction terms (Table 3, first column). Results showed that patients who scored high on trait-anxiety scored low on the MCS (B=-0.36, p<0.01). Moreover, the interaction term depressive symptoms x happiness remained significantly predictive of higher scores on the MCS scale (B=0.23, p=0.02). To facilitate interpretation of this interaction term, a graph is provided in Figure 1a. This graph depicts that patients with many depressive symptoms and a high happiness score reported a higher score.
Table 3: The independent predictive value of depression, anxiety, happiness and optimism for quality of life at two-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>MENTAL QUALITY OF LIFE</th>
<th>PHYSICAL QUALITY OF LIFE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCS</td>
<td>Worries</td>
</tr>
<tr>
<td></td>
<td>$B$</td>
<td>$p$</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>-0.31</td>
<td>0.61</td>
</tr>
<tr>
<td>Disease-complexity§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>-0.57</td>
<td>0.38</td>
</tr>
<tr>
<td>Complex</td>
<td>0.42</td>
<td>0.71</td>
</tr>
<tr>
<td>Functional statusǂ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>0.63</td>
<td>0.42</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>1.29</td>
<td>0.34</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>-4.49</td>
<td>0.03*</td>
</tr>
<tr>
<td>Negative and positive affect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>-0.15</td>
<td>0.38</td>
</tr>
<tr>
<td>Trait-anxiety</td>
<td>-0.36</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Happiness</td>
<td>1.10</td>
<td>0.07</td>
</tr>
<tr>
<td>Optimism</td>
<td>-0.08</td>
<td>0.50</td>
</tr>
<tr>
<td>Depressive symptoms x Happiness</td>
<td>0.23</td>
<td>0.02*</td>
</tr>
<tr>
<td>Depressive symptoms x Optimism</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Trait-anxiety x Happiness</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Trait-anxiety x Optimism</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Note: -- = not included in the model; MCS = Mental Component Summary of the SF-36; Worries = Worries subscale of the TAAQOL-CHD; PCS = Physical Component Summary of the SF-36; Symptoms = Symptoms subscale of the TAAQOL-CHD; NYHA = New York Heart Association functional class; § = reference category is simple; ǂ = reference category is NYHA-I; Depressive symptoms x Happiness = the interaction term of depressive symptoms and happiness; Depressive symptoms x Optimism = the interaction term of depressive symptoms and optimism; Trait-anxiety x Happiness = the interaction term of trait-anxiety and happiness; Trait-anxiety x Optimism = the interaction term of trait-anxiety and optimism; $B$ = B-value; $p$ = p-value; * $p < 0.05$. 
on the MCS scale than patients with many depressive symptoms but a low happiness score. This effect of happiness was largest for patients reporting many depressive symptoms.

Figure 1a: The effect that depressive symptoms have on mental quality of life is mediated by patients’ score on happiness

![Graph showing the effect of depressive symptoms on mental quality of life](image)

Note: Low = one standard deviation below the mean; High = one standard deviation above the mean.

The interaction term trait-anxiety x happiness was significant in the model for the worries scale. We reran the analysis therefore excluding the three non-significant interactions (Table 3, second column). Results showed that high levels of trait-anxiety ($B=-0.35$, $p<0.01$) but low levels of happiness ($B=2.06$, $p<0.01$) were predictive of a lower worries score (i.e. poorer mental QoL). The interaction term trait-anxiety x happiness was no longer significant ($B=0.02$, $p<0.70$).

**Physical quality of life**

In the model for the PCS scale only the interaction terms depressive symptoms x optimism and trait-anxiety x optimism were significant. Therefore we reran the analysis, excluding the two non-significant interactions (Table 3, third column). Results of this analysis showed that high scores on the depressive symptoms ($B=-0.46$, $p=0.02$) and happiness scale ($B=-1.43$, $p=0.02$) were independently predictive of a low score on the PCS scale. The interaction term depressive symptoms x optimism was no longer significant ($B=0.04$, $p=0.29$). There was a significant negative effect of trait-anxiety x happiness ($B=-0.03$, $p=0.02$) (see Figure 1b). This graph shows that patients who scored low on trait-anxiety and low on optimism reported a lower score on the PCS scale, than patients who scored low on trait-anxiety, but high on optimism. For patients with an average score on trait-anxiety, the level of optimism is irrelevant with respect to their score on the PCS.
Lastly, patients with a high score on trait-anxiety and a high score on optimism reported a lower PCS score than patients with a high score on trait-anxiety but a low score on optimism.

Figure 1b: *The effect that trait-anxiety has on physical quality of life is mediated by patients’ score on optimism*

![Figure 1b](image)

Note: Low = one standard deviation below the mean; High = one standard deviation above the mean.

None of the interaction terms were significantly related in the model for the symptoms scale. The analysis was therefore repeated without the four interaction terms (Table 3, fourth column). Patients with a high score on trait-anxiety reported a lower score on the symptoms scale ($B=-0.23$, $p<0.01$), i.e. a poorer physical QoL.

**DISCUSSION**

To our knowledge, this is the first longitudinal study in CHD-patients focusing on the predictive value of negative and positive affect for QoL and examining whether positive affect functions as a buffer. Results show that negative (depressive symptoms and trait-anxiety) as well as positive affect (happiness) are predictive of QoL two years later. Moreover, happiness seems to be protective for the negative effect of depressive symptoms on mental QoL.

Our finding that depressive symptoms, trait-anxiety, and happiness were independently predictive of QoL is in line with previous findings in various patient groups, reporting that both negative and positive affect are simultaneously predictive of QoL.\(^{41-43}\) As one would expect, patients with few depressive symptoms, low trait-anxiety scores, and high scores on happiness reported a better mental QoL. However, unexpected was the negative relation between happiness...
and physical QoL. This finding may be explained by an adaptation effect; patients with the worst physical QoL, may focus on the good things in life, therefore reporting more feelings of happiness.  

Although various studies report that optimism is related to a better mental and physical QoL, we could not confirm this in our study. A possible explanation for this discrepancy is that in addition to optimism, happiness was included as a measure of positive affect. Moreover, we analyzed the predictive value of optimism for QoL independent of depressive symptoms and trait-anxiety. Indeed, in another study that controlled for measures of depression and anxiety, optimism was also found not to be related to mental or physical QoL.

Nonetheless, a secondary role for optimism mediated by levels of trait-anxiety can be suggested for physical QoL. In patients who scored low on trait-anxiety, optimism was beneficial for their physical QoL. Unexpected was the direction of the effect for patients scoring high on trait-anxiety. Here patients who scored low on optimism reported a better physical QoL. We cannot provide a valid explanation based on the results of this study. These findings suggest that the detrimental consequence of trait-anxiety on physical QoL measured by the PCS is not buffered by optimism. A possible explanation may be found in the items of the PCS scale. These are quite literal in their assessment, for example questions assess patients’ ability to climb the stairs, which makes it unlikely that the tendency to be optimistic has a buffering effect for trait-anxiety.

Our study does provide support for the notion that positive affect can function as a buffer for the detrimental consequences of negative affect on mental QoL. Results show that a high level of happiness is a buffer for the negative effect of depressive symptoms on mental QoL. This buffering effect gets larger as depressive symptoms increase. Although this buffering effect was often suggested, to our knowledge there are no studies exploring this relation. Only one previous study reported that persons with high scores on both negative and positive affect reported significantly higher scores on mental and physical QoL, compared to persons with high scores on negative but low scores on positive affect, which is in line with our results.

Consequently, improvement of positive affect, with in particular feelings of happiness may represent a potential target for intervention, in addition to traditional therapies focusing on reducing negative affect. So called, positive psychological interventions teach individuals ways to increase their positive thinking, positive affect, and positive behaviors and can serve as a template for programs aimed at helping people who experience health-related and other types of life stress. Positive psychological interventions often consist of positive exercises such as writing letters of gratitude, counting one’s blessings, practicing optimism, performing acts of kindness, meditating on positive feelings towards others and using one’s signature strengths. Two randomized controlled trials in patients with mild clinical depression have reported promising findings. Increasing feelings of happiness may not only improve patients’ QoL, yet may also have secondary beneficial effects. Several studies have reported on the beneficial effects of positive affect on ones health. Noteworthy is the study by Davidson et al, who demonstrated that positive affect is protective for 10-year incident coronary heart disease independent of negative affect and cardiovascular risk-factors. Possible mechanisms underlying this relation may be behavioral or biological. For example, patients who reported a high life satisfaction are less likely to smoke and
more likely to regularly exercise. On the other hand positive affect (e.g. happiness) has been related to low levels of cortisol, C-reactive protein and interleukin-6, which are found to be related to various chronic diseases such as diabetes mellitus and cardiovascular conditions.

This study has several limitations that need to be addressed. First, other predictors of QoL, such as experienced social support, personality, illness beliefs and level of education and are not measured. Furthermore, our CHD-patients represent a group of patients who feel quite well. Consequently, further research should study patients who report more depressive symptoms, higher levels of trait-anxiety and have a poorer QoL. Therefore, results from this study cannot be automatically generalized to such patient populations.

We would also like to emphasize the strengths of this study. First, we included 845 patients from regional and tertiary centers. That is, we investigated 6.5% of all registered patients in the national database and around 2.5% of the estimated total adult CHD-population in the Netherlands. Therefore, a broad spectrum of Dutch CHD-patients represents our sample. Second, we included measures of both negative and positive affect, examining the range of emotions. Moreover, validated questionnaires to measure depressive symptoms, trait-anxiety, happiness, optimism and QoL were employed. Furthermore, we examined to what extent positive affect buffers the detrimental consequences of negative affect for QoL. In addition, both disease-specific as well as general QoL have been measured in this study. Finally, we employed a longitudinal study design.

Conclusions
Positive affect is a potential target for the improvement of CHD-patients’ mental QoL. This knowledge can help health care providers such as psychologists to improve therapeutic strategies. Patients’ mental QoL may be more rapidly enhanced by this dual policy of decreasing negative affect and simultaneously improving positive affect. In addition to the improvement of QoL, this treatment strategy may also have beneficial secondary effects in patients’ health, such as a reduced risk of coronary heart disease. Future studies examining the therapeutic value of the enhancement of positive affect (e.g. happiness) on QoL and its possible beneficial secondary effects need to be conducted.

ACKNOWLEDGEMENTS
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Chapter 10

Illness perceptions of adults with congenital heart disease and their predictive value for quality of life two-years later

Submitted

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ABSTRACT

Background Patients’ illness perceptions are known to regulate emotional responses and health behavior. Illness perceptions constitute of several components; consequences, control, coherence, changeability and emotional representations. To improve patients’ quality of life (QoL) we need to identify modifiable determinants, such as illness perceptions.

Aims (1) to examine illness perceptions of patients with congenital heart disease (CHD) in comparison to illness perceptions of patients with cystic fibrosis, diabetes mellitus and asthma; (2) to examine the relation between patient characteristics and illness perceptions; and (3) the independent predictive value of illness perceptions for future QoL.

Methods A longitudinal study in 845 CHD-patients was conducted. Patients completed three questionnaires; the IPQ-R (illness perceptions) and two years later the SF-36 and TAAQOL-CHD (QoL). Linear regression analyses were performed relating illness perceptions to patient characteristics (sex, age, disease complexity and functional status) and QoL.

Results CHD-patients reported good illness perceptions compared to patients with other diseases. Within CHD-patients, patients with a complex defect or poor functional status reported poor illness perceptions. Independent of patient characteristics, poor illness perceptions (i.e. a strong belief the illness has severe consequences; a weak belief that you have a coherent illness understanding and that the illness can be controlled by treatment; and a strong belief that the illness is changeable and causes negative emotions) were predictive of future QoL.

Conclusion Illness perceptions independently predict QoL, suggesting that QoL may be improved by altering CHD-patients’ beliefs about their illness. For example, increasing patients’ knowledge regarding their disease and informing them about treatment opportunities may enhance their QoL.
INTRODUCTION

Advances in cardiac surgery have led to a vast increase in the number of children with congenital heart disease (CHD) to reach adulthood. Nonetheless, this adult CHD-population often has residual lesions that have an adverse effect on daily life, therefore needing life-long care.

How patients perceive their illness is known to regulate health behavior and emotional reactions. Such illness perceptions are defined as “cognitive representations or beliefs that patients have about their illness” (p. 163). These beliefs constitute several components, i.e. the identity of the illness (name of the illness and related symptoms), personal consequences for both the patient and his/her family, personal and treatment control, illness coherence (understanding the illness), changeability of the illness and its effects, emotional representations (negative emotions as a result of the illness), and cause of the illness.

Over the last two decades there has been increasing awareness of CHD-patients’ quality of life (QoL). Yet relatively little is known about associating factors. Few studies have researched this topic. They found that QoL is related to disease complexity, disease course, sex, age, educational status, depressive predisposition and social support. Whereas insight into these associating factors is important, the therapeutic value of these studies is limited, since these variables are not (easily) modifiable. To improve patients’ QoL, we need to identify modifiable determinants. Illness perceptions may be a promising determinant of patients’ QoL, representing a potential target for intervention.

The overall aim of this study was to investigate illness perceptions of patients with CHD and their predictive value for QoL. Illness perceptions as such are not very informative. To facilitate the interpretation of CHD-patients’ illness perceptions, they were compared to those of other patient groups that either had similar or contrasting disease characteristics (e.g. stable versus fluctuating over time) compared to CHD. The objectives were (1) to examine illness perceptions of CHD-patients and compare these to those of patients with cystic fibrosis, diabetes mellitus, or asthma; (2) to examine the extent to which patient characteristics (i.e. sex, age, disease complexity and functional status) are associated with illness perceptions; and (3) to examine the independent predictive value of illness perceptions for QoL at two-year follow-up.

METHODS

Study population and procedure

The current study is part of a larger longitudinal study on patient-reported outcomes of adults with CHD. At baseline CHD-patients from five tertiary referral and three regional centers were randomly selected from the CONCOR database, a nationwide registry for CHD-patients. Eligible patients were invited by letter to complete a questionnaire set. Exclusion criteria were: a diagnosis of Marfan syndrome, being mentally impaired, or illiterate in Dutch. A total of 1670 eligible patients were invited to participate. Two years later, the follow-up questionnaires were sent to the respondents. Under Dutch law, ethical approval is not required for questionnaire studies. Therefore, this study was exempted from approval of the Medical Ethics Committee of
the Academic Medical Center in Amsterdam. This study was conducted in accordance with the principles of the “Declaration of Helsinki”.26

Comparing patient groups
Three studies examining illness perceptions of 199 cystic fibrosis (CF) patients,27 158 recently diagnosed diabetes mellitus (DM) patients28 and 79 asthma patients29 respectively, were selected. All three patient groups were of similar age (range: 37-48 year) as our CHD-patients (median=39), yet more females were included in the studies on CF (63%)27 and asthma (78%),29 than in our study (55%). These three patient groups were selected based on similar or contrasting disease characteristics compared to CHD. We hypothesized that CHD-patients’ illness perceptions are comparable or distinct to those of the other patient groups based on these (dis)similarities. More specifically, both CHD and CF are congenital conditions that are difficult to personally control, compared to the acquired conditions DM and asthma. We therefore expected CHD- and CF-patients to have a weaker belief that they can personally control their illness. Additionally, as both CHD- and CF-patients have a congenial disease we expected them to have a stronger belief they have a coherent understanding of their illness. Furthermore, CHD- and DM-patients experience relatively few symptoms compared to the other two patient groups (CF and asthma). We hypothesized that as CHD- and DM-patients report fewer symptoms they consequently have a weaker belief that their illness has severe consequences. Moreover, CHD is a relatively stable condition, whilst CF, DM, and asthma are known to fluctuate over time. As a result we expected CHD-patients to have a weaker belief the illness is changeable compared to the other patient groups. Finally, we did not have any a priori expectations about differences in beliefs about treatment control and emotional representations across patient groups.

Measurements
Clinical factors
At baseline, disease complexity and functional status were assessed. Disease complexity was based on the type of cardiac defect, which was extracted from the CONCOR database and categorized into simple, moderate and complex according to Warnes and colleagues.30 Functional status was assessed according to the New York Heart Association (NYHA) class by means of a patient-based questionnaire.31

Illness perceptions
Illness perceptions were measured by the Illness Perception Questionnaire – Revised form (IPQ-R) at baseline.32 The IPQ-R was adapted for use in CHD-patients such that throughout the questionnaire the word “illness” was replaced by “congenital heart disease”. Moreover, items not applicable to this patient group were deleted. The IPQ-R consists of three parts. The first part measures identity of the illness, and represents questions about the name of the illness and ten associated symptoms. The second part consists of six scales measuring illness representations. Consequences (five items) describe the effects on physical, psychological and social functioning.
Personal (six items) or treatment (three items) control yield questions about whether the illness or its effects can be modified by personal or treatment interference. Illness coherence (four items) measures patients’ understanding of their illness. Timeline - cycle (three items) represents the perceived changeability of the illness and its effects. Emotional representation (five items) addresses the experienced negative emotions (e.g. depressive feelings) caused by the illness. All questions are answered on a 5-point Likert scale ranging from “totally disagree” to “totally agree”. To facilitate comparisons between illness representation scales, the range was adjusted to one through five, by dividing each scale score by the number of items. Higher scores indicate stronger beliefs. The last part lists 15 possible causes of aggravation of CHD-related symptoms. Answers are given on a 5-point Likert scale ranging from “totally disagree” to “totally agree”. The IPQ-R is validated and yield good psychometric properties.32

Quality of life
QoL was measured at two-year follow-up. Patients filled out the Short Form Health Survey-36 (SF-36), yielding a mental (MCS) and physical component summary score (PCS).33 Additionally, disease-specific QoL was measured with the TNO/AZL Adult Quality Of Life-CHD (TAQOL-CHD) forming the subscales Symptoms, Worries, and Impact Cardiac Surveillance.34 For each subscale, higher scores reflect a better QoL. The SF-36 is amply validated.35 The validity of the TAQOL-CHD was confirmed in one study.34

Statistical analyses
To examine CHD-patients’ illness perceptions, descriptive statistics were used. First, to establish the top-10 of most frequently endorsed symptoms (i.e. illness identity) and to indicate the two most and least endorsed causes of CHD-symptom aggravation we calculated frequencies. Second, CHD-patients’ mean scores on the six illness representations scales were compared to those of the other patient groups (i.e. CF,27 DM,28 and asthma29) by means of one-sample t-tests. It is important to note that statistical comparisons were made solely to facilitate interpretation of CHD-patients’ illness perceptions.

The relation between patient characteristics and illness perceptions was examined by means of multivariable linear regression analyses using general linear model (GLM) for each illness representation scale separately. Sex, age, disease complexity, and functional status were simultaneously entered as associating factors.

We examined the extent to which illness perceptions (i.e. the six illness representation scales) were independently predictive of the different QoL scales at two year follow-up while controlling for sex, age, disease complexity, and functional status. Therefore we conducted multivariable linear regression analyses (using GLM) for each QoL scale (i.e. MCS and PCS of the SF-36; and the Symptoms and Worries subscale of the TAQOL-CHD) separately. The Impact Cardiac Surveillance scale of the TAQOL-CHD was not included as this subscale merely focuses on the burden of medical examination. Moreover, baseline QoL scores were not included as predictors, since QoL did not change between assessments or decreased only minimally (PCS mean change = 0.76).
Analyses were conducted in SPSS 16.0 and comparisons were tested at the 5%-significance level. We chose not to use a more stringent alpha level since our hypotheses were theory driven.

RESULTS
Response and patient characteristics
Of the 1670 eligible patients, 1109 filled out the questionnaire at baseline (response rate 66.4%). Two years later, the follow-up questionnaire was sent to our respondents (n=1100, nine patients died during the follow-up period) of whom 845 patients participated (response rate 76.8%).

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Total (n=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>388 (45.3)</td>
</tr>
<tr>
<td>Age in median years (range)</td>
<td>39 (18-85)</td>
</tr>
<tr>
<td>Disease complexity†</td>
<td></td>
</tr>
<tr>
<td>Simple</td>
<td>502 (59.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>270 (32.0)</td>
</tr>
<tr>
<td>Complex</td>
<td>72 (8.5)</td>
</tr>
<tr>
<td>Functional status§</td>
<td></td>
</tr>
<tr>
<td>NYHA-I</td>
<td>591 (71.2)</td>
</tr>
<tr>
<td>NYHA-II</td>
<td>175 (21.1)</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>45 (5.4)</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>19 (2.3)</td>
</tr>
<tr>
<td>Congenital heart defect‡</td>
<td></td>
</tr>
<tr>
<td>VSD / ASD / ASD-I / PDA</td>
<td>306 (36.3)</td>
</tr>
<tr>
<td>TOF / PS</td>
<td>162 (19.2)</td>
</tr>
<tr>
<td>BAV / AS / SubvAS</td>
<td>121 (14.3)</td>
</tr>
<tr>
<td>CoA</td>
<td>106 (12.6)</td>
</tr>
<tr>
<td>TGA / ccTGA</td>
<td>28 (3.3)</td>
</tr>
<tr>
<td>Other CHD-diagnoses</td>
<td>121 (14.3)</td>
</tr>
</tbody>
</table>

Note: Numbers are given in frequencies (valid percentages), age in median years (range). † = for one patient no information was available; NYHA = New York Heart Association functional class; § = information on NYHA class is missing for 15 patients; ‡ = for one patient no information was available; VSD = Ventricular Septum Defect; ASD = Atrial Septum Defect; ASD-I = Atrial Septum Defect primium; PDA = Patent Ductus Arteriosus; TOF = Tetralogy of Fallot; PS = Pulmonary Stenosis; BAV = Bicuspid Aortic Valve; AS = Aortic Stenosis; SubvAS = Subvalvar Aorta Stenosis; CoA = Coarctation of the Aorta; TGA = Transposition of the Great Arteries; ccTGA = Congenital corrected Transposition of the Great Arteries; CHD = Congenital heart defect.

Less than half of the 845 patients were male (Table 1). The median age was 39 years. Almost 60% of patients were diagnosed with a simple malformation, and 71.2% had a NYHA-I classification. Ventricular septal defect (VSD), atrial septal defect (ASD), and patent ductus arteriosus (PDA)
(together 36.3%), were the most common diagnoses (Table 1), which is in concordance with the distribution of diagnoses of the CONCOR database. Non-respondents were not significantly different in terms of type of congenital heart defect and disease complexity ($p>0.05$, data not shown).

**Illness perceptions**

*Illness identity*

On average patients endorsed one (range 0-9) CHD-associated symptom. Table 2 shows the top-10 of most frequently endorsed CHD-related symptoms. Fatigue (26.6%), shortness of breath (19.2%), and dizziness (11.7%) were most frequently endorsed.

**Table 2:** Top-10 of most frequently endorsed CHD-related symptoms

<table>
<thead>
<tr>
<th>Illness identity</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>225 (26.6)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>162 (19.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>99 (11.7)</td>
</tr>
<tr>
<td>Oedema</td>
<td>76 (9.0)</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>71 (8.4)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>68 (8.0)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>68 (8.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>36 (4.3)</td>
</tr>
<tr>
<td>Back pain</td>
<td>23 (2.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (1.5)</td>
</tr>
</tbody>
</table>

Note: Numbers are given in frequencies (valid percentages). The numbers do not add up to 845, since patients could endorse more than one symptom.

**Illness causes**

Smoking (59.1%) and stress & worrying (52.4%) were most often identified as factors causing CHD-related symptoms to worsen, while environmental pollution (9.7%) and previous inadequate medical care (13.9%) were least considered to be of influence.

**Illness representations**

Compared to patients with CF, DM, and asthma, CHD-patients reported the lowest scores on the consequences (mean=2.2), personal control (mean=3.1), timeline – cycle (mean=2.3), and emotional representation scales (mean=2.1), yet the highest scores on the treatment control (mean=4.4) and illness coherence scales (mean=4.0). CHD-patients’ mean scores were significantly different from those of the other patient groups (Table 3). As expected based on the symptomatology inherent to the conditions, both CHD- and DM-patients reported a weaker
belief that their illness has severe consequences compared to CF- and asthma patients. Contrary to what we expected, CHD-patients reported lower scores on the personal control scale than CF-patients. In line with expectations, CHD-patients reported a lower score on the personal control scale than DM- and asthma patients. Although all four patient groups reported high scores on the illness coherence scale, CHD- and CF-patients reported the highest scores, which may be inherent to the congenital character of their conditions. CHD-patients had a weak belief that their illness is changeable, whilst CF-, DM- and asthma patients reported a stronger belief that their illness fluctuates over time. Patients with CHD, DM, and asthma reported relatively low scores (below mid-point; <2.5) on the emotional representation scale, indicating that they experienced relatively few negative emotions as a result of their illness.

Table 3: Illness perceptions of CHD-patients compared to other patient groups

<table>
<thead>
<tr>
<th>Illness representations</th>
<th>CHD (n=845)</th>
<th>CF (n=199)</th>
<th>DM (n=158)</th>
<th>Asthma (n=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consequences</td>
<td>2.2 (0.8)</td>
<td>3.8 (0.6)*</td>
<td>2.5 (0.5)*</td>
<td>3.2 (0.8)*</td>
</tr>
<tr>
<td>Personal control</td>
<td>3.1 (0.8)</td>
<td>4.1 (0.5)*</td>
<td>4.2 (0.4)*</td>
<td>4.2 (0.5)*</td>
</tr>
<tr>
<td>Treatment control</td>
<td>4.4 (0.9)</td>
<td>3.4 (0.4)*</td>
<td>4.0 (0.7)*</td>
<td>4.1 (0.5)*</td>
</tr>
<tr>
<td>Illness coherence</td>
<td>4.0 (0.8)</td>
<td>3.9 (0.8)*</td>
<td>3.5 (0.7)*</td>
<td>3.7 (0.9)*</td>
</tr>
<tr>
<td>Timeline - cycle</td>
<td>2.3 (0.9)</td>
<td>3.3 (0.7)*</td>
<td>NA</td>
<td>3.1 (0.8)*</td>
</tr>
<tr>
<td>Emotional representation</td>
<td>2.1 (0.7)</td>
<td>NA</td>
<td>2.4 (0.6)*</td>
<td>2.2 (0.9)*</td>
</tr>
</tbody>
</table>

Note: Means and standard deviations are provided. CHD = congenital heart disease; CF = cystic fibrosis; DM = diabetes mellitus; NA = not available. a: Timeline – cycle represents the changeability of the illness and its symptoms; b: Emotional representation addresses the negative emotions caused by the illness. * p < 0.01.

The relation between patient characteristics and illness perceptions

Males had a stronger belief that their illness has severe consequences ($B=0.14$, $p=0.01$) and a weaker belief that their illness is changeable ($B=-0.11$, $p<0.05$) (Table 4). Patients with a complex heart defect, had a stronger belief that their illness has severe consequences, that the illness is changeable, and that the illness causes negative emotions ($p's<0.05$, see Table 4 for specific contrasts). Patients with a poor functional status (i.e. higher NYHA class) scored high on the consequences scale, low on the treatment control and the illness coherence scale, and high on the timeline - cycle and emotional representation scale ($p's<0.05$, see Table 4 for specific contrasts).
Table 4: Illness perceptions and their relation with patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Consequences</th>
<th>Personal control</th>
<th>Treatment control</th>
<th>Illness coherence</th>
<th>Timeline - cycle&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Emotional representation&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>0.14</td>
<td>0.01*</td>
<td>-0.01</td>
<td>0.84</td>
<td>&lt;0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.01</td>
<td>0.12</td>
<td>&lt;0.01</td>
<td>0.49</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>Disease complexity&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.37</td>
<td>&lt;0.01*</td>
<td>0.10</td>
<td>0.10</td>
<td>0.09</td>
<td>0.24</td>
</tr>
<tr>
<td>Complex</td>
<td>0.62</td>
<td>&lt;0.01*</td>
<td>0.19</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.95</td>
</tr>
<tr>
<td>Functional status&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA-II</td>
<td>0.70</td>
<td>&lt;0.01*</td>
<td>-0.04</td>
<td>0.56</td>
<td>-0.15</td>
<td>0.08</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>0.97</td>
<td>&lt;0.01*</td>
<td>0.14</td>
<td>0.24</td>
<td>-0.39</td>
<td>0.01*</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>1.37</td>
<td>&lt;0.01*</td>
<td>-0.11</td>
<td>0.58</td>
<td>-0.32</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Note: a = Timeline – cycle represents the changeability of the illness and its symptoms; b = Emotional representation addresses the negative emotions caused by the illness. B = B-value; p = p-value; NYHA = New York Heart Association functional class; § = reference category is simple; † = reference category is NYHA-I; * p < 0.05.
The independent predictive value of illness perceptions for quality of life at two-year follow-up

Multivariable analyses showed that patients’ sex, age, and functional status were independently predictive of QoL two years later (Table 5). More specifically, males reported a better physical QoL (PCS: \( B=2.50, p<0.01 \); Symptoms: \( B=4.49, p<0.01 \)). Older patients reported a better mental, but poorer physical QoL (\( p’s<0.05 \)). Finally, a poor functional status was independently predictive of a poorer mental and physical QoL (\( p’s<0.05 \), see Table 5 for specific contrasts).

Table 5: The independent predictive value of illness perceptions for quality of life at two-year follow-up

<table>
<thead>
<tr>
<th></th>
<th>MENTAL QUALITY OF LIFE</th>
<th>PHYSICAL QUALITY OF LIFE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCS</td>
<td>Worries</td>
</tr>
<tr>
<td></td>
<td>( B )</td>
<td>( p )</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male)</td>
<td>-0.15</td>
<td>0.82</td>
</tr>
<tr>
<td>Age</td>
<td>0.05</td>
<td>0.03*</td>
</tr>
<tr>
<td>Disease complexity( ^{§} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.43</td>
<td>0.54</td>
</tr>
<tr>
<td>Complex</td>
<td>1.54</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Functional status( ^{‡} )</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA- II</td>
<td>0.24</td>
<td>0.79</td>
</tr>
<tr>
<td>NYHA-III</td>
<td>0.10</td>
<td>0.95</td>
</tr>
<tr>
<td>NYHA-IV</td>
<td>-10.48</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td><strong>Illness perceptions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consequences</td>
<td>-0.05</td>
<td>0.60</td>
</tr>
<tr>
<td>Personal control</td>
<td>0.05</td>
<td>0.61</td>
</tr>
<tr>
<td>Treatment control</td>
<td>-0.08</td>
<td>0.57</td>
</tr>
<tr>
<td>Illness coherence</td>
<td>0.18</td>
<td>0.09</td>
</tr>
<tr>
<td>Timeline - cycle( ^{a} )</td>
<td>-0.24</td>
<td>0.10</td>
</tr>
<tr>
<td>Emotional representation( ^{b} )</td>
<td>-0.43</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

Note: MCS = Mental Component Summary of the SF-36; Worries = Worries subscale of the TAAQOL-CHD; PCS = Physical Component Summary of the SF-36; Symptoms = Symptoms subscale of the TAAQOL-CHD; NYHA = New York Heart Association functional class; \( ^{§} \) = reference category is simple; \( ^{‡} \) = reference category is NYHA-I; \( ^{a} \) = Timeline – cycle represents the changeability of the illness and its symptoms; \( ^{b} \) = Emotional representation addresses the negative emotions caused by the illness. \( B = \) B-value; \( p = \) p-value; * \( p < 0.05 \).

Mental quality of life

Multivariable analyses revealed that illness perceptions were predictive of mental QoL two-years later while adjusted for sex, age, disease complexity and functional status (Table 5). A strong belief that the illness has severe consequences was predictive of low scores on the Worries
scale ($B=-0.29$, $p=0.01$). In addition, patients who had a strong belief the illness caused negative emotions reported low scores on the MCS ($B=-0.43$, $p<0.01$) and Worries scale ($B=-0.60$, $p<0.01$).

Physical quality of life
Physical QoL two years later was also predicted by illness perceptions independent of patient characteristics (Table 5). Patients who had a strong belief the illness has severe consequences reported low scores on the PCS ($B=-0.53$, $p<0.01$) and Symptoms ($B=-0.28$, $p=0.01$) scale. Moreover, a weak belief that treatment can control the illness predicted low scores on the PCS scale ($B=0.32$, $p<0.01$). Low scores on the illness coherence scale were predictive of low scores on the Symptoms scale ($B=0.27$, $p=0.03$). Furthermore, a strong belief that the illness is changeable was predictive of low scores on the PCS ($B=-0.39$, $p<0.01$) and Symptoms ($B=-0.97$, $p<0.01$) scale. Finally, patients who had a weak belief that the illness caused negative emotions reported low scores on the PCS scale ($B=0.23$, $p=0.01$).

Further exploration of the relation between high scores on the consequences or emotional representation scale and poor quality of life at two-year follow-up
Strong beliefs that the illness has severe consequences and causes negative emotions are predictive of a poor QoL, irrespective of disease complexity and functional status. This indicates that there may be mild cases (i.e. simple defect or good functional status) reporting a strong belief that their illness has severe consequences or causes negative emotions, and who consequently report a poor QoL. We tested this hypothesis by means of post-hoc analyses. First, four groups were identified based on mild case types (i.e. simple defect or good functional status) combined with scores on the two illness representation scales (i.e. high score on the consequences or on the emotional representation scale [mean > 2.5]). Secondly, QoL-scores of each of the four groups were compared separately to those of the remaining patients (i.e. patients not included in the selected group). All comparisons were conducted by means of t-tests for each QoL scale (i.e. MCS, PCS, Symptoms and Worries) separately. Results of these analyses confirm our hypothesis that the mild cases that have strong beliefs their illness has severe consequences or causes negative emotions, report significantly lower QoL-scores ($p$’s<0.05).

DISCUSSION
To our knowledge this is the first longitudinal study in CHD-patients focusing on the predictive value of illness perceptions for QoL. The main result is that poor illness perceptions indeed are predictive of poor QoL two-years later while controlling for confounders (sex, age, disease complexity and functional status).

Compared to other patient groups, CHD-patients report good illness perceptions. Our results indicate that CHD-patients experience some emotional distress, think that they will benefit from treatment, perceive themselves to have a coherent illness understanding, and that their illness is fairly stable over time. This is in line with a cross-sectional study by Riley et al. examining the illness
perceptions and their relation to QoL in 99 adult outpatients with CHD. Both studies reported similar mean scores on the consequences, personal control, timeline – cycle, and emotional representation scales. In contrast, our patients reported a stronger belief that treatment can control their illness and that they have a coherent understanding of their illness. The distribution of sex and patients’ age across both studies were comparable. This dissimilarity may therefore be due to differences in the distribution of disease complexity (in our study more simple cases were included), selection of patients (outpatients versus patients from a nationwide registry) or variation across countries (UK versus the Netherlands).

Although in general illness, perceptions of CHD-patients are good, subgroups prone to having poor illness perceptions can be identified. The most severe cases (complex defect or poor functional status) reported the poorest illness perceptions – that is, a weak belief that treatment can control the illness and that they have a coherent illness understanding; and a strong belief that the illness has severe consequences and causes negative emotions. In view of these severe cases some of these illness perceptions are valid, for example, a strong belief the illness has severe consequences, although others may be less warranted, such as a weak belief they have coherent illness understanding. Patients with a complex defect or poor functional status thus merit attention, especially since an incoherent illness understanding is associated with inadequate health behavior (i.e. non-adherence to life-style recommendations and bad consultation behavior).7,37 This indicates that these patients may need additional support in changing their illness perceptions.

Independent of patient characteristics, poor illness perceptions are predictive of QoL at two-year follow-up. Although several studies in various patient groups confirm this relation,13-15 Riley et al36 could not corroborate this finding in their sample of CHD-patients. The latter study reported that CHD-patients’ QoL was impaired, whereas the QoL of our patients was not. This discrepancy in QoL scores may explain the absence of the relation between illness perceptions and QoL. Results of our study show in more detail, that patients who have a strong belief their illness has severe consequences and causes negative emotions, report a poor QoL. Moreover, we found a relation between a strong belief the illness is changeable and impairments in QoL. This is in agreement with a previous study in CHD demonstrating that uncertainty regarding illness course intrudes on patients’ daily life.38 In addition, patients who had a weak belief they have a coherent understanding of their illness and that the illness can be controlled by treatment also reported impairments in QoL. Prior studies hypothesizing that sense of coherence (SOC) may be a pathway for a good QoL in CHD-patients are in line with these results, as patients with a strong SOC see their illness as comprehensible, manageable, and meaningful.39

Interestingly, results of the post-hoc analyses show that mild cases – that is, simple defect or good functional status, having a strong belief their illness has severe consequences or causes negative emotions, consequently report a poor QoL at two-year follow-up. In clinical practice it is often observed that mild cases report impairments in their QoL. Our results suggest that patients’ poor illness perceptions may be partly responsible for this phenomenon.

The most important limitation of this study is that other factors that are not included, such as personality or psychological functioning are also likely to be related to patients’ QoL. Indeed, the
explained variance in our models ranged from 7.8% to 39.8%. Second, the illness perception scores of the CF-, DM-, and asthma patients were based on mean scores reported in publications. As a result differences in patient characteristics were not compared across groups and could therefore not be included as confounders when CHD-patients’ illness perceptions were compared to those of the other patient groups.

This study also has a number of strengths that we would like to emphasize. First, the inclusion of 845 patients from eight different centers constitute 6.5% of all registered patients in the national database and around 2.5% of the estimated total adult CHD-population in the Netherlands. Our sample therefore represents a broad spectrum of Dutch CHD-patients. Second, both general as well as disease-specific QoL is measured in this study. Third, this is the first longitudinal study focusing on the predictive value of illness perceptions for QoL in CHD-patients.

**Conclusions**

In adult CHD-patients, a complex defect and poor functional status are related to poor illness perceptions. These poor illness perceptions in turn are predictive of a poor QoL two years later, independent of these patient characteristics. This knowledge can help to identify patients who are susceptible to experiencing a poor QoL and provides a modifiable determinant. Possible interventions aimed at improving illness perceptions and thereby enhancing patients QoL, could focus on increasing patients’ knowledge regarding their disease and informing patients about treatment opportunities. Additionally, nurse practitioners or other health care providers (e.g. psychologists or social workers) may facilitate psychological counseling thereby reducing the belief that the illness has severe consequences and causes negative emotions. It is to be expected that severe cases (complex defect and poor functional status) experience severe consequences and negative emotions as a result of their illness. Nevertheless results show that irrespective of disease complexity and functional status these poor illness perceptions are predictive of a poor QoL. Moreover, our post-hoc analyses show that mild cases (simple defect or good functional status) reporting strong beliefs that their illness has severe consequences or causes negative emotions, consequently report a poor QoL. Psychological counseling could be especially favorable for these mild cases. Besides improving patients’ QoL, these interventions may also have secondary beneficial effects. That is, in various patient groups good illness perceptions are related to adequate health behavior, such as medication adherence and health care utilization. Future studies relating illness perception to health behavior in CHD-patients are therefore warranted.

**ACKNOWLEDGEMENT**

We are grateful to all patients for there willingness to participate. This study was supported by the Interuniversity Cardiology Institute of the Netherlands.
REFERENCES


Chapter 11

Mental quality of life is related to a cytokine genetic pathway

* Both authors contributed equally
ABSTRACT

Background Quality of life (QoL) in patients with a chronic disease is often impaired and cannot be solely explained by disease severity. We explored whether genetic variability and activity contributes to QoL in patients with Marfan syndrome (MFS), a genetic connective tissue disorder.

Methodology/Principal findings In 121 MFS-patients, patient characteristics (i.e. demographics and MFS-related symptoms) were assessed. Patients completed the SF-36 to measure QoL. In addition, transcriptome wide gene expression and 484 Single Nucleotide Polymorphisms (SNPs) in cytokine genes were available. QoL was first analyzed and associated with patient characteristics. Patients' physical QoL was impaired and weakly related to age and scoliosis, whereas mental quality of life (MCS score) was normal. To explain a largely lacking correlation between disease severity and QoL, we related genome wide gene expression to QoL. Patients with lower MCS scores had high expression levels of CXCL9 and CXCL11 cytokine-related genes (p=0.001; p=0.002); similarly, patients with low vitality scores had high expression levels of CXCL9, CXCL11 and IFNA6 cytokine-related genes (p=0.02; p=0.02; p=0.04), independent of patient characteristics. Subsequently, we associated cytokine related SNPs to mental QoL (MCS and vitality). SNP-cluster in the IL4R gene showed a weak association with the MCS and vitality (strongest association p=0.0017). Although overall mental QoL was normal, more than 10% of patients had low scores for MCS and vitality. Post-hoc analysis of systemic inflammatory mediators showed that patients with the lowest MCS and vitality scores had high levels of CCL11 cytokine (p=0.03; p=0.04).

Conclusions/Significance Variations in the cytokine genetic pathway and its activation is related to mental QoL. This finding might allow us to identify and, ultimately, treat patients susceptible to poor QoL.
INTRODUCTION

Quality of life (QoL) is an emerging general parameter of patients’ well-being. QoL can be defined in various ways. It is a multifactorial concept consisting of individual perception of physical, psychological and social functioning. In general, research has documented that patient characteristics, such as age, sex, racial, and psychological factors, such as mood states, and stress, influence patients’ QoL. However, there is a large variation between individuals that is not explained by these factors. This suggests that intrinsic factors, i.e. individual genetic predisposition, contributes to ones perception of his or her well-being. In diverse psychiatric and psychological states a genetic disposition is emerging as an important causative factor. Such examples are negative emotional states (e.g. depression), positive emotional states (e.g. subjective well-being), self-rated health, pain and fatigue. In addition, results from twin studies show that the heritability for subjective well-being and life-satisfaction is up to 40-50%, whereas for both depression and anxiety that is around 30-40%. Different biological pathways have been associated with various QoL elements, i.e. mood, overall well-being, pain and fatigue. Examples of these biological pathways are the hypothalamic-pituitary-adrenal axis, and immune, neuroendocrine, and cardiovascular systems.

The genetic basis for QoL has been largely ignored. Recently, the GENEQOL Consortium was initiated aiming to investigate the genetic disposition of quality-of-life. A first study by Rausch et al has shown that various single nucleotide polymorphisms (SNPs) in cytokine genes are related to QoL in lung cancer survivors.

In this study we investigated the QoL and its genetic basis in patients with Marfan syndrome (MFS). This is a chronic heritable disorder involving many organ systems at young age. Main features are aortic root dilatation with risk of sudden death, skeletal deformities resulting from overgrowth of long bones and dislocation of ocular lens. Most of the features require regular medical follow-up and often operative treatment at young age. Living with MFS can have a profound impact on daily life and one would expect impairments of patients’ QoL. Four studies have examined QoL in MFS-patients. Three of these studies reported impairments in physical QoL, whereas the mental QoL was similar compared to the normal population. Only one study, however, explored the influence of disease characteristics on QoL and concluded that QoL cannot be explained by disease severity in these patients.

In this study we explored the QoL and the influence of disease severity on QoL in MFS-patients. Furthermore, we searched for intrinsic factors which contribute to QoL by exploring gene expression, SNPs and cytokine levels in MFS-patients.

METHODS

Study population and procedure

The patient sample participating in the “COzaar in Marfan PAtients Reduces aortic Enlargement” (COMPARE) study, was included in this study. In short, the COMPARE study investigates the effect of losartan on aortic dilatation in patients with MFS. Inclusion criteria of the COMPARE study were:
diagnosis of MFS according to the Ghent criteria and age ≥18 years. Exclusion criteria were: previous replacement of more than one part of the aorta, previous aortic dissection, angiotensin converting enzyme inhibitor or angiotensin receptor blocker usage, current pregnancy. The COMPARE study was conducted in four Marfan centers in the Netherlands (Academic Medical Center Amsterdam, Leiden University Medical Center, St. Radboud University Medical Center Nijmegen, Groningen University Medical Center). The study was approved by four Medical Ethics Committees of the participating centers. All patients gave written and oral informed consent. Patients were in regular follow-up by a cardiologist. Each patient was seen by a research physician at inclusion to assess Marfan-related symptoms, disease history and medication use. Furthermore, a questionnaire measuring QoL was handed out by a research physician before consultation.

Measurements

Patient characteristics

The following dichotomised (yes/no) MFS-related symptoms were assessed by research physicians at intake in the COMPARE study: aortic root dilatation, aortic root replacement, mitral valve prolapse, beta-blocker usage, pectus deformity, ectopia lentis, joint hypermobility (Beighton score >4/9), severe scoliosis (>20°), hindfoot deformity, wrist and thumb sign, striae, and pneumothorax. All features were scored according to the Ghent diagnostic criteria for MFS. Aortic root dilatation and mitral valve prolapse were assessed by means of echocardiography at inclusion of the COMPARE study. Additionally, age, sex, medication and co-morbidities were obtained at intake when QoL was measured.

Quality of life

QoL was measured with the Short Form Health Survey-36 (SF-36), yielding eight domains, i.e. Vitality (VT; energy level), Social Functioning (SF; ability to participate in social activities), Role Emotional (RE; ability to participate in daily and occupation activities despite emotional constraints), Mental Health (MH; moods), Physical Functioning (PF; the ability to perform usual and energetic activities), Role Physical (RP; ability to participate in daily and occupation activities despite physical constraints), Bodily Pain (BP; pain level), and General Health (GH; current health). The first four domains load on a mental component summary (MCS), whereas the last four load on a physical component summary (PCS). For all eight domains and both subscales, higher scores reflect a better quality of life. The SF-36 is validated and yield good psychometric properties.

Gene expression

Genome wide expression, i.e. expression of all well referenced genes (approximately 18 000 genes) was measured in skin biopsies of patients using Affymetrix Human Exon 1.0 ST Array. Punch skin biopsies were performed in consenting patients, after local anesthesia with ethyl chloride spray. Biopsies were immediately snap frozen in liquid nitrogen and stored at -80°C until further processing. Additional information about the RNA isolation and gene expression measurements is provided in the Supplementary Material, Method section.
**Single Nucleotide Polymorphisms (SNPs)**

Genomic DNA was extracted from peripheral blood using the gentra puregene blood kit (Qiagen, the Netherlands) according to the manufacturer’s instructions. Genotyping of the patients was performed using Illumina Human Omni Express Bead Chip measuring >700,000 SNPs. Multiple quality control measures were implemented. The estimated sex for each individual determined by genotyping was compared with their phenotypic sex. Exclusion criteria included deviation from Hardy-Weinberg equilibrium at $p<10^{-3}$, sample call rate $<0.95$ and SNP call rate $<0.98$. Additional information about the SNP analysis is provided in the Supplementary Material, Method section.

**Cytokine measurements in plasma**

Peripheral EDTA blood was sampled at the time of QoL measurement, centrifuged at 3220 rpm for ten minutes, snap-frozen and stored in small portions at -80°C. Cytokines were measured using the suspension bead assays (Bio-Rad, Richmond, CA) using a Luminex reader (BioRad, BioSource, Linco). Lowest detection rate ranged from 0.12 to 0.91 pg/ml and intra- and inter-assay coefficients of variation $<5%$.

**Statistical analyses**

**Quality of life**

We first compared MFS-patients’ QoL to the normal population. MFS-patients’ mean scores on the eight QoL domains (see table S1) were therefore transformed to standard scores based on the scores of an age- and gender-matched Dutch reference population. Standard scores were calculated by dividing the difference between the mean scores of the MFS-patients and the scores of the age- and gender-matched reference population, by the standard deviation of the reference population. The value of the standard scores can be interpreted according to Cohen’s effect size ($d$), where a score of $<0.2$ indicates a small, 0.5-0.8 a moderate and $>0.8$ a large difference. Additionally, the MCS and PCS scores were compared to the mean of the general population (mean scores=50), by means of two t-tests at a significance level of 5%.

Second, the relation between patient characteristics and QoL was examined. As a first step, several linear regression analyses were employed to identify, which of the in Table 1 listed patient characteristics, were significantly ($p<0.10$) related to each of the QoL outcomes (i.e. the eight QoL-domains and both QoL-subscales). Subsequently, to examine the independent relation between patient characteristics and QoL, all univariately significant variables were simultaneously included in multivariate linear regression analyses. These analyses were performed for each of the QoL outcomes separately ($p<0.05$).

**Relating gene expression and SNPs to quality of life**

First, QoL-outcomes were correlated with the genome wide gene expression in skin using univariate linear regression analyses with permutation testing in Significance Analysis of Microarrays package in R program. In order to avoid multiple testing problems, we chose a conservative False Discovery Rate (FDR) of 0% as significant. Subsequently, multivariate regression analyses were used to test
whether the relation between gene expression and QoL remained significant after controlling for the significantly independently associated patient characteristics ($p<0.05$).

Second, SNPs belonging to the genes of the cytokine pathway found in the gene expression study (in the previous step) were selected for an association study. Only SNPs with a minor allele frequency $>5\%$ were analyzed. Linear regression analysis assuming an additive genetic model with adjustment for age and sex was used. For all analyses we used the GenABEL analysis package in R program.$^{28}$ Bonferroni correction for multiple testing was used to define the target $p$-value.

RESULTS

Patient characteristics and their relation with quality of life

Of the 228 selected patients from the COMPARE study,$^{22}$ 121 patients filled out the SF-36 (response rate 52.6%) and were thus included in this study. Patient characteristics for the patient group included in this study ($n=121$) and non-responders ($n=107$) are presented in Table 1. Only ectopia lentis and usage of beta-blockers were more frequent in the investigated group ($n=121$) compared to the non-responders, Table 1. Gene expression was available for 40 of the 121 patients (33%), whereas genotypes (SNPs) were available for 111 patients. Patient characteristics (Table 1) of both groups were compared to the total group ($n=121$). Results showed that ectopia lentis and two

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics in frequencies (percentages)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
</tr>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
</tr>
<tr>
<td>Sex (male)</td>
</tr>
<tr>
<td>Cardiac features</td>
</tr>
<tr>
<td>Aortic root dilatation</td>
</tr>
<tr>
<td>Root replacement</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
</tr>
<tr>
<td>Beta-blocker usage*</td>
</tr>
<tr>
<td>Ectopia lentis*</td>
</tr>
<tr>
<td>Skeletal features</td>
</tr>
<tr>
<td>Pectus deformity</td>
</tr>
<tr>
<td>Joint hypermobility</td>
</tr>
<tr>
<td>Severe scoliosis</td>
</tr>
<tr>
<td>Hindfoot deformity</td>
</tr>
<tr>
<td>Wrist and thumb sign</td>
</tr>
<tr>
<td>Striae</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
</tbody>
</table>

Note: Frequencies (percentages) for the presence of the symptoms are given for all dichotomous variables. Age is given in mean years (standard deviation). * $p < 0.05$.  

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skeletal features (severe scoliosis and hindfoot deformity) were more frequent in the total group (n=121) compared to the group for whom gene expression was available (n=40).

When QoL of MFS-patients (n=121) was compared to that of an age- and gender-matched population, scores on six of the eight QoL domains were significantly lower in MFS-patients (p<0.01) (Figure 1). MFS-patients had a similar mental QoL (t(116)=-0.5, p=0.63) as the general population. The physical QoL of MFS-patients was significantly lower than that of the age- and gender-matched population (t(116)=-4.8, p<0.01). On average 10% of patients had an impaired QoL (standardized score ≤ 2, data not shown).

Figure 1: Standardized quality of life scores on the eight quality of life domains.

Note: A standardized quality of life (QoL) score <0 indicates a QoL score that is worse than the age- and gender-matched reference population, and scores >0 indicates better QoL-scores. The standardized scores can be interpreted as Cohen’s d, indicating the effect size. VT = Vitality, SF = Social Functioning, RE = Role Emotional, MH = Mental Health, PF = Physical Functioning, RP = Role Physical, BP = Bodily Pain, GH = General Health. Domains which significantly (p<0.05) differed from the age- and gender-matched reference population are marked with *.

Results of the analyses relating patient characteristics to QoL showed that correlations were largely lacking, only age and the presence of severe scoliosis were independently related to the QoL-domains and -subscales (p<0.05). The variance in QoL explained by these characteristics ranged from 8.9% to 28.3%, see Table 2.

Expression of inflammatory genes are independently related to variability in mental quality of life

Since correlations between patient characteristics and QoL were weak and the explained variance was low, we explored whether variation in QoL was related to gene expression in MFS-patients (n=40). Results of these analyses revealed that physical QoL was not correlated with gene expression. Mental quality of life (MCS and vitality), however, was associated with expression of genes coding for cytokines. MCS was associated with the genes CXCL9 and CXCL11 (FDR=0% for all; t(39)=-2.9; t(39)=-2.8 respectively). Vitality was associated with expression levels of CXCL9, CXCL11 and IFNA6 genes (FDR=0% for all; t(39)=-3.2; t(39)=-2.6; t(39)=-2.6, respectively). Thus, patients with a worse mental QoL have more active cytokine genes (Figure 2).
Table 2: Patient characteristics independently related to quality of life

<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>Patient characteristics</th>
<th>Explained variance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCS</strong></td>
<td>Severe scoliosis*</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td>Striae</td>
<td>16.2</td>
</tr>
<tr>
<td></td>
<td>Bblockers*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe scoliosis**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic root replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>Role Emotional</strong></td>
<td>Ectopia lentis</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>Age*</td>
<td></td>
</tr>
<tr>
<td><strong>Social Functioning</strong></td>
<td>Striae</td>
<td>28.3</td>
</tr>
<tr>
<td></td>
<td>Bblockers*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe scoliosis**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aortic root replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>Vitality</strong></td>
<td>Severe scoliosis**</td>
<td>19.9</td>
</tr>
<tr>
<td></td>
<td>Sex*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>PCS</strong></td>
<td>Severe scoliosis*</td>
<td>13.9</td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>General Health</strong></td>
<td>Striae</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td>Severe scoliosis**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumothorax**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td><strong>Bodily Pain</strong></td>
<td>Striae</td>
<td>13.1</td>
</tr>
<tr>
<td></td>
<td>Severe scoliosis*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age*</td>
<td></td>
</tr>
<tr>
<td><strong>Physical Function</strong></td>
<td>Striae</td>
<td>20.2</td>
</tr>
<tr>
<td></td>
<td>Severe scoliosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
<tr>
<td><strong>Role Physical</strong></td>
<td>Aortic dilatation</td>
<td>20.0</td>
</tr>
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<td></td>
<td>Bblocker**</td>
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<td></td>
<td>Aortic root replacement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age**</td>
<td></td>
</tr>
</tbody>
</table>

Note: All 121 patients were included. Presented are the independent variables which were univariately significant associated with quality of life, and simultaneously included in multivariate linear regression analyses. MCS = Mental Component Summary; PCS = Physical Component Summary; Bblocker = beta-blocker; * p < 0.05; **p < 0.01.
This relation between gene expression and mental QoL and vitality remained significant, after controlling for the significant independent related patient characteristics reported in Table 2. Mental QoL (i.e. MSC) was related to the genes $\text{CXCL9}$ ($\beta=-3.6$, $p=0.001$) and $\text{CXCL11}$ ($\beta=-3.4$, $p=0.002$), after controlling for age and the presence of severe scoliosis, which were both no longer significantly related to QoL. The explained variance in mental QoL increased from 13.9% (only patient characteristics) to an average of 35% (patient characteristics and gene expression).

Vitality remained significantly associated with expression levels of, $\text{CXCL9}$ ($\beta=-2.5$, $p=0.02$), $\text{CXCL11}$ ($\beta=-2.5$, $p=0.02$), and $\text{IFNA6}$ ($\beta=-2.2$, $p=0.04$) after controlling for patient characteristics (i.e. age, sex, and the severe scoliosis). Only age remained an independent significant correlate with vitality.

The explained variance in vitality scores increased from 19.9% to an average of 42%. Given the immunological character of the associated genes, we explored the prevalence of immunological co-morbidities and clinical depression. Both prevalence levels were comparable to the general population (Table S2); there were no significant differences.

**SNPs in IL4R gene correlate with mental quality of life**

As mental QoL was associated with the expression of cytokine genes, we selected SNPs in 88 cytokine-related genes and two kb up- and down-stream of these. In total 659 SNPs were found in these genes of which 484 passed the quality control and were included in the analysis. Results of the association study of the 484 SNPs showed that the mental QoL (i.e. MCS) and vitality were associated with several SNPs with a highest $p$-value of 0.0017. MCS was associated with a top SNP rs4787423 ($p=0.0017$) located in the $\text{IL4R}$ gene (Table 3). Several SNPs in $\text{IL4R}$ gene had a significant
A p-value forming a trail (Figure S1). Vitality showed the strongest association in rs2023906 SNP (p=0.0017), single SNP in CCR7 gene which suggests this finding is likely to be incidental.

Table 3: Association of SNP clusters in IL4R gene with mental quality of life

<table>
<thead>
<tr>
<th>QoL</th>
<th>SNP-ID</th>
<th>Chr</th>
<th>Phys. Position</th>
<th>Minor allele</th>
<th>Gene</th>
<th>β</th>
<th>S.E.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCS</td>
<td>rs4787423</td>
<td>16</td>
<td>27367334</td>
<td>C</td>
<td>IL4R</td>
<td>-4.5</td>
<td>1.5</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td>rs3024536</td>
<td>16</td>
<td>27352713</td>
<td>T</td>
<td>IL4R</td>
<td>-3.6</td>
<td>1.7</td>
<td>0.0169</td>
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<tr>
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<td>1.7</td>
<td>0.0169</td>
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<td>1.7</td>
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<td>IL4R</td>
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<td>2.0</td>
<td>0.0198</td>
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<td>27366499</td>
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<td>rs170359</td>
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<td>IL4R</td>
<td>-5.2</td>
<td>2.9</td>
<td>0.0346</td>
</tr>
<tr>
<td></td>
<td>rs3024560</td>
<td>16</td>
<td>27356667</td>
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<td>IL4R</td>
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<td>1.4</td>
<td>0.0363</td>
</tr>
<tr>
<td></td>
<td>rs2234895</td>
<td>16</td>
<td>27359327</td>
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<td>IL4R</td>
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<td>2.1</td>
<td>0.0423</td>
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<tr>
<td></td>
<td>rs3024619</td>
<td>16</td>
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<td>A</td>
<td>IL4R</td>
<td>2.5</td>
<td>1.4</td>
<td>0.0407</td>
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<td></td>
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<td>16</td>
<td>27331894</td>
<td>A</td>
<td>IL4R</td>
<td>2.5</td>
<td>1.5</td>
<td>0.0466</td>
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<tr>
<td></td>
<td>rs223819</td>
<td>16</td>
<td>57394862</td>
<td>C</td>
<td>IL4R</td>
<td>-4.3</td>
<td>2.7</td>
<td>0.0521</td>
</tr>
</tbody>
</table>

Note: a: QoL = Quality of life; b: Chr = chromosome; c: Phys. Position = Position of the SNP on the chromosome; d: β = mean MCS score difference per one minor allele; e: S.E. = standard error of the beta; f: p = p-value; g: MSC = Mental component score.

Although mental QoL and vitality scores were not related to MFS symptoms, there was an overall trend to lower mental QoL scores with approximately 10% of patients having low mental QoL scores. Therefore we post-hoc explored the systemic levels of inflammatory markers (i.e. IL4, IL5, IL13, GM-CSF and CCL11) in patients with the lowest mental QoL and vitality scores. These cytokines are in the same inflammatory pathway as the IL4R gene and are all involved in the pathogenesis of allergy (e.g. asthma and rhinitis). The 25% of patients with the lowest MCS scores were compared to the 25% patients with the highest mental QoL. In this line, patients with the lowest vitality scores (standardized score ≤1.5) were compared to patients with normal scores (standardized score ≥0). Results from both comparisons showed that patients with a low mental QoL had higher levels of CCL11 in plasma blood compared to patients with normal mental QoL (p=0.03; p=0.04), Figure 3.
DISCUSSION

In our study, physical QoL of MFS-patients was impaired and related to age and presence of scoliosis. Mental QoL, however, was comparable to the normal population. Both mental QoL and vitality, one of its components, were associated with genetic variation in cytokine genes and their activity, independently of patient characteristics (i.e. demographics, MFS-related symptoms and co-morbidities). Moreover, the impairments in QoL were not associated with MFS-related genes (i.e. genes in the TGF-β pathway). Therefore, this relation seems to be not MFS specific and might be extrapolated to the normal population. In a small subgroup of patients with impaired mental QoL and vitality high systemic levels of the cytokine CCL11 were found.

Our primary finding, that the variation in mental QoL can be independently explained by cytokine-related genes, is in concordance with the emerging literature about the immunological basis of QoL-related symptoms and disorders such as depression and fatigue. It is important to note that although related, depression, fatigue and QoL are distinct concepts. In our study both mental QoL and vitality were independently, negatively related to CXCL9 and CXCL11 expression levels. These cytokines belong to the same family together with CXCL10 and share the common receptor CXCR3. In normal conditions their levels are generally not detectable but are strongly induced by interferon-gamma (IFN-γ). Previous research has demonstrated that global QoL was negatively related to IFN-γ. Serum levels of the related CXCL10 gene were found to be related to depression. Additionally, in our patient population vitality was negatively related to the IFNA6 gene. Although there is little known about the function of this gene, IFN-induced fatigue is a common phenomenon.

Interestingly, the SNPs in CXCL9, CXCL10, CXCL11 and IFN genes were not significantly associated with QoL. High expression levels of these genes are most likely induced by other inflammatory genes up-stream in a complex immunological cascade. In line with this hypothesis, we found a relation between mental QoL and SNPs in the IL4R gene. This gene codes for the IL4 receptor.
Polymorphisms in this gene are associated with asthma and rhinitis in case-control studies.\textsuperscript{30,41} In our patient population the prevalence of immunological and allergic disorders was not increased suggesting SNPs in \textit{IL4R} gene independently contributed to mental QoL. Numerous studies have shown that higher IL4 levels are protective for depression.\textsuperscript{30,42,43} Mechanisms through which inflammatory genes and QoL are related are unknown. Hypothetically, high expression levels of cytokine-related genes are associated with sickness-behavior which is reflected in impaired QoL. In our previous work we found that inflammation aggravates disease severity in MFS-patients. In this study however, mental QoL was associated with cytokine related genes independently of disease characteristics, suggesting an independent immune-related process which affects the perception of well-being in these patients. Functional immunological studies are needed in order to elucidate the exact mechanism of this relation.

Although mental QoL and vitality were unrelated to MFS, there was a high number of patients, approximately 10\%, with low scores for these two components of mental QoL. These patients showed high systemic levels of CCL11, a cytokine involved in pathogenesis of allergy. Similar results have been found in depressed patients; they showed elevated CCL11 levels compared to age- and gender-matched controls.\textsuperscript{44} In this study only clinical treated depression was documented. We cannot exclude the possibility that some patients with low QoL have depressive symptoms. Other factors which were not measured in this study could also contribute to QoL impairment. For example, MFS-patients are likely to have emotional problems, such as feelings of guilt because of inheritance of MFS and concerns about their career, family planning, insurance and housing.\textsuperscript{45} In addition, factors not related to MFS, such as lack of social support and personality may play a role as well. Future studies should explore additional factors associated with QoL in MFS-patients.

There are some limitations to this study. First, most severe cardiovascular MFS-patients were not included, due to the exclusion criteria of the COMPARE study. This might have led to an underestimation of the impairment in physical QoL and its relation with cardiovascular disease severity. The main limitation of this study is a relatively small sample size. The highest \( p \)-value (\( p=0.0017 \)) in the genetic association study did not reach the targeted \( p \)-value after Bonferroni correction (\( p=0.0001 \)). Most SNPs in \textit{IL4R} gene had \( p \)-values less than 0.05 which suggest the association is not likely to be incidental. As these associations do not seem to be MFS specific, validation in patients with different pathology or even in a healthy population could yield interesting results. This is still the largest study on QoL in MFS-patients and the first study exploring the genetic basis of their QoL.

In conclusion, we found a genetic basis for mental QoL in cytokine genes and their activity. This relation does not seem specific for MFS and is independent of patient characteristics. Knowledge about this genetic component of QoL provides insight and can eventually allow us to identify patients susceptible to poor QoL. This information might guide clinicians in decision making, opting for treatments with the smallest negative impact on QoL. Furthermore, we will be able to better target specific support to those who need it. Note that validation in larger patient populations is warranted. Ultimately, immunological treatment strategies can be developed to improve patients’ QoL.
ACKNOWLEDGEMENT

We thank the GENEQOL consortium for their inspiring initiative to study the genetic disposition of quality of life.
REFERENCES


11. Sprangers MA, Bartels M, Veenhoven R et al. Which patient will feel down, which will be happy? The need to study the genetic disposition of emotional states. *Qual Life Res* 2010; 19(10):1429-1437.


SUPPLEMENTARY MATERIAL

Methods

Gene expression study

Full skin punch biopsies of four mm (~5-15 mg) were used to isolate total RNA. Skin biopsies were pulverized in liquid nitrogen and transferred to 1.5 ml tubes containing Qiazol (Qiagen). Crude RNA extractions were obtained according to manufacturer’s instructions with the addition of Phase-Lock Gel Heavy (5 Prime) to obtain a better phase separation. The crude RNA fractions were further purified with the RNeasy Minelute Cleanup Kit (Qiagen) according to Appendix D protocol: RNA Cleanup after Lysis and Homogenization with QIAzol Lysis Reagent. RNA yield was measured on a Nanodrop ND-1000 (Thermo Fisher Scientific) and the RNA quality was investigated on the BioAnalyzer 2100 (Agilent Technologies) with the RNA 6000 Pico Chip Kit (Agilent Technologies). Only RNA samples with sufficient yield and RIN-values above 6.5 were used for analysis.

Gene expression was analyzed with Affymetric Human Exon 1.0 ST Arrays. Sense-strand cDNA was generated from total RNA using Ambion WT Expression Kit (Applied Biosystems) conform manufacturer’s instructions. Further steps were performed using manufacturer’s protocols for the GeneChip platform (Affymetrix). Those included purification of double-stranded cDNA, synthesis of cRNA by in vitro transcription, recovery and quantitation of biotin-labeled cRNA, fragmentation of this cRNA and subsequent hybridization to the microarray slide, posthybridization washings and detection of the hybridized cRNA using a streptavidin-coupled fluorescent dye. Hybridized Affymetrix Arrays were scanned using Gene-Chip Scanner 3000-7G (Affymetrix). Image generation and feature extraction were performed using Affymetrix GCOS Software v1.4.0.036.

Normalization and quality control were performed using the Expression Console © software by Affymetrix.

Genotyping

Genomic DNA of MFS-patients was extracted from peripheral blood using the gentra puregene blood kit (Qiagen, the Netherlands) according to the manufacturer’s instructions. Microarray-based DNA genotyping was performed at ServiceXS (ServiceXS B.V., Leiden, The Netherlands) using the HumanOmniExpress BeadChip (Illumina, Inc., San Diego, CA, U.S.A). This array interrogates >700 000 loci with a median marker spacing of 2.2 kb. Of each sample, four µl genomic DNA at 50 ng/µl was processed and hybridized to the BeadChips, according to the manufacturer’s instructions. The BeadChip images were scanned on the iScan system and the data was extracted into Illumina’s GenomeStudio software v2010.1. The software’s default settings were used with the cluster file as developed by Illumina for genotype calling.

Statistical analysis was performed using GenABEL package in the R statistical program (R Development Core Team (2010). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org). Linear regression analysis assuming an additive genetic model with adjustment for age and sex was used to analyze the association of the aortic root dilatation rates and genotypes.
Multiple quality control measures were implemented. The estimated sex for each individual determined by genotyping was compared with their phenotypic sex. Only SNPs with a minor allele frequency of >5% were included in the analysis. Exclusion criteria included deviation from Hardy-Weinberg equilibrium at \( p < 10^{-3} \), sample call rate <0.95 and SNP call rate <0.98. Bonferroni correction for the target p-value was applied.

**Table S1: Mean scores on the quality of life domains and subscales**

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MCS</strong></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>75.59 (16.28)</td>
</tr>
<tr>
<td>Role emotional</td>
<td>84.31 (30.94)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>79.58 (21.80)</td>
</tr>
<tr>
<td>Vitality</td>
<td>58.77 (19.43)</td>
</tr>
<tr>
<td><strong>PCS</strong></td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>56.99 (22.46)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>70.58 (23.80)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>79.23 (20.25)</td>
</tr>
<tr>
<td>Role physical</td>
<td>68.80 (41.37)</td>
</tr>
</tbody>
</table>

Note: SD = Standard deviation; MCS = Mental Component Summary; PCS = Physical Component Summary.

**Table S2: Prevalence of immunologically-related disorders and treated depression in MFS- population**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence study population (%)</th>
<th>Prevalence Dutch population (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Asthma</td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>0.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Depression</td>
<td>5.5</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Note: Numbers are provided in percentages.
Note: Locus-specific association map generated from genotyped SNPs in IL4R gene, centered at rs4787423. SNPs in red have $r^2 \geq 0.8$ with rs2824293; SNPs in orange have $0.5 < r^2 < 0.8$; SNPs in yellow have $0.2 < r^2 < 0.5$; and SNPs in white have $r^2 < 0.2$ with the leading SNP. Superimposed on the plot are gene locations (green) and recombination rates (blue). Chromosome positions are based on HapMap release 22 build 36.2 and b was prepared using SNAP2.
References


Chapter 12

Are adults with congenital heart disease at risk for the development of heart failure when feeling depressed? An immunological mechanism

Pediatric Cardiology, 2012; 33(7):1233-1234

Dounya Schoormans
Eddy A Wierenga
TO THE EDITOR

In the article published in *Pediatric Cardiology*, Perry emphasizes the increasing problem of heart failure (HF) among adult patients with congenital heart disease (CHD). We agree with his recommendation for a categorization of risk for HF based on patients’ CHD anatomy and physiology. In addition, we think that other factors associated with HF, such as co-morbidities, should be taken into account as well.

In the field of acquired heart disease, it is well known that co-morbid depression is associated with the development and progression of HF. Prevalence of life-time depression in adult CHD-patients is around 33%. Although the relation between depression and the development of HF needs to be confirmed in CHD-patients, it is not too far-fetched to assume that depressed patients with CHD may be at increased risk of future HF.

The exact pathway underlying the relationship between depression and HF is unknown, but an immunological mechanism is often suggested. Research has shown that depressed individuals display higher serum levels of the pro-inflammatory cytokines interleukin (IL)-1, IL-6 and Tumor Necrosis Factor-alpha (TNF-α) than non-depressed control subjects. These pro-inflammatory cytokines in turn are involved in the development and progression of HF. There is reason to believe that the relationship between depression and pro-inflammatory cytokines may be even more pronounced for CHD-patients because they already show increased levels of these cytokines at an early age. In contrast, patients with acquired heart disease display abnormal levels as the disease develops.

Future studies should therefore examine the relationship between pro-inflammatory cytokines and depression in CHD-patients. Subsequently, longitudinal studies need to investigate the causal relation between elevated pro-inflammatory cytokine levels, depression, and the development and progression of HF in CHD-patients. Ultimately, these results may provide important information on risk categorization for future HF and the development of new treatment options for both depression and HF in CHD-patients. The latter is extremely important because it is unclear if the traditional treatment options for HF in patients with acquired heart disease are equally beneficial for CHD-patients. Perhaps anti-depressants with anti-inflammatory effects, such as serotonin reuptake inhibitors (SSRIs), are an option, not only for treating the depressive symptoms but perhaps also for reducing the risk for development or progression of HF. Although the evidence is controversial, recent studies suggest that SSRIs may prevent future coronary heart disease events and myocardial infarctions.

In summary, besides CHD anatomy and physiology additional factors such as co-morbid depression need to be taken into account in risk categorization for HF in CHD-patients. Moreover, future studies should be conducted relating pro-inflammatory cytokine levels to depression and examining the predictive value of both for future HF in CHD-patients.
ACKNOWLEDGEMENTS

We are very grateful to prof.dr. MAG Sprangers and prof.dr. BJM Mulder for their support.
REFERENCES
Chapter 13

General discussion

Future challenges in providing appropriate care for adults with congenital heart disease

Submitted

Dounya Schoormans
Mirjam AG Sprangers
Barbara JM Mulder
Adults with congenital heart disease (CHD) need lifelong multidisciplinary care to manage the residual cardiac lesions and reduce the impact. Currently provided care is suboptimal as an unknown number of patients receive inappropriate care. Three groups can be distinguished: (1) patients lost to follow-up, (2) patients who use less and (3) patients who use more health care than needed given their clinical status. In this article we provide targets and discuss challenges for the delivery of appropriate and cost-effective care. Currently 32 to 61 percent of patients are lost to follow-up. A future target is therefore pro-active searches to retrieve these lost patients. Moreover, we need to know patients’ reasons for using less or more health care than needed. Research on this topic is largely lacking in CHD. The only two studies conducted found that patients with a Type D personality use less care than needed given their functional status. Furthermore, irrespective of disease complexity and functional status, a poor quality of life and a negative perception of their CHD leads to more health care use. This indicates that a referral to a psychosocial health care provider is probably more appropriate and effective for these patients. The delivery of appropriate care remains challenging. Additional research on at least the following topics is thus needed: the scope of the problem; determinants of health care use; patients’ perspective on current health care; and patients’ needs and treatment preferences.
INTRODUCTION

At present, the adult population with a congenital heart defect (CHD) outweighs the number of children with an estimated population of 1 million in the United States and 1.3 million in Europe.\(^1\) Despite cardiac surgery most patients have residual lesions. As a consequence, patients can have long-term complications such as arrhythmias and heart failure.\(^1\) Moreover, they can experience a number of physical symptoms (chapter 8),\(^2\) psychological impairments,\(^3\) and social problems\(^1\). To manage the congenital malformation and to reduce the negative impact on daily life, lifelong multidisciplinary care is needed (chapter 2).\(^4\) Indeed, in clinical practice CHD-patients have contact with various health care providers such as a general practitioner, cardiologist, physical therapist and social worker (chapter 3).\(^5\) Currently provided care is however suboptimal as an unknown number of patients do not receive appropriate care.\(^6\) Three patient groups can be distinguished: (1) patients who are lost to follow-up, (2) patients who use less care and (3) patients who use more care than they would need given their clinical status (Figure 1). An example of such inappropriate health care use is a patient with a simple defect and a good functional status who may visit his or her cardiologist frequently without a specific clinical reason. It is likely that other non-clinical factors, such as worries about the illness, are responsible for his or her visits. For this patient, multidisciplinary combined care from his or her cardiologist and a psychosocial health care provider may be more effective and less expensive. Consequently currently provided care needs to be improved to enable the delivery of optimal appropriate and cost-effective health care for all CHD-patients.

In this article we will discuss key issues in improving health care provision for CHD-patients. We will therefore address the problem of patients lost to follow-up and reasons for less or more health care use. For each patient group, targets for the delivery of appropriate and cost-effective health care will be provided. Finally, directions for future research are discussed.

![Figure 1: Reasons for receiving inappropriate care](image-url)
PATIENTS LOST TO FOLLOW-UP

It is estimated that 32 to 61 percent of adult patients are lost to follow-up.\(^7,8\) This may be the result of problems in the transition from pediatric to adult cardiology as up to 70% of patients experience a lapse in care during that time. Moreover, young adults may believe that follow-up care is unnecessary since they are asymptomatic. Others may deny their CHD because they do not want to feel different than their peers. As many CHD-patients have residual lesions and are prone to develop long-term complications, continuation of care is of paramount importance. A future target should therefore be the development and evaluation of transition programs. Moreover, a pro-active retrieval of these lost patients is needed.

PATIENTS WHO USE LESS HEALTH CARE

Health care use of CHD-patients is of course determined by the complexity of their defect and functional status (chapter 3 and 4).\(^5,9\) Nevertheless, enabling (e.g. insurance) and psychosocial factors such as knowledge of the condition or feelings of anxiety may also influence patients’ health care use (Figure 1).

Patients who use less health care than needed based on their clinical status, may for example have a low income or need to travel far to the nearest hospital (Figure 1). This may also be the result of lacking awareness of symptoms that warrant medical attention (Figure 1). Empirical research examining factors that determine less health care use in CHD-patients is scarce.

Type D personality

One study\(^9\) (chapter 4) did find that patients with a so called Type D personality, have a poorer functional status and quality of life (QoL) than patients without such a personality, yet they report less health care use (Figure 1). A Type D personality is the tendency to experience negative affect and to be socially inhibited.\(^10\) Around 20% of CHD-patients have such a Type D personality, which is similar to the general population.\(^9\) Due to their social inhibition, doctor–patient communication may be hampered.\(^10\) Therefore physicians may need to help Type D patients to disclose their symptoms and concerns. In general, similar to common clinical practice in oncology, all CHD-patients could fill out a questionnaire on symptoms and concerns prior to the consultation (chapter 8).\(^2\) Physicians can then discuss patients’ answers, thereby lowering their threshold to disclose these issues.

PATIENTS WHO USE MORE HEALTH CARE

Another group of patients uses more health care than needed based on their clinical status. Several factors, such as anxiety and worries about the illness or non-adherence to treatment could play a role (Figure 1). Here too, empirical research is largely lacking. One longitudinal study (chapter 5) examined the predictive value of psychological patient characteristics on health care use, irrespective of disease complexity and functional status. They found that both a poor QoL and a negative perception of their illness are related to more health care use (Figure 1).
Quality of life

Patients with a poor QoL report more health care use, regardless of their disease complexity and functional status (chapter 4 and 5). One possible explanation may be that patients wrongfully contribute their poor QoL to their CHD. Indeed, patients’ disease severity is only marginally related to patients’ QoL (chapter 9 and 10). This finding indicates that a future target should be the timely referral to psychosocial health care providers. They should focus on improving patients’ QoL. Recent studies have shown that CHD-patients with a poor QoL, experience little social support, feel depressed and anxious (chapter 9), experience few feelings of happiness (chapter 9), have little understanding of their CHD and believe their illness can hardly be managed by treatment (chapter 10). Thus psychosocial care should focus on increasing social support by for example stimulating patients to join sport groups and getting family and friends involved. Additionally, nurse practitioners and psychologists should aim to reduce feelings of depression and anxiety, and enhance feelings of happiness. Furthermore, interventions should aim at increasing patients’ knowledge and informing them about treatment options.

How patients perceive their illness

Another important determinant of patients health care use is the way they perceive their illness (chapter 5). Results show that patients who feel their CHD has a large negative impact on their life, report more outpatient health care use, regardless of their disease complexity or functional status. Additional support by nurse practitioners, social workers or psychologists to reduce the negative impact may be more appropriate here. Moreover, patients who believe that their illness can be managed by themselves report more outpatient but less inpatient health care use. Educating patients about self-management may for example increase treatment-adherence, which in turn can prevent them from using expensive inpatient healthcare.

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

Future targets for the organization of current health care are locating patients lost to follow-up and preventing future drop-out. Moreover, we need to make sure that patients are referred to psychosocial health care providers if needed.

Delivering appropriate and cost-effective care remains challenging, as empirical research on how to organize care for CHD-patients is scarce. Future research on the following topics is therefore of paramount importance. First, we need to know the extent of the problem, by estimating how many patients receive inappropriate care. Second, factors that determine health care use need to be identified. For example, we need to study parameters of cardiac functioning and enabling factors. Third, how patients perceive the provided care needs to be investigated, since this knowledge gives us information on the quality of care and can direct its future organization (chapter 6). Fourth, patients’ needs and treatment preferences for both medical and psychosocial care need to be studied as these are vital for the delivery of adequate care.
REFERENCES


The overall aims of this thesis were: (1) to examine health care use and its predictors, patients’ need for health care and patients’ evaluation of health care; (2) to study quality of life (QoL) and its predictors; and (3) to relate patient-reported and clinical outcomes through biological pathways, in adults with congenital heart disease (CHD).

In chapter 1, the background to this thesis and the overall objectives were described. This chapter gave an introduction to health care and QoL within the field of CHD. In addition, the relationship between clinical and patient-reported outcomes and underlying biological pathways was introduced.

The results described in the chapters 3 to 5, and 8 to 10 were part of a longitudinal study in adult CHD-patients. In March, 2009, 1670 adult CHD-patients from five tertiary and three regional Dutch centers were randomly selected from the CONCOR database, a Dutch registry for adults with CHD. Of the 1670 patients, 1109 participated (response rate 66.4%). Patients completed a questionnaire set assessing health care use and needs, Type D personality, QoL, depressive symptoms, trait-anxiety, happiness, optimism, illness perceptions, symptomatology, and perceived health. Two years later, the 1100 first-time respondents (nine died during follow-up period) were asked to fill-out a second questionnaire set assessing health care use and QoL. A total of 845 of the 1100 first-time respondents also completed the second questionnaire set (response rate 76.8%).

HEALTH CARE
In chapter 2, we argued in a letter to the editor that future empirical research on health care is essential to enable appropriate and cost-effective care for the growing population of adult CHD-patients. We stressed the importance of focusing on at least the following three topics. First, insight into current health care use needs to be gained. Studies should therefore focus on multidisciplinary health care as this type of care is ideally needed for CHD-patients. Second, patient characteristics associated with health care use have to be identified, enabling the prediction of future health care utilization and allocation of future health care. Third, patients’ perceived needs for health care have to be investigated, as this is vital information for the provision of tailored care. Chapter 3 described the first empirical study that examined whether health care use meets patients’ needs. In this chapter we described the study-specific questionnaire that we employed to assess in- and outpatient health care use during the past year for CHD-specific reasons and patients’ needs. Outpatient health care use was operationalized as the number of contacts with a cardiologist, general practitioner and other health care providers such as a pulmonologist and psychologist. In addition, the number of contacts with three complementary care givers was assessed. Inpatient health care use was operationalized as the number of hospitalizations, emergency room visits and operations. Furthermore, patients were asked whether they wanted to have more or less contact during the past year, or whether the number of contacts was sufficient. In all, 1109 patients participated in this cross-sectional study. Results showed that a total of 66% and 40% of patients had contact with their cardiologist and general practitioner during the previous year. Other medical specialists were contacted less often, ranging from 1.9% for a rheumatologist to
14.2% for a nurse. Few patients (0.6-1.9%) had contact with complementary health care providers such as an acupuncturist. Six to 10 percent were hospitalized, operated upon, or visited the emergency room. We further found that for the majority of patients (86.9-95.0%), the amount of contact was sufficient. We assessed patients’ perceptions of their general practitioner and cardiologist and whether they perceive health care improvements are needed. Most patients (76.7-98.7%) indicated that both the communication skills and expertise of the cardiologist and general practitioner were sufficient and health care improvements unnecessary. Finally, results showed that patients, who did rate the communication skills of the cardiologist as insufficient, reported a need for more contact. There should be more awareness for the importance of good communicating skills in clinical practice.

To provide adequate and optimal care for adult CHD-patients, knowledge on which patients use what type of health care and to what extent, is important for health care providers and policy makers. This information will enable the prediction and allocation of future health care utilization in a cost-effective manner. Chapters 4 and 5 described the first two studies on this topic within the field of CHD. In chapter 4, we examined the relation between Type D (‘distressed’) personality and health care use. Of the 1109 patients that participated, 302 were excluded due to missing data. Thus, 807 patients were enrolled in this cross-sectional study. Around 20% was categorized as having a Type D personality, which is the tendency to experience negative affect and to be socially inhibited. Similar prevalence levels are reported in other cardiac patient groups and the general population. We found that Type D patients reported a poorer functional status and QoL than non-Type D patients, yet they used less health care. This indicated that Type D patients may be reluctant to contact a health care provider in case of need. Chapter 5 described a longitudinal study relating clinical and psychological patient characteristics to health care use. The main objective was to examine the extent to which psychological patient characteristics – that is, Type D personality, QoL, depressive symptoms, trait-anxiety, happiness, optimism, and illness perceptions, were predictive of health care use, while controlling for disease complexity and functional status. The illness perceptions measured in this study consisted of the belief that the illness has a negative impact, is manageable, is understood, can be changed and causes negative feelings. Data of the 845 enrolled patients were used in this study. Results showed that health care use of CHD-patients was not entirely determined by the complexity of the cardiac defect or functional status, but also for a large part by psychological characteristics. That is, patients who reported more health care use had no Type D personality, yet did report a poor QoL. They moreover felt their CHD had a severe impact on their life and believed their CHD can be managed by themselves or treatment. This indicated that physicians should not only focus on medical care, but they should also be aware that patients may need to be referred to psychosocial health care providers. Nurse practitioners, social workers, or psychologists could then focus on improving patients’ QoL, reducing the negative impact of the CHD, and teaching patients self-management skills.

During their adult life, patients with CHD undergo several medical procedures. Probably the most invasive is open-heart surgery. Given the complex character and the high impact of open-heart surgery, high quality of care during this procedure is of paramount importance. In chapter 6,
we described a first study on patients’ level of satisfaction with the care provided when undergoing open-heart surgery, identifying best and worst valued aspects. Specialized nurses can have a vital function for patients undergoing open-heart surgery, informing them about the procedure, lifestyle adjustments after surgery, and the recovery trajectory. We therefore also examined whether the involvement of specialized nurses was associated with higher levels of patient satisfaction. Between January, 2010 and July, 2011, 132 consecutive patients who had an open-heart surgery at a selected tertiary hospital were invited three to six weeks after their operation to participate in this study. Patients were sent a questionnaire, evaluating nine aspects of care by answering individual items and giving overall grades (range 0-10) In total, 75 patients (response rate 56.8%) returned the questionnaire. We found that, overall, patients were satisfied with the provided care, with grades ranging from 6.74 for “discharge and after care” to 8.18 for “medical care.” The lowest grades were for “discharge and after care” indicating that there is room for improvement. More specifically, 20.0% of patients were dissatisfied with the after care provided by the surgeon, whereas 21.2% of patients were dissatisfied with the clarity of the information about lifestyle adjustments provided by the surgeon. Having contact with a specialized nurse was associated with a higher level of satisfaction with the provided information. We could thus conclude that patients are satisfied with the received peri-operative care, although there is room for improvement, especially with respect to discharge and after care and the clarity of the information provided by the surgeon. This gap in care can be compensated for by specialized nurses, as patients who were counseled by a specialized nurse were more satisfied with the provided information.

QUALITY OF LIFE

The most commonly assessed aspect of QoL is patients’ physical functioning. An indicator of physical functioning in CHD-patients is functional status. In clinical practice, the treating cardiologist assesses patients’ functional status according to the New York Heart Association (NYHA) classification. In large scale medical research where patients cannot be seen by a physician at each time point, it is advantageous if functional status could be assessed by patients themselves. However, the usefulness of such patient-based NYHA class assessment depends on its agreement with the cardiologist-based score. In chapter 7, we described a study aimed to develop and test a patient-based questionnaire to assess functional status. In all, 86 consecutive adult outpatients and four cardiologists participated. They completed three patient-based questionnaires – a patient-based translation of the NYHA classes; a self-constructed questionnaire based on the NYHA classes; and the Specific Activity Scale (SAS). Patient-cardiologist agreement was assessed by calculating percent agreement and weighted kappa. Since co-morbidity is known to affect self-reported health, we also explored the level of agreement for patients without co-morbidity. An agreement of 75.6% (weighted kappa is 0.43), 70.6% (weighted kappa is 0.44), and 74.4% (weighted kappa is 0.28) was found between the cardiologist assessment and the patient-based translation, self-constructed questionnaire, and SAS respectively. The patient-based translation equally over- and underestimated the NYHA class, whereas the self-constructed questionnaire
overestimated and the SAS underestimated the NYHA class. Agreement levels for patients without co-morbidity were higher than agreement levels for the total group. The patient-based translation of the NYHA classes showed the highest agreement and equal over- and underestimation, we therefore recommended its use in future research.

Perceived health is the subjective rating of one’s general health status, and increasingly guides medical decision making in clinical practice. Insight into why patients rate their perceived health the way they do is needed, particularly in the case where there is a discrepancy between patients’ perceived health and physicians’ evaluation. This information may help clinicians in deciding which perspective is more important in the decision-making. Previous research in CHD-patients shows that disease complexity is only marginally related to perceived health. Thus, variation in perceived health across CHD-patients is the result of other factors than disease complexity. In chapter 8, we examined the symptomatological profile of CHD-patients and its relationship with perceived health. We therefore conducted a secondary data analysis on two separate patient samples (629 Belgian and 1109 Dutch patients). Results showed that the most frequently occurring symptoms in CHD-patients are dizziness, palpitations and nycturia. We moreover found that distress about symptoms is more strongly related to perceived health than the mere presence of symptoms. This study suggested that a systematic appraisal of symptoms, in particular symptom distress, is essential in the assessment of perceived health, irrespective of disease complexity. This finding confirmed the clinical observation that there are patients with a complex defect who experience few symptoms and consequently report a better perceived health, than patients with a simple defect who experience many symptoms.

Despite the improvements in medical treatment, many patients have residual lesions, which may lead to impairments in QoL. To improve patients’ QoL, knowledge on modifiable determinants is essential. In chapter 9 and 10 we described two longitudinal studies using data of the 845 participating patients. In chapter 9, we examined the predictive value of negative (depressive symptoms and trait-anxiety) and positive affect (happiness and optimism) and whether positive affect serves as a buffer for the detrimental consequences of negative affect on patients’ QoL at two-year follow-up. Results showed that many depressive symptoms and high trait-anxiety scores were related to poor mental and physical QoL. Happiness was predictive of a better mental but poorer physical QoL. Moreover, patients with many depressive symptoms and high happiness scores reported better mental QoL than patients with many depressive symptoms but low happiness scores. Thus, happiness seems to function as a buffer for the negative effect of depressive symptoms on patients’ mental QoL. Mental QoL of CHD-patients can therefore be improved via a dual policy of decreasing negative affect and enhancing positive affect. In chapter 10, we examined the independent predictive value of illness perceptions for QoL at two-year follow-up. Additionally, we compared CHD-patients’ illness perceptions to those of patients with cystic fibrosis, diabetes mellitus and asthma; and we examined the relation between patient characteristics and illness perceptions. We found that CHD-patients have good illness perceptions compared to patients with other diseases. Within CHD-patients, a complex defect or poor functional status was related to negative illness perceptions. Negative illness perceptions in turn were found to be predictive of
future QoL, independent of disease complexity and functional status. In more detail, patients who
reported a poor QoL have a strong belief that the illness has a negative impact; a weak belief that
they have a good understanding and that the illness can be managed by treatment; and a strong
belief that the illness is changeable and causes negative feelings. Increasing patients’ knowledge
regarding their disease and informing them about treatment options may provide targets to
enhance patients’ QoL.

BIOLOGICAL PATHWAYS
In general, research has documented that patient characteristics, such as age, sex, racial, and
psychological factors, such as mood states, and perception, influence patients’ QoL. However,
there is a large variation among individuals that is not explained by these factors. This suggests that
intrinsic factors – such as, individual genetic predisposition, contributes to one’s perception of his
or her well-being. In chapter 11, we examined whether genetic variability and activity contributes
to QoL in patients with Marfan syndrome (MFS), a genetic connective tissue disorder. One of
the main features of MFS is the congenital cardiac defect; aortic root dilatation. An additional
aim of this study was to explore MFS-patients’ QoL and the extent to which it is influenced by
disease severity. In 121 MFS-patients, patient characteristics (i.e. demographics and MFS-related
symptoms) and QoL were assessed. In addition, transcriptome wide gene expression and 484
Single Nucleotide Polymorphisms (SNPs) in cytokine genes were available. Results showed that
patients’ physical QoL was impaired and weakly related to age and scoliosis, whereas mental QoL
was normal. Results from the genome wide gene expression study showed that patients with a
lower mental QoL had high expression levels of the CXCL9, CXCL11, and IFNA6 cytokine-related
genes. Subsequently, we found an association between mental QoL and a SNP-cluster in the IL4R
gene. Although overall mental QoL was normal, more than 10% of patients had low scores. Post-
hoc analysis of systemic inflammatory mediators showed that patients with lowest mental QoL
scores had high levels of the CCL11 cytokine. We therefore concluded that variation in the cytokine
genetic pathway and its activation is related to QoL. This may allow us to identify and ultimately
treat patients susceptible to a poor QoL.

In chapter 12, we described in a letter to the editor that depressed CHD-patients are possibly
at risk of developing heart failure through an immunological mechanism. We advocated that other
factors than CHD anatomy and physiology, such as co-morbid depression should be taken into
account in risk categorization for heart failure in CHD-patients. Moreover, we stated that future
research should focus on relating immunology to depression and examine the predictive value of
both for future heart failure.

Finally, in chapter 13, we discussed future challenges in providing appropriate care for
adults with CHD. We distinguished three groups of patients who receive inappropriate care: (1)
patients lost to follow-up, (2) patients who use less and (3) patients who use more health care
than needed given their clinical status. We described that currently 32 to 61 percent of patients
are lost to follow-up, who need to be retrieved by pro-active searches. The existing empirical
studies on factors that determine health care use (chapters 4 and 5 of this thesis) were discussed. As described, we found that: first, patients with a Type D personality use less care than needed given their functional status. Second, irrespective of disease complexity and functional status, a poor QoL and a negative perception about their CHD leads to more health care use. Both studies indicated that referral to a psychosocial health care provider is probably more appropriate and effective for these patients. As only two studies were conducted, additional research is needed on at least the following topics: the scope of the problem, by estimating how many patients receive inappropriate care; determinants of health care use; patients’ perspective on current health care; and patients’ needs and treatment preferences.

The take home messages that can be derived from this thesis are presented in the box below.

<table>
<thead>
<tr>
<th>Take home messages</th>
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<tr>
<td>• Patients use care from different health care providers and rate both the amount and quality of care as sufficient. <em>Chapter 3</em></td>
</tr>
<tr>
<td>• Type D patients report a poorer functional status and quality of life than non-Type D patients, yet use less health care. <em>Chapter 4</em></td>
</tr>
<tr>
<td>• Health care use is not entirely determined by the complexity of the cardiac defect or functional status, but also for a large part by psychological characteristics - that is, Type D personality; quality of life; belief that their congenital heart defect has a severe impact, and can be managed by themselves or treatment. <em>Chapter 5</em></td>
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<tr>
<td>• Patients are satisfied with the received peri-operative care, although there is room for improvement, especially in discharge and after care and the clarity of the information provided by the surgeon. Patients who were counseled by a specialized nurse were more satisfied with the provided information. <em>Chapter 6</em></td>
</tr>
<tr>
<td>• The patient-based translation of the New York Heart Association classes shows the highest patient-cardiologist agreement and can therefore be used in future research. <em>Chapter 7</em></td>
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<tr>
<td>• Distress about symptoms is stronger related to perceived health than the mere presence of symptoms. <em>Chapter 8</em></td>
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<tr>
<td>• Happiness functions as a buffer for the negative effect of depressive symptoms on mental quality of life. <em>Chapter 9</em></td>
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<tr>
<td>• Negative illness perceptions are predictive of future quality of life, independent of disease complexity and functional status. <em>Chapter 10</em></td>
</tr>
<tr>
<td>• Variation in the cytokine genetic pathway and its activation is related to mental quality of life. <em>Chapter 11</em></td>
</tr>
<tr>
<td>• Patients who feel depressed are possibly at risk of developing heart failure through an immunological mechanism. <em>Chapter 12</em></td>
</tr>
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Appendix

Nederlandse samenvatting
Dankwoord
List of publications
Curriculum Vitae
Het doel van dit proefschrift was om bij volwassenen met een aangeboren hartafwijking (AHA): (1) gezondheidszorggebruik en voorspellers daarvan, de behoefte van patiënten aan gezondheidszorg en de patiëntevaluatie van de gezondheidszorg te onderzoeken; (2) de kwaliteit van leven (KvL) en voorspellers daarvan te bestuderen; en (3) patiëntgerapporteerde en klinische uitkomstmaten te relateren via biologische mechanismen.

In hoofdstuk 1 zijn de achtergrond van dit onderzoek en de algemene doelen beschreven. Dit hoofdstuk geeft een inleiding over gezondheidszorggebruik en KvL op het gebied van AHA. Daarnaast worden de relatie tussen klinische en patiëntgerapporteerde uitkomstmaten en onderliggende biologische ‘pathways’ geïntroduceerd.

De resultaten die in de hoofdstukken 3 tot en met 5, en 8 tot en met 10 worden beschreven zijn onderdeel van een langlopende studie bij volwassenen met een AHA. In maart 2009 zijn 1670 volwassen AHA-patiënten – die behandeld werden in vijf academische en drie regionale ziekenhuizen – willekeurig geselecteerd uit de CONCOR database, een Nederlandse registratiebank voor volwassenen met een AHA. Van de 1670 patiënten namen er 1109 (respons was 66.4%) deel aan het onderzoek. Patiënten vulden een vragenlijstpakket in waarin gevraagd werd naar gezondheidszorggebruik en -behoefte, Type D persoonlijkheid, KvL, depressieve symptomen, angst, geluk, optimisme, ziektepercepties, symptomatologie en zelfgerapporteerde gezondheid. Twee jaar later werden de 1100 patiënten die de eerste keer hadden deelgenomen (negen mensen waren overleden gedurende de ‘follow-up’ periode) gevraagd een tweede vragenlijstpakket in te vullen. Hiermee werden gezondheidszorggebruik en KvL opnieuw gemeten. In totaal vulden 845 van de 1100 patiënten (respons was 76.8%) het tweede vragenlijstpakket in.

GEZONDHEIDSZORG
In hoofdstuk 2 pleitten we in een brief aan de editor, voor toekomstig empirisch onderzoek naar de gezondheidszorg, aangezien dat essentieel is om geschikte en kosteneffectieve zorg te kunnen bieden aan de groeiende populatie van volwassen AHA-patiënten. We benadrukten dat ten minste de volgende drie onderwerpen zouden moeten worden belicht. Ten eerste moet er inzicht in het huidige gezondheidszorggebruik en de behoefte aan zorg worden verkregen. Studies moeten zich richten op multidisciplinaire gezondheidszorg, aangezien dit type zorg idealiter nodig is voor AHA-patiënten. Ten tweede moeten patiënt eigenschappen die geassocieerd zijn met gezondheidszorggebruik worden geïdentificeerd. Hierdoor kunnen we toekomstig zorggebruik voorspellen en gezondheidszorg toewijzen. Ten derde moet de behoefte aan gezondheidszorg van patiënten worden onderzocht, aangezien dit vitale informatie oplevert voor het bieden van zorg op maat. Hoofdstuk 3 beschreef de eerste empirische studie die onderzocht of gezondheidszorggebruik voldoet aan de behoefte van de patiënt. In dit hoofdstuk beschreven we de studiespecifieke vragenlijst die (poli)klinisch gezondheidszorggebruik van het afgelopen jaar om
AHA-specifieke redenen, en de behoefte van de patiënten aan zorg meet. Poliklinisch zorggebruik werd geoperationaliseerd als het aantal contacten dat een patiënt had met een cardioloog, huisarts en andere zorgverleners, zoals een longarts of psycholoog. Daarnaast werd gevraagd naar het aantal contacten met drie alternatieve genezers. Klinisch zorggebruik werd geoperationaliseerd als het aantal opnames, bezoeken aan de eerste hulp en operaties. Verder werd aan patiënten gevraagd of zij meer of minder contact hadden willen hebben, of dat het aantal contactmomenten genoeg was. In totaal namen 1109 patiënten deel aan deze cross-sectionele studie. De resultaten lieten zien dat in totaal respectievelijk 66% en 40% van de patiënten het afgelopen jaar contact had gehad met hun cardioloog en huisarts. De overige zorgverleners werden minder vaak gecontacteerd, uiteenlopend van 1.9% voor een reumatoloog tot 14.2% voor een verpleegkundige. Een kleine groep patiënten (0.6-1.9%) had contact met een alternatieve genezer, zoals een acupuncturist. Zes tot 10 procent was opgenomen in het ziekenhuis, geopereerd of had de eerste hulp bezocht. Verder zagen we dat voor de meerderheid van de patiënten (86.9-95.0%) het aantal contactmomenten genoeg was. We onderzochten de perceptie van de patiënten ten aanzien van hun huisarts en cardioloog en in hoeverre zij verbeteringen in de gezondheidszorg nodig achten. De meeste patiënten (76.7-98.7%) gaven aan dat zowel de communicatievaardigheden als de expertise van de cardioloog en de huisarts voldoende waren en verbeteringen in de zorg niet nodig. Ten slotte zagen we dat de patiënten die de communicatievaardigheden van de cardioloog als onvoldoende beoordeelden vaker behoefte hadden aan meer contact. We concludeerden dat er meer aandacht zou moeten zijn voor het belang van goede communicatievaardigheden in de klinische praktijk.

Om adequate en optimale zorg voor volwassen AHA-patiënten te kunnen leveren is het voor zorgverleners en beleidsmakers belangrijk te weten welke patiënten welke zorg gebruiken, en in welke mate. Deze informatie stelt ons in staat zorggebruik te voorspellen en op een kosteneffectieve manier toe te wijzen. In hoofdstuk 4 en 5 beschreven we de eerste twee studies over dit onderwerp bij AHA-patiënten. In hoofdstuk 4 onderzochten we de relatie tussen een Type D ('distressed') persoonlijkheid en gezondheidszorggebruik. Van de 1109 patiënten die deelnamen, werden er 302 geëxcludeerd vanwege ontbrekende gegevens. Uiteindelijk werden daarom 807 patiënten geïncludeerd in deze cross-sectionele studie. Ongeveer 20% van de patiënten had een Type D persoonlijkheid. Onder een Type D persoonlijkheid verstaat men de neiging om negatief affect en sociale inhibitie te ervaren. Soortgelijke prevalenties zijn gerapporteerd bij andere groepen hartpatiënten en de algemene populatie. Wij vonden in onze AHA-populatie dat Type D patiënten een slechtere functionele status en KvL rapporteerden dan patiënten zonder Type D persoonlijkheid. Zij maakten echter minder gebruik van de gezondheidszorg. Dit duidt erop dat Type D patiënten wellicht terughoudend zijn om contact op te nemen met een zorgverlener indien nodig. Hoofdstuk 5 beschreef een longitudinale studie waarin klinische en psychologische patiëntieigenschappen werden gerelateerd aan gezondheidszorggebruik. Het belangrijkste doel was om te onderzoeken in hoeverre psychologische patiëntieigenschappen – Type D persoonlijkheid, KvL, depressieve symptomen, angst, geluk, optimisme en ziektepercepties – voorspellend waren voor gezondheidszorggebruik, terwijl we controleerden voor de complexiteit van de hartafwijking en de
functionele status. De ziektepercepties die werden gemeten in deze studie waren de overtuiging
dat de ziekte een negatieve impact heeft, controleerbaar is, begrijpbaar is, veranderbaar is, en
negatieve gevoelens tot gevolg heeft. De gegevens van de 845 deelnemende patiënten werden
gebruikt in deze studie. Resultaten lieten zien dat gezondheidszorggebruik van AHA-patiënten niet
volledig wordt bepaald door de ziektecomplexiteit of functionele status, maar ook voor een groot
deel door psychologische eigenschappen. Specifieker, patiënten die meer gezondheidszorggebruik
rapporteerden hadden geen Type D persoonlijkheid, maar rapporteerden wel een verminderde
KvL. Bovendien waren zij ervan overtuigd dat hun AHA een negatieve impact op hun leven had
en dat hun AHA onder controle kon worden gehouden door henzelf of door behandeling. Dit
suggereert dat artsen zich niet alleen op medische zorg moeten richten, maar zich ook bewust
moeten zijn dat sommige patiënten naar een psychosociale zorgverlener doorverwezen dienen te
worden. Verpleegkundig specialisten, maatschappelijk werkers of psychologen kunnen zich dan
ritten op het verbeteren van de KvL van patiënten, het verminderen van de negatieve impact die
de AHA heeft, en patiënten zelfmanagement-vaardigheden leren.

Gedurende het volwassen leven ondergaan patiënten met een AHA verschillende medische
behandelingen, waarvan een open-hart operatie het meest belastend is. Gezien het complexe
karakter en de grote impact van een open-hart operatie is het van groot belang dat de zorg van hoge
kwaliteit is. In hoofdstuk 6 beschreven we de eerste studie naar patiënttevredenheid ten aanzien
van de zorg die patiënten ontvangen wanneer ze een open-hart operatie ondergaan. Daarbij
identificeerden we de beste en slechtst beoordeelde aspecten. Specialistisch verpleegkundigen
c kunneen een belangrijke functie vervullen voor patiënten die een open-hart operatie ondergaan
door hen te informeren over de procedure, aanpassingen in de leefstijl na de operatie en de
herstelperiode. Daarom onderzochten we tevens of de betrokkenheid van een specialistisch
verpleegkundige samenging met een hogere mate van patiënttevredenheid. Tussen januari 2010
een juli 2011 werden 132 opeenvolgende patiënten die in een specialistisch centrum een open-hart
operatie ondergingen geïdentificeerd. Drie tot zes weken na de operatie werden zij uitgenodigd
om deel te nemen aan de studie. Een vragenlijst werd opgestuurd naar de patiënt. Daarin werden
negen aspecten van zorg geëvalueerd door het beantwoorden van individuele items en het geven
van algemene cijfers (oplopend van 0-10). In totaal stuurd 75 patiënten (response was 56.8%)
de vragenlijst terug. Over het algemeen waren patiënten tevreden over de ontvangen zorg; cijfers
liep uiteen van 6.74 voor “ontslag en nazorg” tot 8.18 voor “medische zorg”. De laagste cijfers
voor “ontslag en nazorg” geven aan dat hier ruimte voor verbetering is. Specifieker, 20.0% van
de patiënten was ontevreden over de nazorg geleverd door de chirurg en 21.2% was ontevreden
over de duidelijkheid van de informatie die de chirurg verstrekte over leefregels. Contact met
een specialistisch verpleegkundige was gerelateerd aan een hogere mate van patiënttevredenheid
over de informatie. We zouden dus kunnen concluderen dat patiënten tevreden zijn met de zorg
rondom hun operatie, maar dat er ruimte is voor verbetering. Die ruimte bestaat met name op
het gebied van ontslag en nazorg en de duidelijkheid van de informatie die de chirurg verstrekt.
Specialistisch verpleegkundigen kunnen hiervoor compenseren, aangezien patiënten die begeleid
werden door een specialistisch verpleegkundige meer tevreden waren over de ontvangen informatie.

**KWALITEIT VAN LEVEN**

Het meest onderzochte aspect van KvL is fysiek functioneren. Een graadmeter van fysiek functioneren in AHA-patiënten is hun functionele status. In de klinische praktijk wordt de functionele status van een patiënt vastgesteld door de cardioloog volgens de ‘New York Heart Association (NYHA)’ classificatie. In grootschalig onderzoek waarin patiënten niet op ieder meetmoment door een cardioloog kunnen worden gezien, is het voordelig wanneer de functionele status door de patiënt zelf kan worden bepaald. Echter, de bruikbaarheid van een dergelijke door de patiënt gerapporteerde NYHA klasse is afhankelijk van de mate waarin die overeenkomt met de bepaling van de cardioloog. In hoofdstuk 7 beschreven we een studie naar de ontwikkeling en toetsing van een dergelijke patiënt-gerapporteerde vragenlijst. In totaal deden 86 opeenvolgende volwassen poliklinische patiënten en vier cardiologen mee aan de studie. De patiënten vulden drie vragenlijsten in – een op de patiënt gebaseerde vertaling van de NYHA klassen; een zelfontwikkelde vragenlijst gebaseerd op de NYHA klassen; en de ‘Specific Activity Scale’ (SAS). Patient-cardioloog overeenkomst werd bepaald door het percentage dat overeenkomt en ‘weighted kappa’ te berekenen. Aangezien we weten dat comorbiditeit van invloed is op zelfgerapporteerde gezondheid, bepaalden we de mate van overeenkomst ook voor mensen zonder comorbiditeit. De mate van overeenkomst tussen de cardioloog en de op de patiënt gebaseerde vertaling van de NYHA klassen, de zelfontwikkelde vragenlijst gebaseerd op de NYHA klassen en de SAS was respectievelijk 75.6% ('weighted kappa' is 0.43), 70.6% ('weighted kappa' is 0.44), en 74.4% ('weighted kappa' is 0.28). De op de patiënt gebaseerde vertaling over- en onderschatte de NYHA klasse in gelijke mate, terwijl de zelfontwikkelde vragenlijst overschatte en de SAS onderschatte. De mate van overeenkomst voor patiënten zonder comorbiditeit was hoger dan die voor de totale groep. De op de patiënt gebaseerde vertaling kwam het beste overeen met de cardioloog en over- en onderschatte de NYHA klasse in gelijke mate. We bevelen daarom deze vragenlijst aan voor gebruik in toekomstig onderzoek.

Zelfgerapporteerde gezondheid is de subjectieve bepaling van iemands gezondheidsstatus. Deze maat bepaalt in toenemende mate medische beslissingen in de klinische praktijk. Inzicht in hoe patiënten hun gezondheid beoordelen is noodzakelijk, in het bijzonder wanneer er een discrepancy is tussen de beoordeling van de patiënt en de arts. Deze informatie kan clinici helpen in de afweging welke visie belangrijker is voor de besluitvorming. Eerder onderzoek onder AHA-patiënten laat zien dat de complexiteit van de hartafwijking maar marginaal gerelateerd is aan zelfgerapporteerde gezondheid. Variatie in zelfgerapporteerde gezondheid in AHA-patiënten is dus het resultaat van andere factoren dan ziektecomplexiteit. In hoofdstuk 8 onderzochten we het symptomatologisch profiel van AHA-patiënten en de relatie met zelfgerapporteerde gezondheid. Daartoe hebben we een secundaire data analyse gedaan op twee verschillende patiënt-steekproeven (629 Belgische en 1109 Nederlandse patiënten). De meest frequent
voorkomende symptomen bij AHA-patiënten zijn duizeligheid, hartkloppingen en een verhoogde urineafscheiding gedurende de nacht. Bovendien lieten de resultaten zien dat ongemak ten gevolge van die symptomen sterker gerelateerd is aan zelfgerapporteerde gezondheid dan alleen de aanwezigheid van de symptomen. Deze studie suggereert dat de systematische beoordeling van symptomen, vooral het ongemak, essentieel is bij het vaststellen van zelfgerapporteerde gezondheid, onafhankelijk van de complexiteit van de hartafwijking. Deze bevinding bevestigt de klinische observatie dat er patiënten zijn met een complexe AHA die weinig symptomen ervaren en daardoor een betere gezondheid rapporteren dan patiënten met een simpele AHA die veel symptomen ervaren.

Ondanks verbeterde medische behandelingen ervaren veel patiënten restlaesies die kunnen leiden tot een verminderde KvL. Om de KvL van patiënten te verbeteren is kennis van veranderbare determinanten essentieel. In hoofdstuk 9 en 10 beschreven we twee longitudinale studies die gebruik maakten van de gegevens van de 845 deelnemende patiënten. In hoofdstuk 9 onderzochten we de voorspellende waarde van negatief affect (depressieve symptomen en angst) en positief affect (geluk en optimisme) voor de KvL twee jaar later. Resultaten lieten zien dat veel depressieve symptomen en hoge angstscores gerelateerd waren aan een slechte mentale en fysieke KvL. Tevens rapporteerden patiënten die veel depressieve symptomen ervaarden en daarnaast hoog scoorden op geluk een betere mentale KvL dan patiënten met veel depressieve symptomen maar een lage score op geluk. Gevoelens van geluk lijken dus te functioneren als een buffer voor het negatieve effect dat depressieve symptomen hebben op mentale KvL. Mentale KvL van AHA-patiënten kan dus verbeterd worden via een tweesporenbeleid; verminderen van negatief affect en versterken van positief affect. In hoofdstuk 10 onderzochten we de afzonderlijke voorspellende waarde van ziektepercepties voor de KvL twee jaar later. Bovendien vergeleken we de ziektepercepties van AHA-patiënten met die van patiënten met cystische fibrose, diabetes mellitus en astma. Tenslotte onderzochten we de relatie tussen patiëntieigenschappen en ziektepercepties. We vonden dat AHA-patiënten goede ziektepercepties hebben in vergelijking met patiënten met andere aandoeningen. Bij AHA-patiënten is een complex defect en een slechte functionele status gerelateerd aan negatieve ziektepercepties. Negatieve ziektepercepties zijn op hun beurt weer voorspellend voor toekomstige KvL, onafhankelijk van ziektecomplexiteit of functionele status. Specifieker lieten de resultaten zien dat patiënten die een slechte KvL rapporteerden een sterke overtuiging hadden dat de ziekte een negatieve impact heeft; een zwakke overtuiging dat zij een goed begrip hadden en dat de ziekte kon worden gecontroleerd door behandeling; en een sterke overtuiging dat de ziekte veranderbaar is en negatieve gevoelens veroorzaakt. Het vergroten van de kennis die patiënten hebben ten aanzien van hun ziekte en hen informeren over behandelingenmogelijkheden zijn wellicht mogelijkheden om de KvL van patiënten te verbeteren.

BIOLOGISCHE ‘PATHWAYS’
In het algemeen heeft onderzoek laten zien dat patiëntieigenschappen, zoals leeftijd, geslacht, ras en psychologische factoren zoals, stemming en perceptsies, de KvL van patiënten beïnvloeden.
Er is echter een grote variatie tussen individuen die niet te verklaren is door deze factoren. Dit suggereert dat er intrinsieke factoren, zoals een individuele genetische predispositie, bijdragen aan de perceptie van welzijn. In hoofdstuk 11 onderzochten we of genetische variabiliteit en activiteit bijdragen aan de KvL van patiënten met Marfan syndroom (MFS), een genetische aandoening aan het bindweefsel. Eén van de belangrijkste kenmerken van MFS is de aangeboren hartafwijking; verwijding van de aorta. Een tweede doel van deze studie was het exploreren van de KvL van MFS-patiënten en de mate waarin die wordt beïnvloed door ernst van de ziekte. Onder 121 MFS-patiënten werden patiëntieigenschappen (demografische gegevens en MFS-gerelateerde symptomen) en KvL gemeten. Daarnaast waren ‘transcriptome wide gene expressie’ en 484 ‘Single Nucleotide Polymorphysms (SNPs)’ in cytokine genen beschikbaar. Resultaten lieten zien dat de fysieke KvL van patiënten verminderd was en zwak gerelateerd aan leeftijd en scoliose, terwijl de mentale KvL normaal was. Resultaten van de ‘genome wide expressie’ studie lieten zien dat patiënten met een lagere mentale KvL hogere expressie waarden hadden van de CXCL9, CXCL11 en IFNA6 cytokine gerelateerde genen. Bovendien vonden we een verband tussen mentale KvL en een SNPs-cluster in het IL4R gen. Alhoewel mentale KvL over het algemeen normaal was, had meer dan 10% van de patiënten een lage score. Post-hoc analyses van de systemische inflammatoire mediatoren lieten zien dat patiënten met de laagste KvL scores de hoogste CCL11 cytokine waardes hadden. Wij concludeerden daarom dat variantie in het cytokine genetische ‘pathway’ en de activiteit ervan gerelateerd zijn aan KvL. Deze informatie zal ons mogelijk in staat stellen om patiënten die gevoelig zijn voor een verminderde KvL te identificeren en uiteindelijk te behandelen.

In hoofdstuk 12 beschreven we in een brief aan de editor dat depressieve AHA-patiënten mogelijk risico lopen om hartfalen te ontwikkelen door een immunologisch proces. Wij pleitten voor het in ogenschouw nemen van andere factoren zoals comorbide depressie naast de AHA anatomie en fysiologie bij risico categorisatie voor hartfalen in AHA-patiënten. Bovendien pleitten we voor toekomstig onderzoek gericht op het relateren van immunologische factoren aan depressie en de voorspellende waarde van beide voor toekomstig hartfalen.

Ten slotte bespraken we in hoofdstuk 13 toekomstige uitdagingen voor het bieden van adequate zorg aan volwassenen met een AHA. Wij maakten onderscheid tussen drie groepen die ongeschikte zorg kregen: (1) patiënten die geen zorg meer ontvangen, (2) patiënten die minder en (3) patiënten die meer zorg gebruiken dan nodig gezien hun klinische status. We beschreven dat op dit moment 32 tot 61 procent van de patiënten geen zorg meer ontvangen. Aan de hand van pro-actieve zoekacties dienen zij te worden teruggevonden. De bestaande empirische studies naar factoren die gezondheidszorggebruik bepalen (hoofdstuk 4 en 5 van dit proefschrift) werden bediscussieerd. Zoals eerder beschreven vonden we ten eerste dat patiënten met een Type D persoonlijkheid minder zorg gebruikten dan nodig gezien hun functionele status. Ten tweede, onafhankelijk van ziektecomplexiteit en functionele status, waren een slechte KvL en negatieve ziektepercepties verantwoordelijk voor meer gezondheidszorggebruik. Beide studies suggereren dat een verwijzing naar een psychosociale zorgverlener waarschijnlijk geschikter en effectiever is voor deze patiënten. Aangezien er maar twee studies zijn uitgevoerd is aanvullend onderzoek naar ten minste de volgende onderwerpen nodig: de omvang van het probleem, door te bepalen
hoveel mensen ongeschikte zorg krijgen; determinanten van gezondheidszorggebruik; het patiëntperspectief ten aanzien van de huidige gezondheidszorg; en de behoefte en behandelvoorkeuren van patiënten.

De ‘take home messages’ uit dit proefschrift staan hieronder vermeld.

**Take home messages**

- Patiënten gebruiken zorg van verschillende zorgverleners en beoordelen zowel het aantal als de kwaliteit van de contacten als voldoende. *Hoofdstuk 3*
- Patiënten met een Type D persoonlijkheid rapporteren een slechtere functionele status en kwaliteit van leven dan niet-Type D patiënten, maar gebruiken minder gezondheidszorg. *Hoofdstuk 4*
- Gezondheidszorggebruik wordt niet volledig bepaald door de complexiteit van de hartafwijking of functionele status, maar voor een groot deel door psychologische eigenschappen – namelijk: Type D persoonlijkheid, kwaliteit van leven, en de overtuiging dat hun aangeboren hartafwijking een ernstige impact heeft en door henzelf of behandeling gecontroleerd kan worden. *Hoofdstuk 5*
- Patiënten zijn tevreden met de zorg die zij rondom hun open-hart operatie ontvangen, hoewel er ruimte voor verbetering is, in het bijzonder tijdens het ontslag en de nazorg, en wat betreft de duidelijkheid van de door de chirurg verstrekte informatie. Patiënten die worden begeleid door een specialistisch verpleegkundige zijn meer tevreden met de ontvangen informatie. *Hoofdstuk 6*
- De op de patiënt gebaseerde vertaling van de ‘New York Heart Association’ classificatie had de hoogste patiënt-cardioloog overeenkomst en kan daarom in toekomstig onderzoek worden gebruikt. *Hoofdstuk 7*
- Ongemak als gevolg van symptomen is sterker gerelateerd aan zelfgerapporteerde gezondheid dan de symptomen op zich. *Hoofdstuk 8*
- Geluk functioneert als buffer voor het negatieve effect dat depressieve symptomen hebben op mentale kwaliteit van leven. *Hoofdstuk 9*
- Negatieve ziektepercepties zijn voorspellend voor toekomstige kwaliteit van leven, onafhankelijk van ziektecomplexiteit en functionele status. *Hoofdstuk 10*
- Variatie in het cytokine genetische ‘pathway’ en de activiteit daarvan is gerelateerd aan mentale kwaliteit van leven. *Hoofdstuk 11*
- Patiënten die zich depressief voelen lopen mogelijk risico op het ontwikkelen van hartfalen door een immunologisch proces. *Hoofdstuk 12*
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_Dounya_
LIST OF PUBLICATIONS

Published


**Submitted**


Dounya Schoormans was born on January 11th 1985 in Tilburg, the Netherlands. She finished secondary school at Theresia Lyceum in 2003. That same year she started her academic education at Tilburg University. In 2006 she obtained her Bachelor’s degree in Psychology. She subsequently obtained her Research Master’s degree in Social and Behavioral Sciences, with a specialty in Medical Psychology, in September 2008. Her Master’s thesis was on the relation between pro- and anti-inflammatory cytokines and health-related quality of life in patients with chronic heart failure. Immediately after graduating she started her PhD project *Mind your Heart: Health Care, Quality of Life, and Biological Pathways in Adults with Congenital Heart Disease* at the Academic Medical Center (AMC) – University of Amsterdam. In addition to her PhD project, Dounya taught communication skills in the medical curriculum at the AMC, supervised bachelor students and obtained her ‘learning and teaching in higher education’ certificate in 2012.