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HEALTHCARE USE IN ADULTS WITH CONGENITAL HEART DISEASE: EXAMINING ILLNESS IDENTITY, HEALTHCARE SYSTEM FACTORS AND THE END OF LIFE

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Zorggebruik bij volwassenen met een aangeboren hartaandoening: onderzoeken van de ziekte-identiteit, de gezondheidszorgsysteemfactoren en het levenseinde

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Voor Marlies

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English lay summary

Healthcare spending has never been higher and is expected to continue to rise in all parts of the world over the next few years. One solution to reducing healthcare costs is to reduce avoidable healthcare use, which is healthcare use that could have been avoided by proper prevention, precautions or timely referrals. Avoidable healthcare use is common, unfortunately. To gain a good understanding of this concept, a detailed review of the factors that contribute to differences in healthcare use and outcomes is necessary. The most widely used theoretical model for mapping healthcare use is the Andersen Behavioral Model of Health Services Use, developed in 1968. This model has been modified and expanded several times over the past 50 years as a result of research about the concepts and relationships of the model.

The model includes a lot of factors. However, not all relationships between these factors have been well investigated yet. Indeed, some important gaps in the literature can be identified. First, it remains unknown to what extent a person's identity influences healthcare use. The concept of "illness identity," the degree to which the illness is integrated into one's identity, has not yet been investigated in association with healthcare use. However, since this variable was found to be clinically relevant in patients with chronic conditions, illness identity could play a key role in explaining individual variation in healthcare use. Second, the Andersen model indicates that healthcare system characteristics are an enabling factor influencing healthcare use and patient-reported outcomes, such as quality of life or self-reported health. However, international comparisons of healthcare systems have not yet paid much attention to these outcome measures. Therefore, the exact relationship between healthcare systems characteristics and patient-reported outcomes is still unclear. Third, for some chronic patient populations, almost no research has been done about the end-of-life care use or use of palliative care.

Thus, there is a need for a comprehensive examination of the associations between illness identity, healthcare system characteristics, palliative care, healthcare use (at the end of life) and patient-reported outcomes. As a sample population to examine these associations, we selected adults with congenital heart diseases. This is a heterogeneous population with high healthcare use.

Thus, the goal of this doctoral project was to examine (predictors of) healthcare use and patient-reported outcomes in adults with congenital heart disease, guided by the Andersen Behavioral Model of Health Services Use.

In Part 1 of this PhD project, we examined the predictive value of illness identity for healthcare use and patient-reported outcomes. We found that illness identity was associated with healthcare use and patient-reported outcomes. In more detail, we found that patients who did not integrate their illness well into their identity (i.e., engulfment or rejection) reported more hospitalizations, visits to the primary care physician and medical specialist, and poorer health status, quality of life and psychological distress. In contrast, patients who integrated their illness well into their identity (i.e., acceptance) reported less healthcare use and better outcomes.

Part 2 examined the relationship between healthcare system characteristics and patient-reported outcomes in adults with congenital heart disease. We found that healthcare system characteristics were associated with these outcomes. More specifically, unhealthy behaviours and physical health were associated with elements of the healthcare system performance. We also showed that more physicians could ensure better physical and mental health and quality of life. In addition, more nurses were found to be related to better physical and psychological health and fewer unhealthy behaviours in adults with congenital heart disease.

Part 3 of this doctoral project describes the development of a large international research project on patient-reported outcomes in adults with congenital heart disease. The data of this project were used in Part 4.

In Part 4, we studied palliative and end-of-life care provision to adults with congenital heart disease. Worldwide, 45% of participants indicated that they had not discussed with their physician their health status in the future, and only 9% had written down what care they would like to receive at the end of life. Moreover, we found that care provision at the end of life is intensive and potentially avoidable, with only limited attention for palliative care. In more detail, in the last year of life, 87% of patients were hospitalised, 78% had emergency department contact, and 19% had an intensive care admission. Specialised palliative care was provided to 17% of patients, and to only 4% of patients who died due to cardiovascular causes.

In conclusion, this doctoral project contributed to knowledge about (predictors of) healthcare use and patient-reported outcomes of adults with congenital heart disease. Illness identity was found to be related to healthcare use and outcomes. In addition, associations were found between healthcare system characteristics and outcomes. Furthermore, there is reasonable evidence that end-of-life and palliative care for adults with congenital heart disease can be optimized. More research is needed to clarify the direction of the relationships and the extent to which the results described in this thesis apply to other chronic patient populations.

Nederlandstalige samenvatting

De uitgaven voor gezondheidszorg zijn nog nooit zo hoog geweest en er wordt verwacht dat deze uitgaven zullen blijven stijgen wereldwijd. Een oplossing om kosten in de gezondheidszorg te beperken is het verminderen van vermijdbaar zorggebruik, hetgeen zorggebruik is dat vermeden had kunnen worden door een goede preventie, voorzorgsmaatregelen of tijdige doorverwijzing. Om een goed begrip te krijgen op dit concept is een gedetailleerd overzicht van de factoren die bijdragen tot verschillen in zorggebruik en uitkomsten noodzakelijk. Het meest gebruikte theoretische model om zorggebruik in kaart te brengen is het gedragsmodel van Andersen, dat in 1968 is ontwikkeld. Dit model is de afgelopen 50 jaar verschillende keren gewijzigd en uitgebreid, als gevolg van grondig onderzoek naar de concepten en relaties van het model.

Het model includeert een hele resem van factoren. De verbanden tussen deze factoren zijn echter nog niet allemaal goed onderzocht. Ten eerste is de invloed van de identiteit van de persoon op het zorggebruik nog onduidelijk. Het concept "ziekte-identiteit", de mate waarin de ziekte is geïntegreerd in de identiteit, werd nog niet onderzocht in verband met het zorggebruik. Aangezien deze variabele wel al klinisch relevant bleek bij patiënten met een chronische aandoening, zou ziekte-identiteit een sleutelrol kunnen spelen bij het verklaren van het zorggebruik. Ten tweede geeft het model van Andersen aan dat gezondheidszorgsysteemkenmerken een faciliterende factor zijn dat het zorggebruik en de door de patiënt-gerapporteerde uitkomsten, zoals kwaliteit van leven of zelf-gerapporteerde gezondheid, beïnvloeden. Bij internationale vergelijkingen van het gezondheidszorgsysteem wordt echter nog niet veel aandacht besteed aan deze uitkomstmaten. Het precieze verband tussen de kenmerken van de gezondheidszorgsystemen en de patiënt-gerapporteerde uitkomsten is dus nog onduidelijk. Ten derde is er voor sommige chronische patiëntenpopulaties nog maar zeer weinig onderzoek gedaan naar het zorggebruik in de terminale fase van het leven en naar palliatief zorggebruik.

Er is dus behoefte aan een uitgebreid onderzoek naar de verbanden tussen ziekte-identiteit, kenmerken van het gezondheidszorgsysteem, palliatieve zorg, zorggebruik (aan het einde van het leven) en patiënt-gerapporteerde uitkomsten. Als voorbeeldpopulatie om deze verbanden te onderzoeken

selecteerden we volwassenen met aangeboren hartafwijkingen. Dit is een heterogene populatie met een hoog gezondheidszorggebruik.

Het doel van dit doctoraatsproject was dus om (voorspellers van) zorggebruik en patiënt-gerapporteerde uitkomsten bij volwassenen met een aangeboren hartafwijking te onderzoeken, aan de hand van het gedragsmodel van Andersen.

In Deel 1 van dit doctoraatstraject hebben we de voorspellende waarde van ziekte-identiteit voor het zorggebruik en de patiënt-gerapporteerde uitkomsten onderzocht. Wij stelden vast dat ziekte-identiteit samenhangt met het zorggebruik en met uitkomsten. Meer in detail vonden we dat patiënten die hun aandoening niet goed integreerden in hun identiteit (d.w.z. overweldiging of rejectie), meer ziekenhuisopnames, bezoeken aan de huisarts en medisch specialist en een minder goede gezondheidstoestand, kwaliteit van leven en meer depressie of angst rapporteerden. Patiënten die daarentegen hun ziekte wel goed integreerden in hun identiteit (d.w.z. acceptatie) rapporteerden net minder zorggebruik en betere uitkomsten.

In Deel 2 werd het verband onderzocht tussen gezondheidszorg-systeemkenmerken en patiënt-gerapporteerde uitkomsten bij volwassenen met een aangeboren hartaandoening. Wij stelden vast dat kenmerken van het gezondheidszorgsysteem inderdaad geassocieerd waren met deze uitkomsten. Meer bepaald werd de mate waarin iemand ongezond gedrag stelde en de fysieke gezondheid in verband gebracht met hoe goed het gezondheidszorgsysteem functioneerde op bepaalde domeinen. Ook vonden we dat een groter aantal artsen zou kunnen zorgen voor een betere fysieke en mentale gezondheid en levenskwaliteit. Daarnaast bleek ook dat meer verpleegkundigen zouden kunnen zorgen voor een betere fysieke en psychologische gezondheid en minder ongezond gedrag.

Deel 3 van dit doctoraatsproject betreft de ontwikkeling van een groot internationaal onderzoeksproject met betrekking tot patiënt-gerapporteerde uitkomsten bij volwassenen met een aangeboren hartaandoening. De data van dit project werden gebruikt in Deel 4.

In Deel 4 hebben wij de palliatieve en levenseindezorg voor volwassenen met een aangeboren hartaandoening bestudeerd. Wereldwijd gaf 45% van de deelnemers aan niet met hun arts te hebben gesproken over hoe hun

gezondheid zal zijn in de toekomst en slechts 9% had genoteerd welke zorgen zij zouden willen krijgen aan het levenseinde. Ook bleek het zorggebruik aan het levenseinde relatief intensief en potentieel vermijdbaar, met slechts beperkte aandacht voor palliatieve zorgen. Meer in detail, in het laatste levensjaar had 87% van de patiënten een ziekenhuisopname, 78% contact met de spoedeisende hulp en 19% een opname op intensieve zorgen. Gespecialiseerde palliatieve zorg werd slechts verleend aan 17% van de patiënten, en aan slechts 4% van de patiënten die overleden omwille van een cardiovasculaire oorzaak.

Concluderend heeft dit doctoraatsproject bijgedragen aan de kennis over (voorspellers van) zorggebruik en patiënt-gerapporteerde uitkomsten van volwassenen met een aangeboren hartaandoening. Ziekte-identiteit bleek gerelateerd te zijn aan zorggebruik en uitkomsten. Bovendien werden verbanden gevonden tussen kenmerken van het gezondheidszorgsysteem en uitkomsten. Verder zijn er redelijke aanwijzingen dat de levenseinde- en palliatieve zorg voor volwassenen met aangeboren hartaandoeningen geoptimaliseerd kan worden. Er is meer onderzoek nodig dat duidelijkheid kan brengen over de richting van de verbanden en over de mate waarin de resultaten beschreven in dit proefschrift ook van toepassing zijn voor andere chronische patiëntenpopulaties.

List of abbreviations

ACHD	Adult Congenital Heart Disease
ACHD-AP	Adult Congenital Heart Disease Anatomical and Physiological Classification System
ACP	Advance Care Planning
ADs	Advance Directives
AHA	American Heart Association
AMI	Acute Myocardial Infarction
APPROACH-IS	Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart diseases – International Study
APPROACH-IS II	Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart diseases – International Study 2
BELCODAC	BELgian COngenital heart disease Database combining Administrative and Clinical data
BIC	Bayesian Information Criterion
CCCs	Complex Chronic Conditions
CHD	Congenital Heart Disease
CI	Confidence Interval
CISS	Chronic Illness Stigma Scale
CONCOR	CONgenital CORvitia
CVD	Cardiovascular Disease
E	Entropy
ED	Emergency Department
EHCI	Euro Health Consumer Index
EHI	Euro Heart Index
EQ-VAS	EuroQoL-Visual Analogue Scale
ESC	European Society of Cardiology
FIML	Full Information Maximum Likelihood
GAD	General Anxiety Disorder
GDP	Gross Domestic Product
GES	Gothenburg Empowerment Scale
GLM	Generalized Linear Model
GLMM	General Linear Mixed Models

GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HBS-CHD	Health-Behavior Scale–Congenital Heart Disease
HCP	Healthcare Provider
ICD	International Classification of Diseases and Related Health Problems
ICMJE	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IE	Infective Endocarditis
IF	Impact Factor
IIQ	Illness Identity Questionnaire
IMA	InterMutualistic Agency
IQR	Interquartile Range
LAS-QOL	Linear Analogue Scale-Quality of Life
LCGA	Latent Class Growth Analysis
LMR-LRT	Lo-Mendell-Rubin Loglikelihood Ratio Test
MCS	Mental Component Summary
mHCCQ	modified Health Care Climate Questionnaire
MoCA	Montréal Cognitive Assessment
MSPSS	Multidimensional Scale of Perceived Social Support
NYHA	New York Heart Association
OR	Odds Ratio
p	*p*-value
PCS	Physical Component Summary
PHQ	Patient Health Questionnaire
PREMs	Patient-Reported Experience Measures
PRIUS	Patient-Reported Inpatient and outpatient Utilization Survey
PROs	Patient-Reported Outcomes
REDCap	Research Electronic Data Capture
SD	Standard Deviation
SOP	Standard Operating Procedure
SPSS	Statistical Package for Social Science
StatBel	Statistics Belgium
SWLS	Satisfaction With Life Scale
US	United States
WHO	World Health Organization

Chapter 1

General introduction, research questions and outline

General introduction

Healthcare use of patients with chronic conditions

The number of people suffering from one or more chronic conditions is high and is increasing rapidly.[1,2] Chronic conditions can be defined as conditions that last a year or more and result in functional limitations and/or require ongoing medical attention.[3] In Europe, 40% of the population above the age of 15 years has a chronic condition, making it the leading cause of death in Europe.[4,5] It is estimated that, around 2030, chronic conditions will account for 70% of global disease.[6] The total number of people with multimorbidity (i.e., the coexistence of multiple chronic conditions) in the European Union is about 50 million.[7] The increased prevalence of chronic conditions is due to an epidemiological transition that has brought a diminished attention on infectious diseases and an increased attention on chronicity.[8] This epidemiological shift is the result of improvements in the medical field, such as the implementation of improved public health policies, innovative diagnostic techniques and effective treatments.[8,9] Additionally, aging of the general population, changes in health behaviours and genetic predispositions are also associated with increased prevalence of chronic conditions.[5]

The high prevalence of chronic conditions causes societal challenges, public health issues and a high medical cost burden at a global level.[6] Indeed, chronic conditions may trigger societal costs such as lower salaries, lower labour force participation, lower labour productivity, early retirement and disability.[10] For the healthcare domain, chronic conditions represent one of the principal challenges of today.[6] Healthcare systems need to shift their focus from treating an acute onset of illness of short duration to caring for the complex chronic patient and, therefore, to start implementing models that ensure accessibility, continuity of care and collaborations between healthcare professionals from different domains.[5,6] Moreover, the increasing prevalence of chronic conditions also results in rising healthcare costs. In the 1980s, the prevalence of major chronic diseases, such as diabetes, cardiovascular disease, and hypertension rose from 40% to 150% and healthcare expenditures tripled.[11] Today, 86% of healthcare costs are attributable to chronic conditions.[2] These costs are generated by high use of healthcare services, such as hospitalizations, emergency department admissions, surgeries and ambulatory visits to medical specialists.[12]

Some of these admissions to hospitals and emergency departments are avoidable.[12,13] An avoidable hospitalization is defined as *"an admission or readmission related to an exacerbation or acute illness episode associated with a chronic health condition that could have been avoided through health promotion, precautionary measures, or timely access to primary health care"*.[14,15] Reducing avoidable and unnecessary healthcare use can offer an opportunity to relieve pressure on the health system.[14] To avoid overuse, underuse and misuse of the healthcare system, a good understanding of the healthcare use of patients with chronic conditions, which is determined by contextual and individual factors, is imperative.[16]

Some models have been developed to identify predictors of healthcare access and use, such as the models of Levesque, Penchansky & Thomas and Andersen.[17-19]

The Behavioral model of Health Services Use of Andersen

The most widely used theoretical framework to analyse and predict multiple dimensions of healthcare use is the Behavioral Model of Health Services Use of Andersen.[19] This model is an authoritative and conceptual behavioural model to analyse factors affecting healthcare services use.[19] The model was developed in 1968 and aimed to investigate why the healthcare use of families was so different.[19] Andersen intended to identify contextual and individual predictors of healthcare use and outcomes and see how the access to healthcare could be improved. Therefore, he studied 2,367 families and found that their healthcare use was influenced by predisposing, enabling and need factors.[19] Predisposing factors were defined as existing conditions that sensitize patients to use services, even though these conditions are not directly responsible for healthcare use (e.g., demographics).[19] Enabling resources are conditions that facilitate or impede healthcare use (e.g., number of physicians available) and need factors are conditions that patients or healthcare workers recognize as requiring medical treatment (e.g., patient's health status).[19] Andersen found that the biggest differences in healthcare use between families were due to predisposing and enabling factors and not so much due to need factors.[19]

Over the past 50 years, the model was modified and expanded several times.[20,21] The revisions occurred in response to emerging issues and developments with regard to health policy, healthcare delivery and health

services research. Or they were the consequence of critiques on earlier versions of the model, based on thorough investigations of the model's concepts and relationships.[21] The revisions resulted in minor changes and additions to the model, but did not fundamentally change the model. Examples of elements that were added to the model over time are consumer satisfaction, types of health behaviours, genetic susceptibility and quality of life.[21]

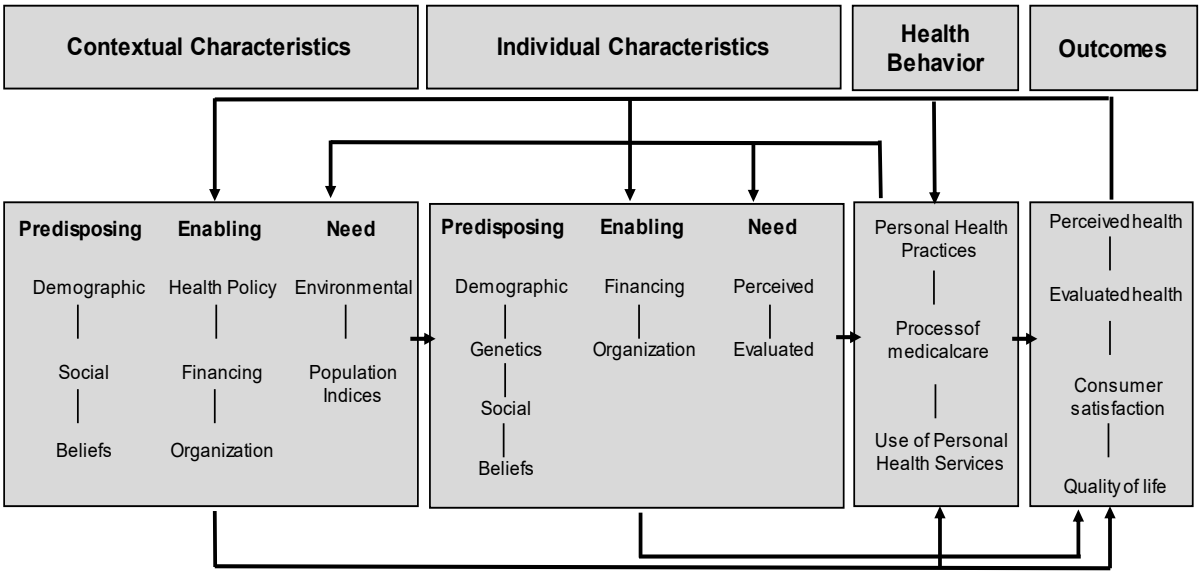

Figure 1. Andersen Behavioral model of Health Services Use, sixth revision [20], reproduced with permission

The sixth and latest revision of the Behavioral model of Health Services Use of Andersen is shown in Figure 1. Still, the core determinants of the model are predisposing characteristics, enabling resources and need factors, distinguishing between contextual and individual characteristics.[20] Contextual elements refer to the circumstances and environment of healthcare access and are measured at an aggregate level rather than at an individual level.[20] These concepts are found to influence health behaviours and outcomes. Health behaviours comprise personal health practices (e.g., diet), the process of medical care (e.g., quality of provider-patient-communication), and healthcare use (e.g., hospitalizations). Outcomes are perceived health (i.e., patient's judgement), evaluated health (i.e., professional's judgement), consumer satisfaction and quality of life.[20] According to Andersen, all elements are connected to each other both directly and indirectly and there are feedback loops. These feedback loops imply that not only contextual and individual characteristics influence health behaviour and outcomes, but that outcomes and

health behaviour can also impact the contextual and individual characteristics.[20] Indeed, outcomes and health behaviours are, for example, taken into account when reforming the healthcare system or for accreditation systems.[20]

The framework is broad and includes many factors. However, not all presumed associations between factors have been empirically confirmed. When looking at the Behavioral Model of Andersen, several gaps in the current body of literature can be identified.

Gaps in the literature

Gap 1. Illness identity

First, the model describes the association between predisposing health beliefs and healthcare use. However, the predictive value of the person's sense of self or identity is not yet well investigated in relation to healthcare use. The concept of 'illness identity', which is "*the degree to which the illness is integrated into the identity",*[22] was shown to be clinically relevant for patients with chronic conditions.[23,24] As compared to illness perceptions, illness identity not only expresses how a person views the illness and the treatment, but also how much the illness has affected the way they think about themselves and the degree to which the disease became integrated into one's sense of self.[24] When an individual is confronted with a chronic disease, this might substantially impact their identity, because of many potential disruptions in daily life and functioning.[25] Individuals need to understand what their illness means to their identity and it is an important task to integrate the illness into their identity.[26] Illness identity is also related to the concept of personal identity.[27] Illness identity could play a key role in explaining individual variation in healthcare use. For instance, previous research has indicated that illness identity was related to how patients cope(d) with their chronic illness and their treatment adherence, variables which are closely related to healthcare use.[22]

The overarching framework of illness identity comprises four different but interrelated dimensions: engulfment, rejection, acceptance, and enrichment (see Figure 2).[22] Engulfment indicates the degree to which patients feel that their disease dominates their identity.[22,28] These patients completely define themselves in terms of their disease. Another construct pertaining to illness identity is rejection, which refers to the degree to which the disease is rejected as part of the patient's identity and is seen as a threat or as unacceptable to the

self.[22,29] Patients with high rejection scores tend to refute their disease, which often results in suboptimal disease self-management and adherence.[22,30] A more adaptive dimension of illness identity is acceptance, defined as the degree to which patients accept their disease as part of their identity aside from other self-defining identity assets, without being overwhelmed.[22,28,29] These patients try to lead a life as normal as possible, in which they do not deny having a disease. Finally, enrichment is the fourth illness identity dimension. Some people feel that their disease has changed their values and how they look at life and their disease actually enabled them to grow as a person.[22,31]

Illness identity can be seen as a modifiable and dynamic factor. Studies in type 1 diabetes have shown that illness identity can develop over time, as some individuals changed cluster membership over time.[27] Several interventions have been described in the literature that can transform maladaptive illness identity integration, such as cognitive-behavioural therapy, emotion-focused group interventions or narrative enhancement.[32-34] These therapies help individuals reframe their beliefs and attitudes towards their condition, to address self-stigmatizing views and become more aware of their emotions and needs.[27,32,34] This can improve illness identity integration.

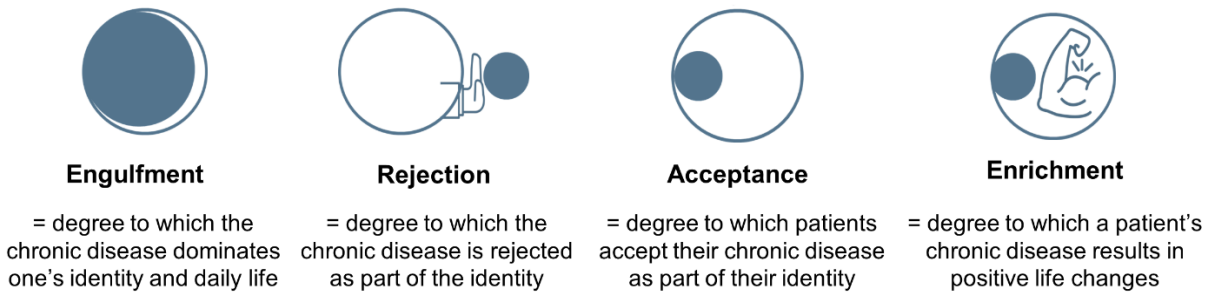

Figure 2. Visualisation of the four illness identity dimensions [22]. The dot represents the chronic disease and the circle represents one's sense of identity.

Gap 2. The association between healthcare system characteristics and patient-reported outcomes

In recent decades, international organisations, such as the World Health Organization (WHO), Organization for Economic Co-operation and Development (OECD), and Health Consumer Powerhouse, have tried to measure and compare the overall healthcare system performances of different

countries. In general, healthcare administrators and policymakers are increasingly interested in measuring the performance of their healthcare systems.[35] Doing so, high- and low-quality service delivery can be identified, healthcare system reforms can be designed, patients and payers can be protected, and decisions on appropriate investments can be made.[35] The overarching goal of measuring the healthcare systems' performance is to improve the quality of care.[35] Healthcare systems can also be characterised by their human resources or infrastructure. Human resources of healthcare systems can be defined as *"all people engaged in actions whose primary intent is to enhance health"*.[36] Healthcare systems' infrastructure are all *"formal and enduring structures that support health"*, such as hospitals and the number of available hospital beds.[37] International comparisons in health workforce and infrastructures can help us understand differences in quality of care.[38,39] This became even more relevant in recent years, because of the major shortages of healthcare personnel worldwide, which is a big challenge to the achievement of health goals.[38,39]

The Andersen Behavioral Model has included healthcare system characteristics as a contextual enabling factor that directly influences healthcare use and outcomes, including patient-reported outcomes (PROs).[20] PROs are *"any report of the status of a patient's health condition, health behaviour, or experience with health care that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"*.[40,41] Examples of PROs are self-reported health status or quality of life, and these outcomes are included as such in the Andersen Behavioral model.[20] In light of the current priority on patient-centred, holistic, and comprehensive care, the patient perspective is important and should be incorporated in healthcare system evaluations.[42]

However, the association between contextual healthcare system characteristics and PROs has rarely been investigated. Some prior studies have discussed the associations between healthcare system characteristics (e.g., performance, human resources and infrastructure for health) and patient outcomes.[43-47] Physician and nurse staffing ratios and the availability of hospital beds per population have been associated with various outcomes including mortality, stage of diagnosis, prognosis, and quality of care.[44-46,48,49] However, minimal attention has been devoted to the associations between healthcare system characteristics and outcomes which are particularly relevant from the patients'

perspective, namely PROs.[47,50,51] Hence, the precise relationship between contextual healthcare system characteristics and PROs, which is presumed in the Andersen Behavioral Model, requires further investigation.

Gap 3. End-of-life and palliative care

Third, the Andersen Behavioral model does not provide particular attention to the end-of-life stage. It is widely known that healthcare use is significantly more pronounced in the terminal phase of life. Approximately 10 to 25% of all healthcare expenditures is generated in the last year of life.[52,53] In addition, end-of-life care is complex and often fragmented across different services and care providers. Hence, it would be interesting to investigate associations of factors of the Andersen Behavioral Model in the final stage of life and to see whether the Andersen Behavioral Model can be of value for the specific context of the end of life. It could be that certain associations with healthcare use are more or less pronounced or that certain factors become more important at the end of life. Thinking about the increased healthcare use and costs at the end of life, it is worthwhile to scrutinize healthcare use and its predictors at the end of life in more detail.

Palliative care or advance care planning will have to be investigated. Palliative care can be defined as *"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering"*.[54] Palliative care aims to improve the quality of life of patients with a life-limiting disease and their families.[55] It addresses advance care planning, symptom relief, caregiver and family support, and the suffering of patients. It should be seen as complementary to standard curative and life-prolonging medical care and it can be provided at all stages throughout the disease course.[56] Multiple studies have shown the benefits of palliative care, as patients with life-limiting diseases reported improved quality of life, lower rates of depression, better prognostic awareness, less aggressive medical care at the end of life, and even improved survival.[56,57] Advance care planning (ACP) is *"a process that supports and empowers individuals at any stage of their lives or disease process to consider, communicate, and document preferences for future health care"*.[58] It is based upon consideration of situations that might arise in the future in a person's life and helps to identify personal values and goals in an effort to align future medical treatment and care with these convictions.[58] There are many benefits of ACP for individuals, their

families, the healthcare system and society.[58] Studies have shown that ACP can lead to a better quality of life, spiritual well-being, reduced hospitalisation, reduced inappropriate care, higher chances of dying at the preferred place, and reduced costs in general.[59-61] Indeed, previous studies in patients with chronic conditions have shown that palliative care and ACP can lead to a reduction of (inappropriate) healthcare use at the end of life.[60,62]

Congenital heart disease: an excellent sample case of a chronic condition

As a sample case population to test these associations, adults with congenital heart disease (CHD) were selected.

Definition and epidemiology of adult congenital heart disease

CHD is the clinical manifestation of anomalies in the embryonic heart development during pregnancy and has been defined by Mitchell and colleagues as "*a gross structural abnormality of the heart and/or intrathoracic great vessels that is actually or possibly of functional significance"*.[63] For most patients, the underlying cause of the congenital heart disease remains unknown, but some genetic and environmental factors have been identified, such as maternal diabetes mellitus, rubella infection or influenza.[64] Around 15% of the CHD cases can be linked to a genetic cause.[64]

CHDs are heterogeneous, on a spectrum from mild and moderate to complex, with functional consequences of varying degrees.[65] Examples of mild diseases are an atrial septum defect or pulmonic stenosis. Moderate diseases are, for example, a tetralogy of Fallot or coarctation of the aorta. Complex diseases comprise, among others, a transposition of the great vessels or truncus arteriosus.[65,66]

CHD is the most common congenital defect in newborns, and accounts for almost one-third of major congenital anomalies in Europe.[67] Over the past century, the birth prevalence of CHD has substantially increased over time, due to better screening and diagnostics.[67,68] Around the 2000s, the birth prevalence stabilized at 9 CHD patients per 1,000 live births.[68] Throughout the world, significant differences in birth prevalence can be noticed. The reported birth prevalence was highest in Asia (9.3 per 1,000 live births) and lowest in Africa (1.9 per 1,000 live births).[68] The birth prevalence was reported to be 8.2 CHD patients per 1,000 live births in Europe and 6.9 CHD patients per 1,000 live births in North America.[68] These observed differences are likely due to

differences in the quality of the healthcare system, screenings rates, environmental, genetic, socioeconomic and cultural influences.

Adults born with CHD embody a notable success story in the field of cardiac surgery, cardiovascular disease management and neonatal care.[69] Life expectancy in patients with CHD used to be very low, with the survival of children with CHD being only 15% in the 1950s.[69] Especially patients with complex CHD lesions had bad prospects, with most of them dying in early childhood.[70] Due to great innovations in early detection and treatment, including improvements in cardiac surgery, interventional cardiology, and paediatric intensive care, currently, over 90% of children born with CHD are expected to reach adulthood.[71] Whereas children with CHD used to outnumber adults, two-thirds of patients with CHD are nowadays adults.[72] There is even a growing population of patients above the age of 60 years.[73] The absolute number of adults with CHD of 60 years or older has increased by 10-fold from 2000 to 2013 and is now estimated to be 5-10% of the CHD population.[72,73] Furthermore, improvements in echocardiography have led to better detection of minor lesions, which can be of hemodynamic significance, and which might have been missed before.[74] These evolutions are resulting in a growing and aging population of adults with CHD for whom new challenges arise at all stages of life and which encompass a growing burden on the healthcare system.[75]

Irrespective of the significantly improved survival rates, there is still a substantial number of patients with CHD who prematurely die. The current median age at death is 55 years.[76] Mortality in patients with CHD is complex and multifaceted and differs across the lifespan. In children, peri- and post-operative complications (43%) as well as cardiac failure (33%) are the most common causes of death.[77] In adults, the most common causes of death are progressive heart failure (21%-26%) and sudden cardiac death (19%-26%).[78-81]

Healthcare use of adults with CHD

Even though many patients underwent surgical repair for their CHD, most patients cannot be considered cured. Many adults with CHD have residual abnormalities and have a high risk of developing complications, such as heart failure or thromboembolic events, and face psychosocial and behavioural challenges.[82] Hence, these patients remain regular consumers of health care.

Because of the rising number of CHD patients and the increasing complexity of their medical profiles, healthcare use is high and is expected to continue to rise for adults with CHD.[83] In the period 1998 to 2005, a 102% increase in CHD hospital admission rates was found and the estimated total national charges for these hospitalisations increased with 357%.[75] It was reported that, in 2015, 21% of patients visited a CHD specialist, 86% had a general practitioner visit, 17% of patients had an emergency department visit, and also 17% were hospitalised at least once.[84] Moreover, in- and outpatient healthcare use was found to be higher in adults with CHD as compared to the general population.[83] For example, patients with moderate and complex lesions were 4 times more likely than their matched controls to have more than 20 visits to a general practitioner in a 3-year period. Moreover, the absolute number of hospitalizations, outpatient cardiology visits, and visits to the emergency room will continue to increase, due to the rapid growth and aging of this population.[83] When specifically looking at the end of life, healthcare use seems to be very high for adults with CHD as well.[85] Steiner et al. described that 39% of patients were hospitalised, 39% had an admission to the intensive care unit, and 3% had a visit to the emergency department in the last month of life.[85]

Thinking about the expected growth of the population and the already existing burden on the healthcare system, the healthcare use of this group of patients ought to be scrutinized in detail and associated factors should be identified. The Andersen Behavioral model can be used as a theoretical model to guide this research.

Research objectives of the PhD

Overall aim

The overarching aim of this PhD project was to examine (predictors of) healthcare use and PROs in adults with congenital heart disease, guided by the Andersen Behavioral Model of Health Services Use.

Specific aims

The overall aim was divided into three specific research objectives.

Obj 1. To scrutinize the predictive value of illness identity for healthcare use and patient-reported outcomes in adults with congenital heart disease.

Obj 2. To evaluate the association between healthcare system characteristics and patient-reported outcomes in adults with congenital heart disease.

Obj 3. To describe palliative and end-of-life care provision to adults with congenital heart disease.

A visual representation of the formulated objectives of this PhD is provided in Figure 3.

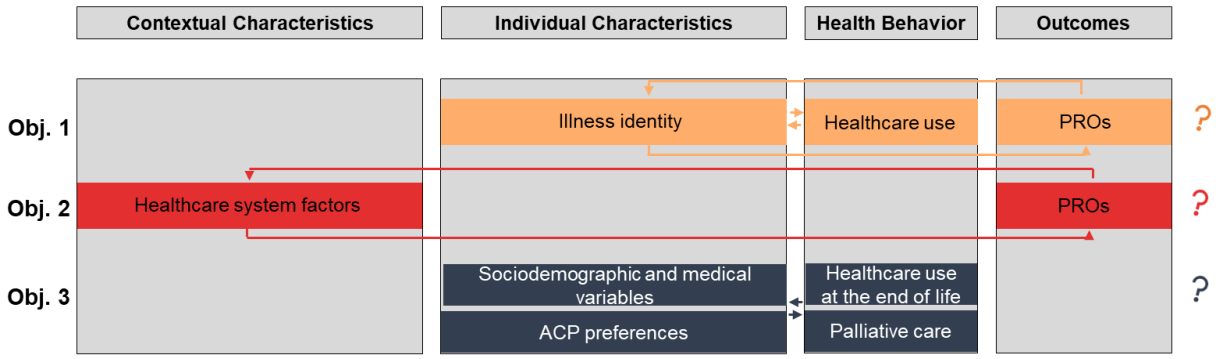

Figure 3. Visual representation of the objectives of the PhD on the Andersen Behavioral Model

Methods

The studies included in this PhD manuscript are based on the results from three research projects, being APPROACH-IS, APPROACH-IS II and BELCODAC.

1. Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart diseases – International Study (APPROACH-IS)

APPROACH-IS is an international multicentric cross-sectional research project in adults with CHD with data collection performed from 2013 to 2015.[86] This project aimed to examine the differences in of adults with CHD who are living in different areas around the world. In addition, the project aimed to gain an understanding of how potential differences in PROs can be understood. Researchers and clinicians from 15 countries, across 6 continents participated in this research project. A total of 4,028 patients have been included in the project. The study protocol has been registered at ClinicalTrials.gov (NCT02150603) and has been approved by the institutional review board of the University Hospitals Leuven (S55330). Whereas APPROACH-IS was a cross-sectional study, the Belgian branch of this project comprised a longitudinal 3-wave cohort design with 1-year intervals (T_{2013}, T_{2014} and T_{2015}). For the Belgian branch, 400 patients were randomly selected from the database of the University Hospitals Leuven. On T_{2013}, 276 patients responded. On T_{2014}, 255 patients responded and on T_{2015}, 229 patients responded.

2. Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart diseases – International Study 2 (APPROACH-IS II)

APPROACH-IS II is the follow-up study of APPROACH-IS. The methodology of the APPROACH-IS II project is described in Chapter 6. It is an international multicentric cross-sectional research project on PROs in adults with CHD. The data collection ran from 2019 to 2022. The objectives of this project were twofold: 1) to explore differences in a modified selection of PROs; 2) to explore the profile and healthcare needs of a subgroup of older adults with CHD, with a particular focus on the frailty phenotype and cognitive functioning. Over 8,000 patients from 53 centres in 32 countries around the world were included. The protocol was approved by the institutional review board of the University Hospitals Leuven (S62537) and was registered at ClinicalTrials.gov

(NCT04902768). In the centres in Seoul (South Korea), Oslo (Norway), and Leuven (Belgium), the project comprised a longitudinal 2-wave cohort design with a 1-year interval. On the first wave (August 2019-February 2020), 873 patients from the three centres participated. On the second wave (September 2020-April 2021), the same patients were invited again and 716 patients (response rate: 82%) participated.

3. BELgian COngenital heart disease Database combining Administrative and Clinical data (BELCODAC)

BELCODAC is a population-level database that comprises data on patients with CHD from Flanders in Belgium. This dataset includes data on healthcare consumption from the InterMutualistic Agency, clinical data from three Belgian hospitals (i.e., University Hospitals Leuven, Saint-Luc University Hospitals and Ghent University Hospital) and demographic characteristics and mortality from Statistics Belgium.[87] The data from these sources were merged under the supervision of the Data Protection Authority of Belgium and included a quadruple coding system to ensure privacy for all patients. Approval of the ethics committees of University Hospitals Leuven (file numbers S59859 and S59858), Ghent University Hospital (file numbers 2017/0436 and 2017/0437) and Saint-Luc University Hospitals (file numbers 2017/26JUI/333 and 2017/26JUI/332) was obtained. At the governmental level, approval was obtained from the Statistical Supervisory Committee (SA2/STAT-MA-2017-021) and the Sectoral Committee of Social Security and of Health (CSSSS/17/184 and SCSZG/17/184).

Outline of the dissertation

This doctoral dissertation contains an English and Dutch summary, an introduction (Chapter 1), four parts with seven chapters that describe research results (Chapters 2-8), a discussion (Chapter 9), and a couple of appendices. The chapters can also be read independently.

The three main aims of this dissertation are addressed in separate parts. Each part consists of one or two chapters.

Part 1 offers two chapters that discuss the predictive value of illness identity for healthcare use and patient-reported outcomes in adults with congenital heart disease. In Chapter 2, the association between illness identity and healthcare use is investigated in an observational cohort study. In Chapter 3, the development of illness identity was investigated by identifying trajectory classes and describing these classes in terms of age, sex, disease complexity, patient-reported outcomes and healthcare use.

Part 2 contains two chapters that evaluate the association between healthcare system characteristics and patient-reported outcomes in adults with congenital heart disease. Chapter 4 focuses on the relationship between components of the healthcare system performance and patient-reported outcomes. Chapter 5 reports on the predictive value of human resources and infrastructure of a country's healthcare system on patient-reported outcomes of adults with congenital heart disease.

Part 3 consists of one chapter. In this chapter, the design and methodology of the APPROACH-IS II project is described.

Part 4 includes two chapters and aimed to determine palliative and end-of-life care provision to adults with congenital heart disease. Chapter 7 reports the global provision, preferences and needs with regard to advance care planning of adults with congenital heart disease. Eventually, Chapter 8 describes the causes of death and patterns of healthcare consumption in the last year of life of adults with congenital heart disease.

In Chapter 9, the overall discussion of the dissertation, a reflection on the main findings, methodological considerations, implications for practice and avenues for future research are presented.

Table 1. An overview of the different studies of the PhD project

	Objectives	Chapter	Project	Study design	N	Geography of the sample
PART 1	1. To scrutinize the predictive value of **illness identity** for healthcare use and patient-reported outcomes in adults with congenital heart disease.	**Chapter 2**	APPROACH-IS	Ambispective observational cohort	216	University Hospitals Leuven, Belgium
		Chapter 3	APPROACH-IS	Retrospective observational cohort	276	University Hospitals Leuven, Belgium
PART 2	2. To evaluate the association between **healthcare system characteristics** and patient-reported outcomes in adults with congenital heart disease.	**Chapter 4**	APPROACH-IS	Cross-sectional	1591	Europe
		Chapter 5	APPROACH-IS	Cross-sectional	3588	Worldwide
PART 3		**Chapter 6**	APPROACH-IS II	Methods paper	/	/
PART 4	3. To **describe palliative and end-of-life care provision** to adults with congenital heart disease.	**Chapter 7**	APPROACH-IS II	Cross-sectional	8285	Worldwide
		Chapter 8	BELCODAC	Retrospective observational cohort	390	Flanders and Brussels, Belgium

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PART 1

Illness identity, healthcare use and patient-reported outcomes

Chapter 2

Illness identity: a novel predictor for healthcare use in adults with congenital heart disease

This chapter is published as:

Van Bulck L, Goossens E, Luyckx K, Oris L, Apers S, Moons P. Illness Identity : A Novel Predictor for Healthcare Use in Adults With Congenital Heart Disease. Journal of the American Heart Association 2018;7(11):e008723. Peer reviewed.

Abstract

Background: To optimize healthcare use of adults with congenital heart disease (CHD), all important predictors of healthcare utilization should be identified. Clinical and psychological characteristics (e.g., age and depression) have been found to be associated with healthcare use. However, the concept of illness identity, which assesses the degree to which CHD is integrated into one's identity, has not yet been investigated in association with healthcare use. Hence, the purpose of the study is to examine the predictive value of illness identity for healthcare use.

Methods and Results: In this ambispective analytical observational cohort study, 216 adults with CHD were included. The self-reported Illness Identity Questionnaire was used to assess illness identity states: engulfment, rejection, acceptance, and enrichment. After one year, self-reported healthcare use for CHD or other reasons over the past 6 months was assessed including hospitalizations; visits to general practitioner; visits to medical specialists; and emergency room visits. Binary logistic and negative binomial regression analyses were conducted, adjusting for age, sex, disease complexity, and depressive and anxious symptoms. The more profound the heart defect dominated one's identity (i.e., engulfment), the more likely this person was to be hospitalised (OR=3.76; 95%CI=1.43-9.86), to visit a medical specialist (OR=2.32; 95%CI=1.35-4.00) or a general practitioner (OR=1.78; 95%CI=1.01-3.17), because of their heart defect.

Conclusions: Illness identity, more specifically engulfment, has a unique predictive value for the occurrence of healthcare encounters. This association deserves further investigation, in which the directionality of effects and the contribution of illness identity in terms of preventing inappropriate healthcare use should be determined.

KEYWORDS

Chronic disease; Engulfment; Healthcare use; Heart Defects, Congenital; Illness identity

Introduction

Congenital heart disease (CHD), comprising a wide spectrum of simple, moderate, and complex structural heart lesions, is the most common birth defect in newborns (9:1,000 births).[1] Thanks to medical advances, 90% of children with CHD nowadays survive into adulthood and the number of adults with CHD increases exponentially.[2,3] Despite surgical repair during childhood, many adults with CHD have residual abnormalities and complications, and face psychosocial and behavioral challenges.[4,5] Hence, these patients cannot be considered to be cured and remain regular consumers of health care [6]. In- and outpatient healthcare use is higher in adults with CHD as compared to the general population.[7-10] For instance, patients with moderate to complex lesions were about four times more likely than their matched controls, to have more than 20 visits to a general practitioner in a three-year period.[8] Moreover, the absolute number of hospitalizations, charges, and visits to the emergency room will continue to increase, due to the growing and aging population of adults with CHD.[11-13] For example, the absolute number of hospitalizations in this population increases by 4% annually.[12] Hence, the expected increase of healthcare use in the near future in adults with CHD is alarming.

To be able to influence the increase in demands and expenditures, modifiable predictors of healthcare use should be determined.[14] Demographic (e.g., age)[15], clinical (e.g., disease complexity) [9,15], and psychological characteristics (e.g., depression, anxiety, type D- personality) [16] have been shown to be predictors of healthcare use in adults with CHD. Another particularly relevant concept in this regard could be 'illness identity', which is the degree to which a chronic health condition or illness, such as CHD, is integrated into one's identity.[17,18] Identity can be defined as the degree to which an individual integrates different self-assets into a coherent sense of self, which guides choices and values in daily life.[19] Patients with a chronic illness need to integrate their illness into their identity in order to achieve such a coherent sense of self.[17,20]

Illness identity generally comprises four different states: engulfment, rejection, acceptance, and enrichment.[18] Engulfment captures the degree to which the illness dominates one's identity and daily life. High engulfment scores are observed in patients who completely define themselves in terms of their illness.[21] Rejection refers to the degree to which the illness is rejected as part of the patient's identity and is seen as a threat or as unacceptable to the self.[18,22] Patients with high rejection

scores tend to neglect their illness, resulting in suboptimal self-management and adherence.[18,23] These former two states represent less adaptive forms of illness integration in one's identity. Next, acceptance can be defined as the degree to which patients accept their illness as part of their identity, beside other social roles and without being overwhelmed.[18,21,22] Finally, enrichment refers to the degree to which a patient's illness results in positive life changes, enriches a patient's sense of self, and enables one to grow as a person.[18,24] These latter two states represent more adaptive forms of illness integration in one's identity.

To date, no study has investigated the association between these four illness identity states and healthcare use. However, illness identity may partly explain individual variation in healthcare use because, for instance, patients who feel very engulfed by their illness and completely define themselves in terms of their illness, may be more inclined to turn to healthcare professionals when experiencing certain problems or bodily sensations. Hence, the current study aimed to explore the predictive value of illness identity on healthcare use in adults with CHD, above and beyond known demographic, clinical and psychological predictors. More specifically, we explored: (a) the association between illness identity and the occurrence of healthcare encounters, adjusted for age, sex, disease complexity, depressive and anxious symptoms; and (b) the association between illness identity and the number of visits at a healthcare service, adjusted for the same set of confounders.

Methods

The data, analytic methods, and study materials could be made available on request to other researchers for purposes of reproducing the results or replicating the procedure.

Participants and data collection procedure

The present study was part of the Belgian branch of an international study entitled 'Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study' (APPROACH-IS), which included over 4,000 adults with CHD from 15 countries around the globe.[25,26] The rationale, design, and methods of APPROACH-IS have been detailed elsewhere.[25] Whereas APPROACH-IS was a cross-sectional study, the Belgian branch of this project comprised a longitudinal three-wave cohort design with one-year intervals (T_{2013};

T_{2014}; and T_{2015}). A diagram of the recruitment process and response rates of the Belgian branch can be found in Figure 1. For the present study, we used data collected at the last two measurement waves (i.e., T_{2014} and T_{2015}). Since we needed full data for the analysis technique, only patients who participated at both T_{2014} and T_{2015} were included (n=216).

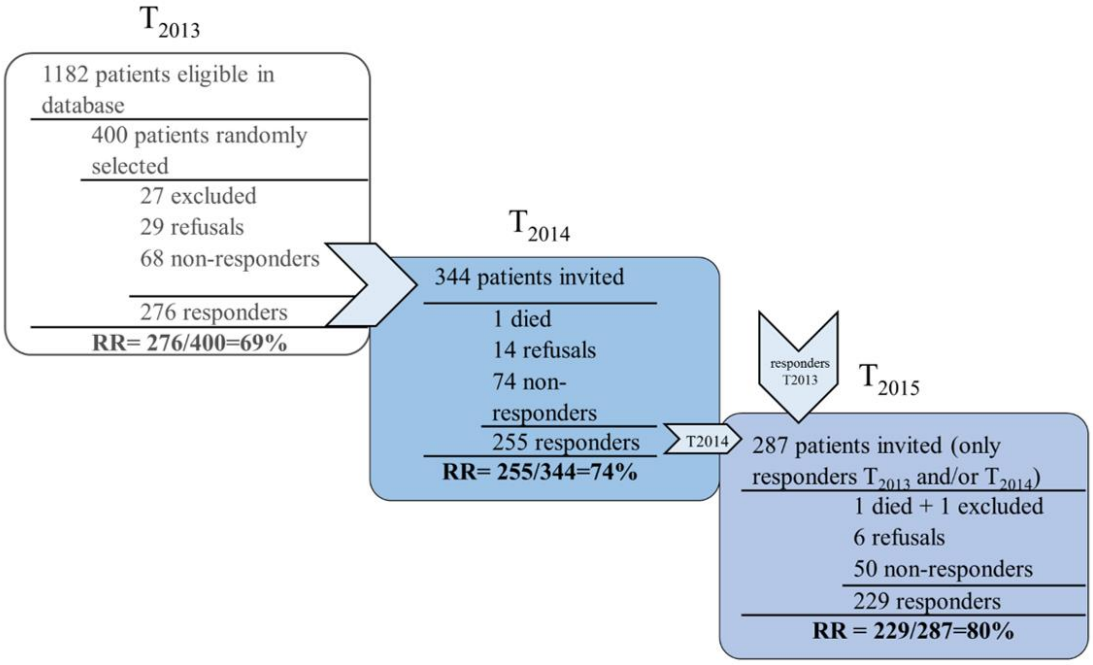

Figure 1. Diagram of the recruitment process and response rates of the Belgian branch of APPROACH-IS

Note. RR= response rate

Inclusion criteria for the Belgian branch were: (i) diagnosis of CHD, according to the definition of Mitchell (1971) [27]; (ii) patients were born before 1991; (iii) diagnosis established before the age of 10 years (i.e., before adolescence to warrant sufficient experience of living with CHD); (iv) continued follow-up at the University Hospitals Leuven; (v) Dutch-speaking; and (vi) demonstrating physical, cognitive, and language proficiency to complete self-report questionnaires. Exclusion criteria were: (i) prior heart transplantation; and (ii) isolated pulmonary hypertension [25]. Patients were randomly selected from the database of congenital cardiology of the University Hospitals Leuven, a large-volume university hospital in Belgium. Eligible patients were asked to complete a set of self-reported questionnaires. A modified Dillman approach, as described earlier, was used to increase the response rate.[28,29] Study approval was given by the institutional review board of the University Hospitals Leuven. Informed consent was obtained from each patient and procedures were in accordance with the declaration of Helsinki.[30] The study protocol was registered at

ClinicalTrials.gov: NCT02150603. Data collection for T_{2014} and T_{2015} ran from September 2014 to March 2016.

Demographic and clinical characteristics at T_{2014} of participants included in the present study are presented in Table 1. Age ranged from 23 to 79 years (median=35y; Q1=29y; Q3=45y) and 49.5% of patients were men. Disease complexity was categorized according to the classification of Task Force 1 of the 32nd Bethesda conference, as simple (33.8%), moderate (53.7%), or complex (12.5%).[31]

Table 1. Demographic and clinical characteristics of adults with congenital heart disease at T_{2014} (n=216)

Characteristics	**n (%)**
Men	107 (49.5)
Median age (in years)	35 (Q1=29; Q3=45)
Highest level of education	
Less than high school	9 (4.2)
High school	97 (45.3)
College degree	65 (30.4)
University degree	43 (20.1)
Employment status	
Full-time paid work	126 (58.3)
Part-time paid work	46 (21.3)
Homemaker	6 (2.8)
Job seeking	2 (0.9)
Unemployed	3 (1.4)
Disability/government financial assistance	22 (10.2)
Retired	9 (4.2)
Other	2 (0.9)
Disease complexity, Task Force 1 [31]	
Simple	73 (33.8)
Moderate	116 (53.7)
Complex	27 (12.5)

Variables and measurement

Demographic information, disease-related information, illness identity scores, and depressive and anxiety symptoms were obtained at T_{2014}, while data on healthcare use were obtained at T_{2015}.

Demographic and clinical information

Demographic variables were collected through self-report and clinical variables were derived from medical records.

Illness Identity

Illness identity was measured using the Illness Identity Questionnaire (IIQ). This is a self-report measure developed by Oris et al. (2016), which has been initially used and validated in adolescents and young adults with type 1 diabetes.[18] Patients were asked to indicate how much they agreed with 25 statements, using a five-point Likert scale ranging from one (i.e., strongly disagree) to five (i.e., strongly agree).[18] The IIQ consists of a five-item rejection scale, seven-item enrichment scale, five-item acceptance scale, and eight-item engulfment scale. Sample items for the different subscales are, respectively, 'I just avoid thinking about my illness', 'Because of my illness, I have become a stronger person', 'I am able to place my illness in my life', and 'My illness completely consumes me'. A mean score was calculated per subscale. A prior study, performed on data from T_{2013} of the Belgian branch of APPROACH-IS, demonstrated that the IIQ is valid and reliable to be used in adults with CHD.[32] More specifically, exploratory and confirmatory factor analysis indicated that IIQ subscale scores could differentiate among the four intended illness identity states in patients with CHD and multisystem connective tissue disorders (i.e., factorial validity). In those samples, patients' responses to the IIQ were related to psychological and physical functioning (i.e., concurrent criterion validity). In the present study, Cronbach's alpha values were 0.76 for rejection, 0.81 for acceptance, 0.92 for engulfment, and 0.95 for enrichment.

Depressive and anxiety symptoms

Depressive and anxiety symptoms (i.e., psychological distress) were measured using the Hospital Anxiety and Depression Scale (HADS; [33,34]). This scale is a 14-item questionnaire on a 4-point Likert scale with values ranging from 0 to 3. The highest achievable overall HADS score is 53 and high scores indicate more psychological distress. A sample item is "I still enjoy the things I used to enjoy". A general psychological distress score was used, instead of using two subscores for

depression and anxiety, because the HADS was found to be more accurate when screening psychological distress.[35]

Healthcare use

To measure healthcare use, we devised a survey developed for the purpose of this study, partly based on existing literature [36,37], comprising healthcare services particularly relevant for patients with CHD. Participants completed the survey form, which consisted of eight questions about healthcare use over the past six months. A recall time frame of six months was chosen to reduce under- and over-reporting and thus to increase the accuracy of the results.[37] More specifically, participants were asked to indicate how many times they were hospitalised, and have visited a medical specialist, emergency room, and general practitioner, for their heart disease and for other reasons. Sample question is 'How many times in the past six months were you hospitalised due to your heart disease?'.

Statistical analyses

Patient characteristics and healthcare use were presented as median and interquartile ranges for continuous variables and as frequency and percentage for categorical variables.

Firstly, associations between the occurrence of healthcare encounters (yes/no) and illness identity were computed using univariable binary logistic regression analysis. Afterwards, eight multivariable binary logistic regression analyses, with adjustments for potential confounders (i.e., age, sex, disease complexity, and depressive and anxiety symptoms), were run separately for all the different healthcare services use (i.e., hospitalization(s) and visit(s) at general practitioner, medical specialist or emergency room, both related and unrelated to CHD). These results are presented as odds ratios (OR) and 95% confidence intervals (95%CI). Secondly, the associations between the number of visits to a particular healthcare service and illness identity were first measured using univariable negative binomial regression analyses. In these analyses, solely patients who used the respective service at least once were included. The number of hospitalizations and visits to an emergency room could not be analyzed due to small event rates (i.e., 2.8%-11%). Indeed, only analyses about visits to general practitioners and medical specialists were performed. A negative binomial model was preferred to a Poisson model, as the former was more appropriate given the data were overdispersed. Afterwards, four multivariable negative binomial regression analyses were run, adjusted for the

above mentioned set of confounders. The results are presented as visit rate ratios and 95% confidence intervals (95%CI).

There was no multicollinearity among the predictors. P-values were based on two-sided hypotheses and compared to a significance level of 5%. Statistical analyses were performed using the statistical package SPSS version 24 (Armonk, NY: IBM Corp.).

Results

Description of healthcare use

A description of the healthcare use is given in Figure 2. For their heart defect, 15 patients (7.1%) required hospital admission, 109 patients (50.9%) went to a medical specialist, 6 (2.8%) patients went to the emergency room (ED), and 54 (25.7%) patients went to the general practitioner (GP). For other reasons than their heart defect, 23 (11.0%) patients were hospitalised, 62 (29.9%) patients went to see a medical specialist, 17 (8.0%) patients went to the ED, and 141 (67.1%) patients went to the GP at least once.

Illness identity as predictor of healthcare use

Illness identity and the occurrence of healthcare encounters

Univariable binary logistic regression analyses showed that patients who had not accepted their illness as part of their identity (i.e., low acceptance), who were overwhelmed by their illness (i.e., high engulfment), and who's illness had enriched the patient's identity (i.e., high enrichment) at T_{2014}, were more likely to use health care at T_{2015}, both for their heart defect and for other reasons (see online supplementary material: eTable 1).

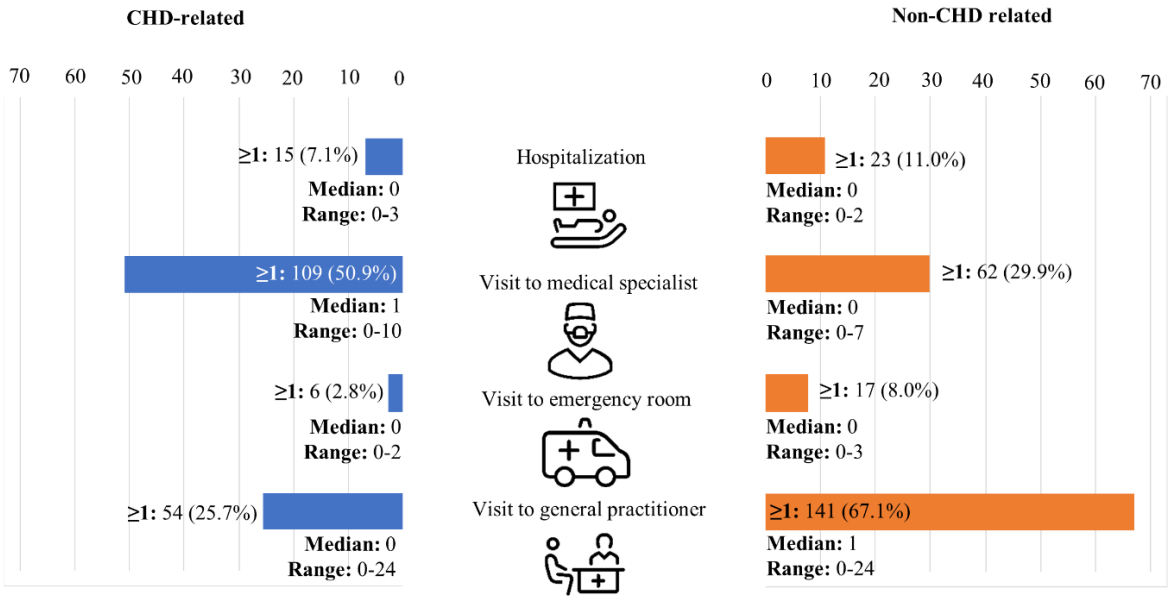

Figure 2. Description of CHD-related and non-CHD related healthcare use at T_{2015} (n=210)

Note. CHD=congenital heart disease. The icons are created by Delwar Hossain from the Noun Project.

When adjusted for age, sex, disease complexity, and depressive and anxiety symptoms, multivariable analyses revealed that patients who felt very engulfed by the heart defect at T_{2014} were more likely to be hospitalised (OR=3.76; 95%CI=1.43-9.86), to have a visit to a medical specialist (OR=2.32; 95%CI=1.35-4.00), and a GP (OR=1.78; 95%CI=1.01-3.17) at T_{2015}, related to their heart condition (Figure 3).

Illness identity and the number of visits to general practitioner and medical specialist

More than one quarter of the patients reported visits to a GP or medical specialist. Hence, for these outcomes, the association between illness identity and the number of visits could be investigated. Univariable negative binomial regression analyses, which included participants who used a particular healthcare service at least once, showed that rejection, engulfment and enrichment, measured at T_{2014} were associated with an increased number of visits at general practitioner at T_{2015}, both related and unrelated to CHD (see online supplementary material: eTable 2).

When adjusting for age, sex, disease complexity, and depressive and anxiety symptoms, no associations between illness identity and healthcare use were found to be significant anymore (Figure 4).

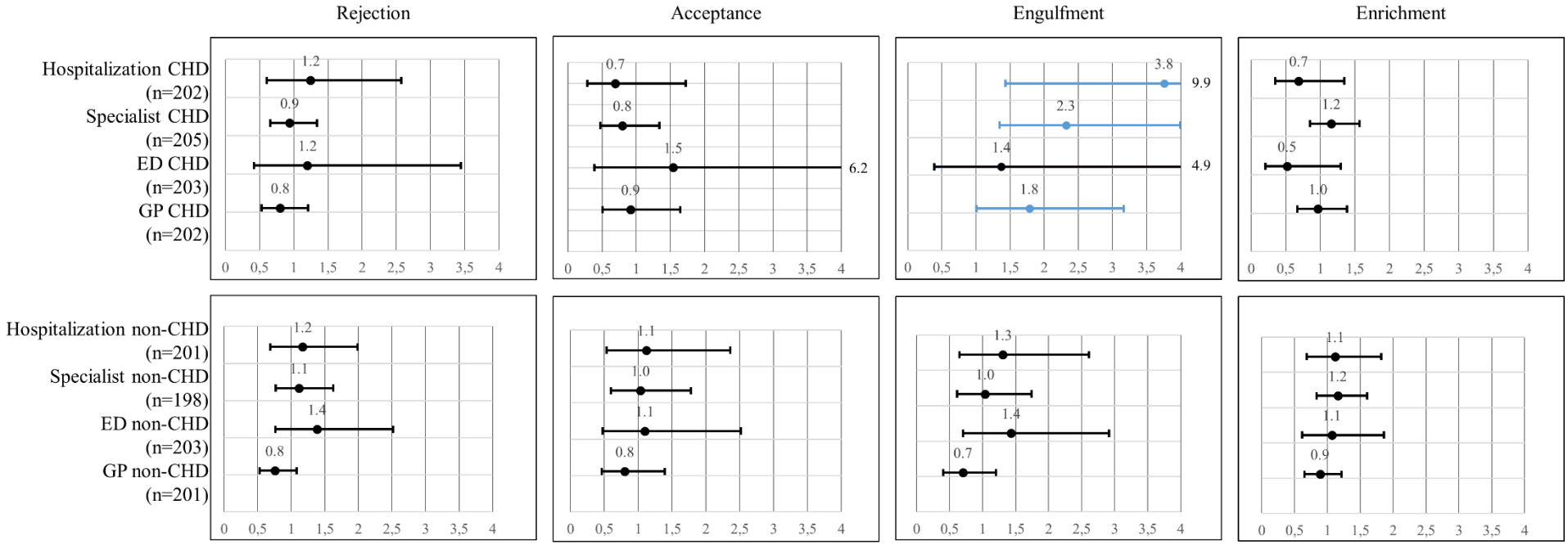

Figure 3. Association between illness identity and the occurrence of healthcare encounters (yes/no)

Note. Binary logistic regression, adjusted for age, sex, disease complexity, and depressive and anxiety symptoms. Forest plots with odds ratios and 95% confidence intervals. CHD=congenital heart disease, ED=emergency department, GP=general practitioner

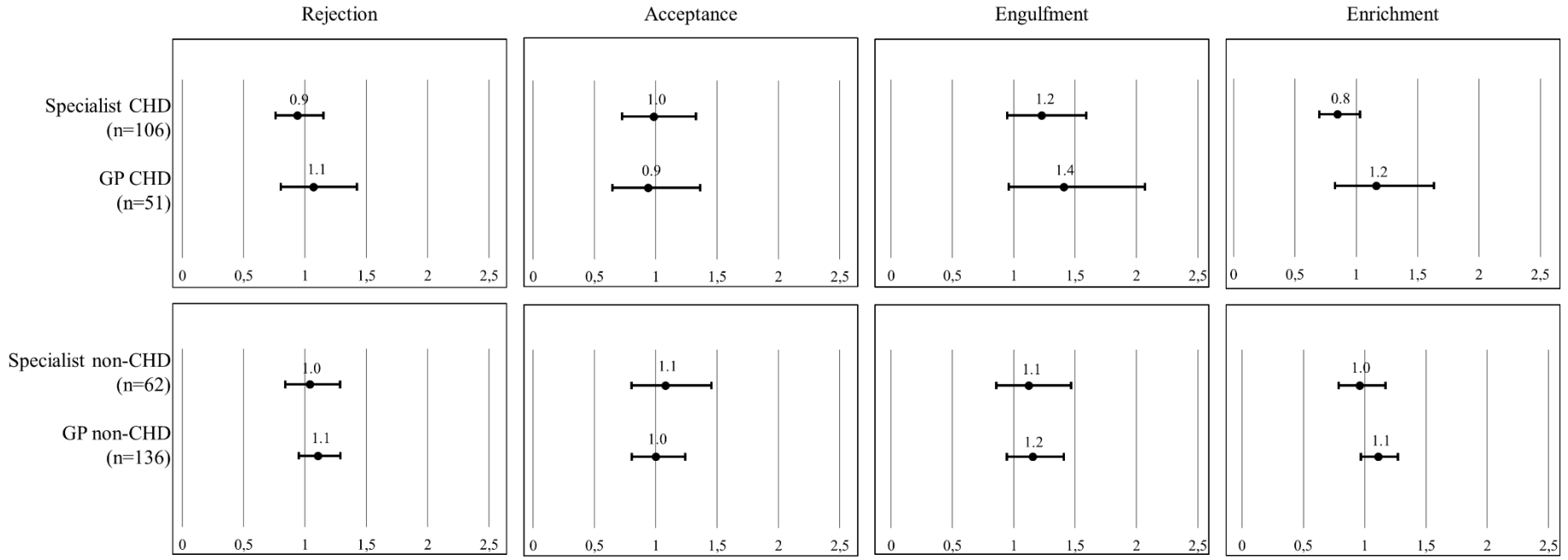

Figure 4. Association between illness identity and the amount of healthcare use

Note. Negative binomial regression, adjusted for age, sex, disease complexity, and depressive and anxiety symptoms. Forest plots with visit rate ratios and 95% confidence intervals. CHD=congenital heart disease, GP=general practitioner

Discussion

In the current study, we explored whether illness identity was a predictor for future healthcare use in adults with CHD. We found that the level of engulfment predicted the occurrence of hospitalizations, visits to medical specialists, and visits to general practitioners, for medical reasons related to CHD, when adjusted for potential confounders. Furthermore, the univariable associations of rejection, engulfment, and enrichment with the number of visits at a general practitioner were no longer significant when adjusted for the confounding factors.

The findings of the present study indicate that illness identity has a unique contribution, above and beyond known factors, when predicting the occurrence of a visit to a healthcare service, related to the heart disease. A potential explanation for this association could be that patients who are overwhelmed by their condition have a lower threshold to seek care. Alternatively, this association may be bidirectional, reflecting that consumers of healthcare services could be overwhelmed by their defect more easily, because they are confronted with the downside of the condition. The role of engulfment with respect to healthcare use has only been described in previous research in a specific population of patients with psychiatric disorders.[38,39] One of these studies showed that hospitalization is a threat to the patients viewing themselves as competent and can lead to an identity crisis.[39] This study suggested that healthcare use might lead to engulfment and not the other way around. Since patients with psychiatric disorders and adults with CHD are very different patient populations and have different healthcare utilization patterns, direct comparisons are not possible and more research about the directionality of effects is needed.

This was the first investigation on the predictive value of illness identity toward healthcare utilization. Several univariable associations have been found, which were no longer significant when adjusting for confounding factors. This indicates that only the level of engulfment is associated with the occurrence of healthcare encounters for the heart defect. However, it is also possible that a more complex underlying mechanism is present. Indeed, a prior study has shown that patients who felt very engulfed by their condition, reported more depressive and anxiety symptoms. [32 89] Such symptoms, in turn, are risk factors for higher healthcare

use in adults with CHD.[16,40] Hence, it could be possible that depressive and anxiety symptoms (i.e., psychological distress) are a mediator or an intervening mechanism of the relationship between illness identity and healthcare use, rather than merely a confounding factor. However, mediation analyses could not be done in the present study due to too small event rates and too little variation in the number of visits to a service. In addition, the mediating or moderating role of other psychological concepts related to illness identity, such as illness perceptions, should be investigated. Furthermore, also illness symptoms could be a mediator, since illness symptoms are related to illness identity [18] and can cause healthcare use. Hence, in future research, the underlying mechanisms should be scrutinized with a specific focus on depressive and anxiety symptoms, illness perceptions, and illness symptoms.

Clinical implications

Provided that subsequent studies would show that illness identity influences healthcare use, illness identity could be taken into account by healthcare practitioners as a modifiable predictor of healthcare use in adults with CHD. Therefore, our findings might improve the awareness of healthcare practitioners that psychological factors, such as illness identity, might contribute to increased healthcare use. Alternatively, if future studies show that the direction of the association is the other way around (i.e., healthcare use influencing illness identity), the possible consequences for the patient's illness identity should be taken into account by healthcare practitioners when patients consume health care.

Strengths, limitations and suggestions for further research

This is the first study investigating the association between the four states of illness identity and healthcare use. The strengths of the study are the large sample size, random sampling technique applied, and high response rates. In the analyses, we adjusted for confounding factors, such as age, sex, disease complexity, depressive, and anxiety symptoms. Furthermore, both CHD-related and non-CHD related healthcare use were taken into account.

However, results should be interpreted in the light of certain limitations. First, data on healthcare use over the past 6 months were gathered through self-report. Hence, the responses may be subjected to recall bias or telescoping. Nonetheless, the recall time frame of six months is more valid than broader time

frames [37] and previous research in chronic patients showed that self-reported healthcare use correlated strongly with medical records,[41] supporting the validity of our findings. Second, due to too small event rates and too small sample sizes, particular analyses could not be performed in the present study. Future studies should investigate these associations profoundly in longitudinal causal research in a larger sample of patients that have used healthcare services, so that all types of healthcare use could be related to illness identity. Third, the directionality of effects remains unknown. To investigate the direction of the relationships, longitudinal research with multiple measurements of all variables is needed. Indeed, in our study, healthcare use was only measured at one occasion (i.e., T_{2015}). Fourth, our sample consisted of adults from a single center in Belgium and patients with severe cognitive and/or language difficulties were excluded from the study. These two factors might reduce the generalizability of our findings. In addition, participation bias might have affected the results. However, no significant differences were found when comparing age and sex of participants in the present study with patients who were selected, but have not or only partly participated in this Belgian branch of APPROACH-IS. Furthermore, a recent study on data of the Swedish branch of APPROACH-IS showed that differences in demographic, clinical, and health status characteristics between participants and non-participants were small.[42] Fifth, the present study aimed to explore the potential of illness identity as a predictor for healthcare use, and has already corrected for a confounding factor. However, an in-depth investigation of the role of illness identity, beyond concepts such as personality, illness perceptions, and other psychological concepts is yet to be undertaken. Furthermore, as we have only adjusted for the anatomic disease complexity of the patients, future studies should also include other clinical factors, such as cardiac symptoms, in order to correct for the true severity status of the patients. Finally, while interpreting the results, it should be kept in mind that a fairly large amount of analyses were performed, also on smaller datasets.

Conclusion

Engulfment was positively associated with having at least one hospitalization, a visit at the medical specialist and the GP for CHD. This study indicated that illness identity, and more specifically the level of engulfment, is a novel predictor for healthcare use, above and beyond sex, age, disease complexity, and

depression and anxiety. If the role of illness identity can be confirmed in future research, it might be a target for intervention to prevent inappropriate healthcare use.

Author list

Liesbet Van Bulck, Eva Goossens, Koen Luyckx, Leen Oris, Silke Apers, Philip Moons. All persons listed as authors meet authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE). SA, PM, KL, LO, and EG drafted the research protocol and/or assisted with the data collection. In collaboration with PM, EG, and KL, LVB performed the statistical analysis, interpreted the results and wrote the manuscript. PM, EG, KL, LO, and SA provided critical feedback several times throughout the process. All co-authors have read the manuscript and approved its submission to the Journal of American Heart Association.

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Potential conflicts of interest

No conflict(s) of interest to be declared for the purpose of this study.

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Supplementary material – Chapter 2

eTable 1 - Univariable analyses: association between illness identity and the occurrence of healthcare encounters (yes/no)

eTable 2 - Univariable analyses: association between illness identity and the amount of healthcare use

eTable 1. Univariable analyses: association between illness identity and the occurrence of healthcare encounters

Predictors	Hospitalization for CHD related issues	Hospitalization for non-CHD related issues	Visit specialist for CHD related issues	Visit specialist for non-CHD related issues	Visit emergency room for CHD related issues	Visit emergency room for non-CHD related issues	Visit general practitioner for CHD related issues	Visit general practitioner for non-CHD related issues
Rejection (OR; 95%CI)	1.43 (0.84-2.44)	1.26 (0.81-1.95)	1.20 (0.91-1.59)	1.00 (0.73-1.37)	1.07 (0.44-2.42)	1.38 (0.84-2.30)	1.15 (0.83-1.58)	0.81 (0.60-1.08)
Acceptance (OR; 95%CI)	**0.34 (0.17-0.66)**	0.81 (0.47-1.48)	**0.62 (0.41-0.91)**	0.78 (0.52-1.17)	0.79 (0.31-2.58)	0.87 (0.47-1.77)	0.82 (0.54-1.25)	0.90 (0.58-1.37)
Engulfment (OR; 95%CI)	**3.26 (1.82-6.21)**	**1.69 (1.03-2.76)**	**2.73 (1.83-4.22)**	1.30 (0.90-1.88)	1.46 (0.54-3.36)	1.52 (0.86-2.62)	**2.01 (1.37-3.00)**	0.90 (0.63-1.29)
Enrichment (OR; 95%CI)	0.96 (0.60-1.55)	1.22 (0.83-1.85)	**1.33 (1.04-1.72)**	1.10 (0.84-1.45)	0.75 (0.36-1.56)	1.23 (0.79-1.99)	1.20 (0.91-1.60)	0.89 (0.68-1.16)
Age (OR; 95%CI)	1.02 (0.98-1.06)	1.02 (0.99-1.06)	**1.04 (1.01-1.06)**	1.00 (0.97-1.02)	1.00 (0.93-1.07)	1.02 (0.98-1.06)	**1.05 (1.02-1.07)**	1.00 (0.98-1.03)
Sex (OR; 95%CI)	0.86 (0.29-2.48)	0.51 (0.20-1.22)	0.89 (0.52-1.53)	1.61 (0.89-2.96)	1.02 (0.18-5.62)	0.53 (0.18-1.45)	1.10 (0.59-2.06)	1.66 (0.93-2.99)
Complexity (OR; 95%CI)	1.03 (0.45-2.30)	0.90 (0.45-1.73)	1.16 (0.77-1.77)	0.85 (0.53-1.34)	**3.79 (1.07-15.68)**	1.10 (0.50-2.34)	**1.67 (1.03-2.74)**	1.14 (0.73-1.79)
Depressive and anxiety symptoms (OR; 95%CI)	**1.08 (1.01-1.16)**	**1.07 (1.01-1.14)**	**1.07 (1.02-1.12)**	**1.08 (1.03-1.13)**	1.06 (0.96-1.18)	1.03 (0.96-1.11)	**1.07 (1.02-1.12)**	1.04 (0.99-1.09)

Note. Binary logistic regression, adjusted for age, sex, and disease complexity. Statistically significant ($p<0.05$) odds ratio's (OR) are in bold. CHD=congenital heart disease; CI=confidence interval

eTable 2. Univariable analyses: association between illness identity and the amount of healthcare use

Predictors	Visit general practitioner for CHD related issues	Visit general practitioner for non-CHD related issues	Visit specialist for CHD related issues	Visit specialist for non-CHD related issues
Rejection (OR; 95%CI)	1.09 (0.84-1.42)	**1.17 (1.02-1.35)**	1.02 (0.87-1.19)	0.98 (0.82-1.17)
Acceptance (OR; 95%CI)	1.07 (0.79-1.43)	0.94 (0.78-1.15)	0.86 (0.70-1.08)	1.00 (0.82-1.24)
Engulfment (OR; 95%CI)	**1.39 (1.02-1.92)**	**1.37 (1.17-1.61)**	1.18 (0.98-1.40)	1.08 (0.90-1.28)
Enrichment (OR; 95%CI)	**1.35 (1.07-1.71)**	**1.20 (1.06-1.35)**	0.90 (0.77-1.06)	1.03 (0.88-1.21)
Age (OR; 95%CI)	1.02(1.00-1.04)	**1.02 (1.01-1.03)**	1.00 (0.99-1.01)	1.00 (0.99-1.02)
Sex (OR; 95%CI)	1.35 (0.83-2.22)	**1.33 (1.00-1.76)**	0.90 (0.66-1.22)	1.26 (0.87-1.85)
Complexity (OR; 95%CI)	0.69 (0.47-1.01)	1.00 (0.80-1.25)	1.10 (0.86-1.39)	1.22 (0.87-1.73)
Depressive and anxiety symptoms (OR; 95%CI)	1.06 (0.99-1.14)	**1.05 (1.03-1.08)**	**1.04 (1.01-1.07)**	**1.06 (1.01-1.11)**

Note. Negative binomial regression, adjusted for age, sex, and disease complexity. Statistically significant ($p<0.05$) odds ratio's (OR) are in bold. CHD=congenital heart disease; CI=confidence interval

Chapter 3

Illness identity in adults with congenital heart disease: Longitudinal trajectories and associations with patient-reported outcomes and healthcare use

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Abstract

Aims: The aims of this study were to investigate the development of illness identity, the degree to which the disease is integrated into one's identity, by identifying trajectory classes in adults with congenital heart disease (CHD) and to describe these classes in terms of age, sex, disease complexity, patient-reported outcomes (PROs) and healthcare use.

Design: This three-wave observational cohort study was carried from 2013 till 2015 and includes 276 adults (median age: 34y; 54% men) with CHD.

Methods: Illness identity entails four dimensions: engulfment, rejection, acceptance and enrichment. PROs included perceived health status, quality of life and psychological distress. Latent class growth analysis, analysis of variance, Poisson regression and negative binomial regression analyses were performed.

Results: Illness identity was relatively stable over time. The identified classes were meaningfully different in terms of age, disease complexity, PROs and healthcare use. Patients who did not reject their disease, patients who were not overwhelmed, or patients who accepted their disease over time reported better health status and quality of life and less psychological distress. Less hospitalizations, and visits to the general practitioner and medical specialist were reported by patients who were not overwhelmed or patients who accepted their disease over time. Patients with low rejection and high enrichment scores over time reported more visits at the general practitioner.

Conclusion: These findings indicate that illness identity should be taken into account when trying to understand and optimize PROs and healthcare use of adults with CHD.

Impact: This study scrutinizes the development and clinical meaningfulness of illness identity measured over time for adults with CHD. Illness identity was found to be stable over time. Moreover, the illness identity trajectories differed in terms of PROs and healthcare use, showing that measuring and intervening upon illness identity could be a potential pathway to optimize PROs and healthcare use.

Keywords

Anxiety, Congenital heart defects, Depression, Health Services Research, Nursing, Psychology, Quality of Life

Introduction

Survival of patients with congenital heart disease (CHD) has improved remarkably over the past decades, introducing a growing and aging population of adults with CHD [1,2]. However, despite surgeries in childhood, the majority of patients have residual abnormalities and complications and cannot be considered to be cured [3]. This has two important consequences for the health care system.

The healthcare perspective for these patients has widened with increased attention for aspects of optimal living, expressed in research on patient-reported outcomes (PROs) such as quality of life, perceived health and psychosocial functioning [4]. PROs have been shown to be of clinical relevance in cardiac populations because they independently predict cardiovascular events, hospitalizations and mortality [5].

Also, long-life follow-up for this rapidly growing population causes an exponential rise of healthcare use of these patients. Over the past decades, the absolute number of hospitalizations and outpatient cardiology visits has expanded, showing high and changing healthcare demands for this population. These changes will put an increased burden on the healthcare system and society [6]. To reduce this, a good understanding of the predictors of high healthcare use is needed.

For both PROs and healthcare use, differences between patients with CHD are not sufficiently understood yet. Some patients experience substantial difficulties related to their disease resulting in unfavorable PROs and high healthcare use, while others succeed in coping with the disease-related challenges [7,8]. Therefore, a good understanding of the modifiable predictors of PROs and healthcare use is needed. One modifiable predictor that has shown to be related to both PROs and healthcare use in adults with CHD is ‘illness identity’[9].

Previous literature has indicated that illness identity may play a key role in regulating PROs and healthcare use in adults with CHD [9-11]. However, so far, these associations are only investigated in cross-sectional research, leaving questions about how illness identity may predict these variables over time unanswered.[9] Indeed, there is a need for longitudinal research to examine the development and stability of illness identity in adults with CHD and to explore whether illness identity over time could be a helpful tool to understand why certain patients do better in terms of PROs and healthcare use than others.

Background

Illness identity is defined as "*the degree to which a condition is integrated into one's identity*" and encompasses four dimensions: engulfment, rejection, acceptance, and enrichment (see Figure S1) [12,13]. The first two dimensions represent dysfunctional illness identity dimensions and induce maladaptive responses, such as excessive concern or avoidance. Engulfment refers to the degree to which the disease dominates one's identity and daily life. Patients with high engulfment scores mainly define themselves in terms of their disease as they pay a lot of attention to their restrictions in daily life [13,14]. Rejection captures the degree to which the disease is seen as unacceptable to the self [13,15]. Patients with high rejection scores are usually characterized by suboptimal self-management and adherence and refuse to see their disease as part of their identity [13,16]. Acceptance and enrichment represent more adaptive dimensions of illness integration. Individuals who accept their disease find the right balance between devoting attention to their illness and other aspects of their identity [13-15]. Enrichment is the degree to which the disease enriches one's sense of self, enables one to grow as a person and results in positive life changes [13,17].

Illness identity has been investigated in several patient populations during the past years, that is, young adults with refractory epilepsy [18], adolescents with celiac disease [19], youth with type 1 diabetes [13 20], patients with systemic diseases [10], and adults with CHD [10,11]. In all these populations, associations between the four illness identity dimensions and clinical parameters, patient-reported outcomes, and healthcare utilization were found, indicating that illness identity could be a valuable concept that has the potential to support clinical practice. In adults with CHD, the illness identity dimensions were shown to be related to depression, anxiety, self-reported health, hospitalizations and visits at

the general practitioner and medical specialist [9-11]. However, further studies ought to investigate the potential of illness identity further, before it can be used in interventions or guidelines to ameliorate clinical care.

The study

Aims

The aims of this study were a) to identify classes of individuals with CHD characterized by similar longitudinal trajectories of illness identity dimensions, and b) to describe these classes in terms of age, sex, disease complexity, patient-reported outcomes and healthcare use.

Design

The present study is a secondary data analysis that used the data of the Belgian branch of the APPROACH-IS project [21]. The Belgian branch of APPROACH-IS is a longitudinal three-wave observational cohort study with one-year intervals (T_{2013}; T_{2014}; and T_{2015}). A total of 276 patients (RR: 69%), 255 patients (RR: 74%) and 229 patients (RR: 80%) responded on T_{2013}, T_{2014} and T_{2015}, respectively. A more detailed description of the recruitment process can be found as supplementary material (Figure S2) [9].

Participants

Patients have been selected randomly from the database of adults with CHD of the University Hospitals Leuven in Belgium. Patients were eligible if they were: (i) diagnosed with CHD, according to the definition of Mitchell and colleagues [22]; (ii) born before 1991; (iii) diagnosed before the age of 10 years (to warrant ample experience of living with CHD); (iv) in follow-up at the University Hospitals Leuven; (v) Dutch-speaking; and (vi) demonstrating language, cognitive and physical proficiency to complete self-reported surveys. Patients were excluded if they had: (i) prior heart transplantation; or (ii) isolated pulmonary hypertension [21].

Data collection

The study was carried out from 2013 till 2015. Eligible participants were asked to fill out a set of self-reported surveys. Patients received a study package by postal service, including a study information letter, an informed consent form, a

survey package and an addressed prestamped envelope. To increase the response rate, a modified Dillman approach was used [23].

Variables and instruments

Illness identity was measured at all three waves. Patient-reported outcomes (i.e., perceived health status, quality of life and psychological distress) and healthcare use were measured at T_{2015}. More information about the instruments used to measure PROs and healthcare use can be found in Table 1.

Validity, reliability and rigour of the instruments

The psychometric properties of the instruments used are described in Table 1 as well.

Table 1. Overview of the properties of instruments

Variable	Instrument	Structure of the instrument	Reliability	Validity	Use in cardiac samples	Interpretation
Illness identity	Illness Identity Questionnaire (IIQ) [13]	- 25 statements - 5-point Likert scale ranging from strongly disagree to strongly agree - Consists of 4 subscales: • rejection scale with 5 items • acceptance scale with 5 items • engulfment scale with 8 items • enrichment scale with 7 items	Supported [13] Cronbach α values in present study for T_{2013}, T_{2014} and T_{2015} respectively: • 0.75, 0.77 and 0.78 for rejection • 0.83, 0.81 and 0.83 for acceptance • 0.92, 0.92 and 0.93 for engulfment • 0.95, 0.94 and 0.95 for enrichment	Supported [13]	Yes, in adults with CHD [10]	- Mean score per subscale - Higher scores = higher level of rejection, acceptance, engulfment or enrichment
Perceived health status	EuroQoL-Visual Analogue Scale (EQ-VAS) [24]	Ranges from 0 (worst imaginable health state) to 100 (best imaginable health state)	Supported [25]	Supported [25]	Yes, in adults with CHD [7]	Higher scores = better perceived health
	12-item Short-Form Health Survey version 2 (SF-12v2) [26]	Ranges from 0 to 100 on 8 health domains: physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems and mental health	Supported [27]	Supported [27]	Yes, in adults with CHD [7]	Higher scores = better perceived health

Quality of life (QOL)	Linear Analog Scale (LAS) [28]	Vertically oriented, 10-centimeter line graded, ranges from 0 (worst imaginable QOL) to 100 (best imaginable QOL)	Supported [25]	Supported [25]	Yes, in patients with CHD [25]	Higher scores = better QOL
	Satisfaction with Life Scale (SWLS) [29]	- Comprises of 5 statements with a response ranging from strongly disagree to strongly agree - Total score ranges from 5 (extremely dissatisfied) to 35 (extremely satisfied)	Supported [25] Cronbach α value of present study: 0.89	Supported [25]	Yes, in patients with CHD [25]	- Score of 20 = neutral point - Higher scores = better QOL
Psycho-logical distress	Hospital Anxiety and Depression Scale (HADS) (HADS; [30,31])	- 14 items - 4-point Likert scale with values ranging from 0 to 3 - Total score ranges from 0 to 42	Supported [31] Cronbach α value of present study: 0.86	Supported [32]	Yes, in adults with CHD [7]	Higher scores = more psychological distress
Healthcare use	Patient-Reported Inpatient and outpatient Utilization Survey (PRIUS) [9]	- 3 items, recall time frame of 6 months, healthcare use that is related to the heart disease - Only variables that have shown to be significantly related to illness identity in a previous study on the same dataset were included. [9]	NA	NA	Yes, in adults with CHD [9]	Higher number = more healthcare use

Legend. NA: not applicable

Ethical considerations

Ethics approval was obtained from a university. Procedures were in accordance with the declaration of Helsinki. Written informed consent was obtained from each patient. The protocol was registered at ClinicalTrials.gov (NCT02150603).

Data analyses

First, to identify trajectory classes of the illness identity dimensions over time (research aim 1), Latent Class Growth Analysis (LCGA) was conducted. LCGA is a person-centered approach that summarizes longitudinal information by classifying individuals into trajectory classes [33]. Each class consists of individuals showing similar development of illness identity over time and is characterized by unique initial levels (intercepts) and rates of change (slopes). To identify the optimal number of classes within the data, LCGA models for 1 to 4 classes ran for each illness identity dimension separately. The best-fitting model was selected based on several fit indices (i.e., the Bayesian Information Criterion (BIC), entropy (*E*) and the Lo-Mendell-Rubin Loglikelihood Ratio Test (LMR-LRT)) and the size of the classes. Supplementary material contains additional information on the LCGA (Annex S1).

Second, to describe the classes in terms of age, sex, disease complexity and PROs, respectively (research question 2), Kruskal-Wallis H, chi-square tests and multivariable analyses of variance with pairwise comparisons using Gabriel's test procedure (i.e., post-hoc tests) were performed. An expectation–maximization algorithm was performed to estimate the missing PROs. To investigate to what extent the trajectory classes differed from each other in terms of healthcare use, multivariable Poisson (for hospitalizations and visits to medical specialists) and negative binomial regression analyses (for visits to general practitioners) were performed, adjusting for age, disease complexity and PROs.

LCGA was conducted in Mplus 8.0. The remaining analyses were conducted in SPSS version 26 with the significance level at $p \leq 0.05$ (2-tailed).

Results

Sample characteristics

Table 2 shows the sociodemographic variables, derived through self-report, and clinical variables, derived through chart review of the medical records, of the study sample at baseline (T_{2013}). Age ranged from 22 to 78 years, 46.0% of patients were women, almost all patients (96.0%) finished at least high school and most patients (63.3%) worked full time. Disease complexity was categorized following the classification of Task Force 1 of the 32nd Bethesda conference, as simple (33.7%), moderate (54.3%) or great (12.0%) [34].

Descriptive statistics of included variables

The mean, standard deviation, median and range of all included variables are reported in Table 3.

Table 2. Patient characteristics of the total sample at T_{2013} (n=276)

Characteristics	n (%)
Median age at T_{2013}	34y (Q1=28y; Q3=42y)[A]
Men	149 (54.0)
Highest level of education	
Less than high school	11 (4.0)
High school	131 (47.8)
College degree	80 (29.2)
University degree	52 (19.0)
Employment status	
Full-time paid job	174 (63.3)
Part-time paid job	47 (17.1)
Homemaker	8 (2.9)
Job seeking	5 (1.8)
Unemployed	2 (0.7)
Disability/government financial assistance	24 (8.7)
Retired	10 (3.6)
Other	5 (1.8)
Disease complexity, Task Force 1	
Simple	93 (33.7)
Moderate	150 (54.3)
Complex	33 (12.0)

Legend. [A] Interquartile range

Table 3. Descriptive overview of the included variables

	T_{2013}	T_{2014}	T_{2015}
ILLNESS IDENTITY DIMENSIONS			
Rejection	2.6 (0.9) [A]	2.6 (0.9) [A]	2.6 (1.0) [A]
Acceptance	4.2 (0.8) [A]	4.2 (0.7) [A]	4.3 (0.7) [A]
Engulfment	1.8 (0.9) [A]	1.8 (0.8) [A]	1.8 (0.8) [A]
Enrichment	3.0 (1.2) [A]	3.1 (1.1) [A]	3.1 (1.1) [A]
PATIENT-REPORTED OUTCOMES			
Perceived health			
EuroQoL-Visual Analogue Scale			78.1 (13.8) [A]
Physical Component Summary			76.2 (19.6) [A]
Mental Component Summary			72.1 (16.5) [A]
Psychological distress			
Hospital Anxiety and Depression Scale			8.6 (5.8) [A]
Quality of life			
Linear Analogue Scale-Quality of Life			77.8 (13.5) [A]
Satisfaction With Life Scale			25.5 (5.6) [A]
HEALTHCARE USE			
Hospitalizations in past 6 months (reason related to the heart disease)			0 (3) [B] 8% [C]
Visits at general practitioner in past 6 months (reason related to the heart disease)			0 (24) [B] 28% [C]
Visits at medical specialist in past 6 months (reason related to the heart disease)			0 (10) [B] 50% [C]

Legend. [A] Mean and standard deviation are reported. [B] Median and range are reported. [C] Percentage of the sample with at least one hospitalization/visit at general practitioner/visit at medical specialist.

Objective 1: Illness identity trajectories

Using LCGA, classes of illness identity dimensions were identified. A graphical presentation of the observed means of the classes for the illness identity dimensions on the three time points is provided in Figure 1 (Panel A). A detailed description of how the most appropriate models have been selected can be found in Annex S2 and Table S1.

For engulfment, the model with three classes was selected (BIC=1374.6; *E*=0.891; LMR-LRT p=0.03). Class 1 (n=28; 10.1%, mean intercept=3.614) was characterised by persistent high scores on engulfment (*Chronically high*). Class 2 (n=74; 26.8%, mean intercept=2.409) consisted of patients having moderate engulfment scores at the three time points (*Intermediate stable*). Class 3 represented the majority of the sample (n=174; 63.0%, mean intercept=1.309) and demonstrated low engulfment scores over time (C*onsistently low)*.

Also for rejection, three trajectory classes were identified (BIC=1682.0; *E*=0.803; LMR-LRT p=0.0014). The first class (n=22; 8.0%, mean intercept=4.294), which included a minority of patients, showed persistently high rejection scores (*Chronically high*). In Class 2 (n=124; 44.9%, mean intercept=3.067), patients with moderate rejection scores that remained stable over time were included (*Intermediate stable)*. Finally, the remaining patients (n=130; 47.1%, mean intercept=1.928) had consistently low scores on the rejection subscale (*Consistently low*).

For acceptance, a 2-class solution was selected (BIC=1489.1; *E*=0.823; LMR-LRT p=0.004). The first class was labelled '*Consistently high'* (n=212; 76.8%; mean intercept=4.484). These patients consistently accepted their disease as part of their identity. The second class (n=64; 23.2%; mean intercept=3.137; mean slope=0.201) consisted of patients who demonstrated moderate acceptance levels at baseline and showed slightly better acceptance levels over time (*Intermediate increasing)*.

For enrichment, the model with three classes was most favourable (BIC=1836.0; *E*=0.839; LMR-LRT p<0.00001). The '*Consistently high'* class (n=102; 37.0%; mean intercept=4.147) consisted of patients that felt highly enriched over the three time points. The second class (n=126; 45.7%; mean intercept=2.768) had enrichment scores that were moderate and remained stable over time (*Intermediate stable).* Finally, the remaining participants (n=48; 17.4%; mean intercept=1.448) followed a trajectory of persistently low enrichment (*Chronically low).*


A. Longitudinal trajectories
B. Patient characteristics
C. Patient-reported outcomes
D. Healthcare use
Engulfment
Chronically High
n=28
Intermediate Stable
n=74
Consistently Low
n=174
T2013 T2014 T2015
3.6 3.4 3.5
2.4 2.3 2.3
1.3 1.4 1.4
Median age
34
35
31.5
18 23 28 33 38 43
61% 39%
58% 42%
51% 49%
21% 61% 18%
33% 47% 20%
36% 56% 8%
66 74 82
63 75 81
14 10 7
56 68 83
56 70 76
20 24 27
EQ-VAS
LAS QOL
HADS
PCS
MCS
SWLS
Compared to patients with Chronically High Engulfment
Hospitalizations
0.5
0.1
0.02
General Practitioner
0.6
0.4
Medical Specialist
1.2
0.7
0,0625 0,25 1 4
Rejection
Chronically High
n=22
Intermediate Stable
n=124
Consistently Low
n=130
4.4 4.2 4.4
3.1 3.0 3.0
1.9 1.8 1.8
Median age
43.5
34
33
18 23 28 33 38 43
50% 50%
55% 45%
54% 46%
55% 36% 9%
33% 53% 14%
31% 58% 11%
76 76 80
75 76 80
9 10 8
67 75 79
68 71 74
25 25 26
EQ-VAS
LAS QOL
HADS
PCS
MCS
SWLS
Compared to patients with Chronically High Rejection
Hospitalizations
0.6
1.1
6.1
General Practitioner
2.2
3.6
9.9
Medical Specialist
1.2
1.8
0,0625 0,25 1 4
Acceptance
Consistently High
n=212
Intermediate Increasing
n=64
4.5 4.5 4.5
3.1 3.3 3.6
Median age
34
34.5
18 23 28 33 38 43
54% 46%
55% 45%
36% 53% 11%
27% 59% 14%
79 75
79 73
8 11
77 72
73 69
26 23
EQ-VAS
LAS QOL
HADS
PCS
MCS
SWLS
Compared to patients with Consistenly High Acceptance
Hospitalizations
4.8
16.5
General Practitioner
4.0
7.1
Medical Specialist
2.7
0,0625 0,25 1 4
Enrichment
Consistently High
n=102
Intermediate Stable
n=126
Chronically Low
n=48
4.1 4.1 4.1
2.7 2.9 2.9
1.4 1.4 1.5
Median age
42
34
33
18 23 28 33 38 43 48
49% 51%
57% 43%
56% 44%
26% 58% 16%
33% 57% 10%
52% 40% 8%
78 77 82
78 77 80
8 10 8
73 76 84
73 70 74
26 25 26
EQ-VAS
LAS QOL
HADS
PCS
MCS
SWLS
Compared to patients with Chronically Low Enrichment
Hospitalizations
0.3
0.06
0.3
0.06
General Practitioner
4.0
9.3
1.2
1.2
Medical Specialist
1.1
0,0625 0,25 1 4

Figure 1. Trajectory classes of illness identity dimensions and their clinical relevance

Legend. Bold results = significantly different; Blurred results = not significantly different **Panel A.** Graphical presentation of illness identity trajectories across three time points. Observed means are reported. **Panel B.** Trajectories in terms of age, sex and disease complexity. Medians and percentages are reported. =simple disease complexity; =moderate disease complexity; =great disease complexity. **Panel C.** Trajectories in terms of patient-reported outcomes. Means are reported. EQ-VAS = EuroQoL-Visual Analogue Scale; LAS-QOL = Linear Analogue Scale-Quality of Life; HADS = Hospital Anxiety and Depression Scale; PCS = Physical Component Summary; MCS = Mental Component Summary; SWLS = Satisfaction With Life Scale. **Panel D.** Trajectories in terms of healthcare use (of the past 6 months; related to heart disease). Odds ratios and confidence intervals are reported (on a logarithmic scale).

Objective 2a: Trajectories in terms of sociodemographic and clinical variables

Kruskal-Wallis H and chi-square tests were performed to describe the illness identity classes in terms of age, sex, and disease complexity. The distribution of age, gender and disease complexity for the different trajectory classes is shown in Figure 1 (Panel B) and in Table S2. Age seemed to be a predictor for the classes of engulfment ($p=0.013$; $\eta^2=0.046$) and rejection ($p=0.019$; $\eta^2=0.048$). More specifically, patients with C*onsistently low* engulfment scores were significantly younger than the other patients. Patients with *Chronically high* rejection scores were older compared to the other rejection classes. Furthermore, the classes of engulfment ($p=0.031$; $\varphi_c=0.139$) and enrichment ($p=0.029$; $\varphi_c=0.190$) significantly differed in terms of disease complexity. The majority of patients with simple and moderate lesion complexity had *Consistently low* engulfment scores. Moreover, most complex patients were located in the class with *Consistently high* enrichment scores.

Objective 2b: Trajectories in terms of PROs

Multivariable analyses of variance with pairwise comparisons using Gabriel's test procedure (i.e., post-hoc tests) were performed to describe the illness identity classes in terms of PROs. Figure 1 (Panel C) shows the mean values of perceived health status, quality of life (QOL) and psychological distress, measured using the EQ-VAS, LAS-QOL, HADS, SF-12 (PCS and MCS) and SWLS for all trajectory classes. The F-values and η^2-values of these associations can be found in the supplementary material (Table S3).

The three trajectory classes of engulfment were significantly different from each other for all PROs. Patients with *Chronically High* engulfment scores reported lower perceived health, QOL and more psychological distress compared to patients with *Intermediate Stable* and *Consistently Low* scores on engulfment. Patients with *Consistently Low* engulfment scores reported opposite results and, hence, showed more favourable PROs. The η^2-values show large effect sizes for all PROs, except MCS for which a medium effect size was found.

The classes of rejection significantly differed from each other in terms of QOL (LAS-QOL), psychological distress (HADS) and physical health (PCS). More specifically, patients who did not reject their disease over time (*Consistently Low*) reported better QOL and less psychological distress compared to patients

with *Intermediate Stable* rejection scores and reported better physical health compared to patients who reject their disease over time (*Chronically High*). In terms of effect sizes, η^2-values show small effect sizes for all PROs.

Perceived health (EQ-VAS), quality of life (LAS-QOL & SWLS) and psychological distress (HADS) were significantly different for the two trajectory classes of acceptance. Patients that accepted their disease as part of their identity over time (*Consistently High*), reported better perceived health, better QOL and less psychological distress, compared to patients with an *Intermediate Increasing* level of acceptance. The η^2-values show small effect sizes for all PROs.

Physical health (PCS) was different for the three trajectory classes of enrichment. This score was higher in patients with *Chronically Low* enrichment scores, compared to patients with *Consistently High* enrichment scores and patients with *Intermediate Stable* enrichment scores. Small effect sizes (η^2) were found for all PROs, except for QOL and SWLS for which negligible effect sizes were found.

Objective 2c: Trajectories in terms of healthcare use

Based on multivariable Poisson and negative binomial regression analyses, odds ratios and confidence intervals of healthcare use of the different classes of the four illness identity dimensions are reported in Figure 1 (Panel D) and Table S4.

Patients with low engulfment scores over time (*Consistently Low*) were less likely to be hospitalised and to visit a general practitioner in the past 6 months for a reason related to their health disease, compared to participants who were overwhelmed by their CHD over time (*Chronically High*).

For rejection, patients who did not reject their disease as part of their identity (*Consistently Low*), reported more visits at the general practitioner because of the CHD, compared to patients who tend to refuse to experience their disease as part of their identity (*Chronically High*).

Compared to individuals who accepted their disease over time (*Consistently High*), participants with *Intermediate Increasing* acceptance scores were more likely to be hospitalised, to visit a general practitioner and to visit a medical specialist, for a reason related to their CHD.

Patients who are highly enriched by their disease (*Consistently High*), were more likely to visit a general practitioner for a reason related to the CHD, compared to patients who did not experience positive life changes due to their disease (*Chronically Low*).

Discussion

To the best of our knowledge, this is the first study that investigated illness identity in adults with CHD using a longitudinal research design. This study aimed to identify classes of individuals with CHD characterized by similar trajectories and to describe these classes in terms of sex, age, disease complexity, PROs and healthcare use.

Overall, illness identity has shown to be a stable concept in adults with CHD. Previous research showed that illness identity dimensions are likely to change over the different stages of the illness trajectory [13], but patients with CHD in the present study received their diagnosis at birth or at least 10 years before inclusion in the study, which could explain the stability of the concept in this sample.

The identified trajectory classes did not differ from each other in terms of sex, which is in line with preceding studies [10,11,13,18]. In the present study, patients with C*onsistently low* engulfment scores were younger than the other patients and patients with *Chronically high* rejection scores were older compared to the other rejection classes. Previous literature showed conflicting results about the association between age and illness identity dimensions [10,11,13,18]. In our sample, disease complexity was found to be significantly associated with classes of engulfment and enrichment, with complex patients situated in higher levels of engulfment and enrichment over time. This could be because patients with complex heart defects are more prone to experiencing physical limitations and illness symptoms are positively associated with engulfment and enrichment [10,35]. For enrichment, it is stated that individuals have to experience a substantial impact of the disease to be able to grow as a person, which could also explain why patients with complex heart disease tend to have higher enrichment scores [36]. Moreover, for certain patients, enrichment could be a coping mechanism to seek something positive in previous negative experiences [37].

The identified classes have shown to be clinically relevant in terms of PROs. The directions of the associations remain unknown. One can assume that these

results highlight the negative effects of being overwhelmed by the disease, or when rejecting the disease as part of the identity and the positive impact of accepting the disease on the health of patients. However, PROs can also impact the illness identity dimensions. That would explain why patients with low enrichment levels reported better physical health, as a certain severity and impact of the disease should be experienced, to be enriched by the disease [36]. The findings of this longitudinal study are in line with prior cross-sectional research in patients with CHD that showed associations between illness identity and emotional distress [10,11].

The classes were also meaningfully differentiated in terms of healthcare use. High engulfment scores or low acceptance scores seem to induce higher healthcare use, as very engulfed patients or patients with intermediate acceptance scores may have a lower threshold to seek care [9]. Oppositely, it could also be that patients who regularly consume healthcare are more often confronted with their disease, which can induce engulfment or can oppose acceptance of the disease [9]. The finding that patients who reject their disease were less likely to visit a general practitioner is not surprising as these patients might more often cancel clinic visits or might not attribute certain complaints, for which they seek care, to their CHD. Moreover, when looking at the opposite direction of effects, if patients consume no healthcare related to their CHD, they are not often confronted with their disease and can easily neglect it. The positive association between visits at the general practitioner and enrichment scores could be explained because enriched patients experience more illness symptoms, which could lead to healthcare use [10].

Clinical implications

Both Oris et al. [10] and Andonian et al. [11] have described illness identity as a possible helpful tool to understand how patients with CHD experience their disease and suggested to develop interventions to ameliorate clinical and patient-reported findings. The results of the present study provide additional insights that can contribute to the development of tailored interventions or to the routine measurement of illness identity in practice.

First, illness identity has been shown to be a relatively stable concept over time, showing that a one-time assessment of illness identity could already provide interesting information for clinical practice. Oppositely, frequent short-term

measurements seem less useful. This could be good news in terms of feasibility of implementing such assessment in clinical practice. However, it could also be that no change over time was noticed, because the data were collected over a relatively short period of 3 years and all patients received their diagnosis at least 10 years before inclusion in the study. To examine the stability further, it would be interesting to look at a broader time frame and to include patients in different phases of the illness trajectory.

Second, when measuring illness identity in practice, the question will remain on who to target. Therefore, it is interesting to know that older patients are more prone to be overwhelmed by the disease or to reject the disease over time and that patients with more complex heart disease might have higher chances of being overwhelmed and enriched. If this is confirmed in future studies, older patients could be seen at risk for less favourable outcomes and should therefore receive more attention in the clinic. Moreover, patients with complex heart disease could also benefit from monitoring of the level of engulfment and enrichment.

Third, the associations between illness identity and PROs indicate that identifying illness identity trajectories could be a potential pathway for targeting patients with poor PROs. PROs could be enhanced when challenging maladaptive illness identity integration and inducing acceptance, for example by referring patients to psychotherapy [16] or by actively challenging the negative thoughts. This could be facilitated by administering the IIQ or by letting the patient draw a circle that symbolizes the identity (based on the PRISM-D [38]). These strategies to ameliorate illness identity integration can be part of tailored interventions to optimize PROs and reach a holistic approach towards care for patients with CHD.

Fourth, as the present study confirmed that illness identity is associated with healthcare use in adults with CHD, this could be taken into account when trying to understand why certain people consume more healthcare compared to others.

Finally, for all identity dimensions, a group of patients with less favourable scores over time could be identified, which shows that, although patients might have lived with their CHD for a long time, some patients still have trouble integrating their disease into their identity. These patients with a maladaptive illness identity require additional support from healthcare practitioners, starting with the acknowledgment of the identity issues [10].

Limitations and suggestions for future research

First, only three waves with a one-year time interval were included, which represents a relatively short period of time. This could be one of the reasons why we found little change in the development of illness identity. Longitudinal research with a continuous follow-up would provide additional information on the development of illness identity over time. Second, data on illness identity, PROs and healthcare use were self-reported, which could have introduced single-reporter bias, recall bias or telescoping. However, self-report questionnaires are the most appropriate method to gather PROs, as patients' views should be captured, as well as to gather information regarding internal processes, such as illness identity. The recall time frame of six months for healthcare use is more valid than larger time frames [39] and earlier research in chronic patients demonstrated that self-reported healthcare use correlated strongly with data from medical records [40]. Third, due to the study design, significant differences among the classes cannot be interpreted in terms of causality. They provide a first insight into potentially relevant factors for clinical practice. To examine the predictors of illness identity or predictive value of illness identity over time, cross-lagged path analysis could be applied. Fourth, we could not distinguish between appropriate and inappropriate healthcare use. In the light of optimizing healthcare use in this population, it is important to take this into account in future studies. Fifth, only adults with CHD have been included in the study. It could be interesting for future studies to include children and adolescents with CHD, as these patients could have gone through different stages of the illness trajectory. Indeed, that way, the development of illness identity in patients with CHD can be understood even better. Sixth, there is limited generalizability, due to the single-center setting, exclusion of patients with severe cognitive/language difficulties, and exclusion of patients who received their CHD diagnosis after the age of 10 years. It would be interesting to investigate illness identity in a multicentric international study and in other patient populations and thereby investigate to what extent the results can be generalized.

Conclusion

This is the first study that examined the development of illness identity in adults with CHD, which has shown to be relatively stable over time. The identified classes were meaningfully differentiated in terms of age, disease complexity, patient-reported outcomes and healthcare use. These findings indicate that illness identity should be taken into account when trying to understand and optimize PROs as well as healthcare use of adults with CHD.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary material – Chapter 3

Figure S1 - Visualization of illness identity dimensions
Figure S2 - Diagram of the recruitment process and response rates of the Belgian branch of APPROACH-IS
Annex S1 - Detailed information on the Latent Class Growth Analysis
Annex S2 - Identifying developmental classes of illness identity
Table S1 - Results of Latent Class Growth Analyses to identify the most appropriate developmental trajectories for the four illness identity dimensions
Table S2 - Comparison of age, sex and disease complexity of the identified illness identity classes
Table S3 - Analyses of variance and post hoc comparisons based upon Gabriel's pairwise test procedure for the classes of the four illness identity dimensions
Table S4 - Healthcare use (on T_{2015}) for the different classes of illness identity development (n=209)

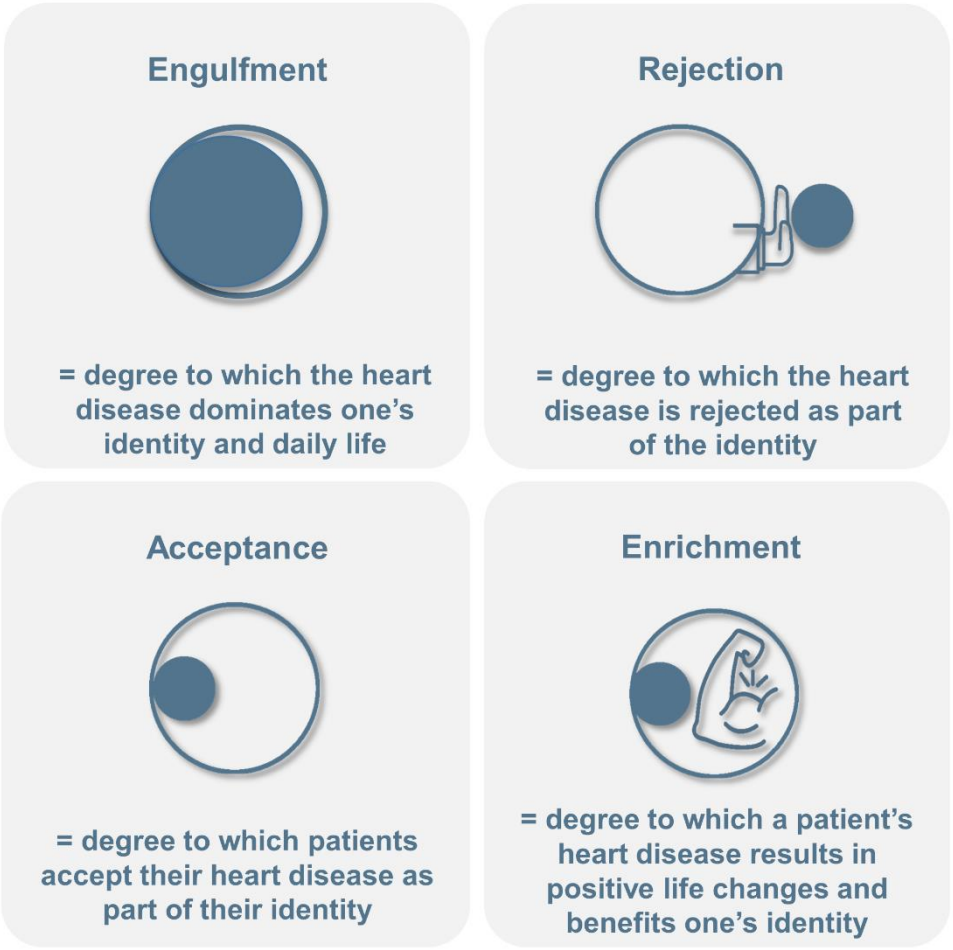

Figure S1. Visualization of illness identity dimensions

Legend. Sphere = disease; circle = one's identity**.** Modified from Van Bulck et al.[1]

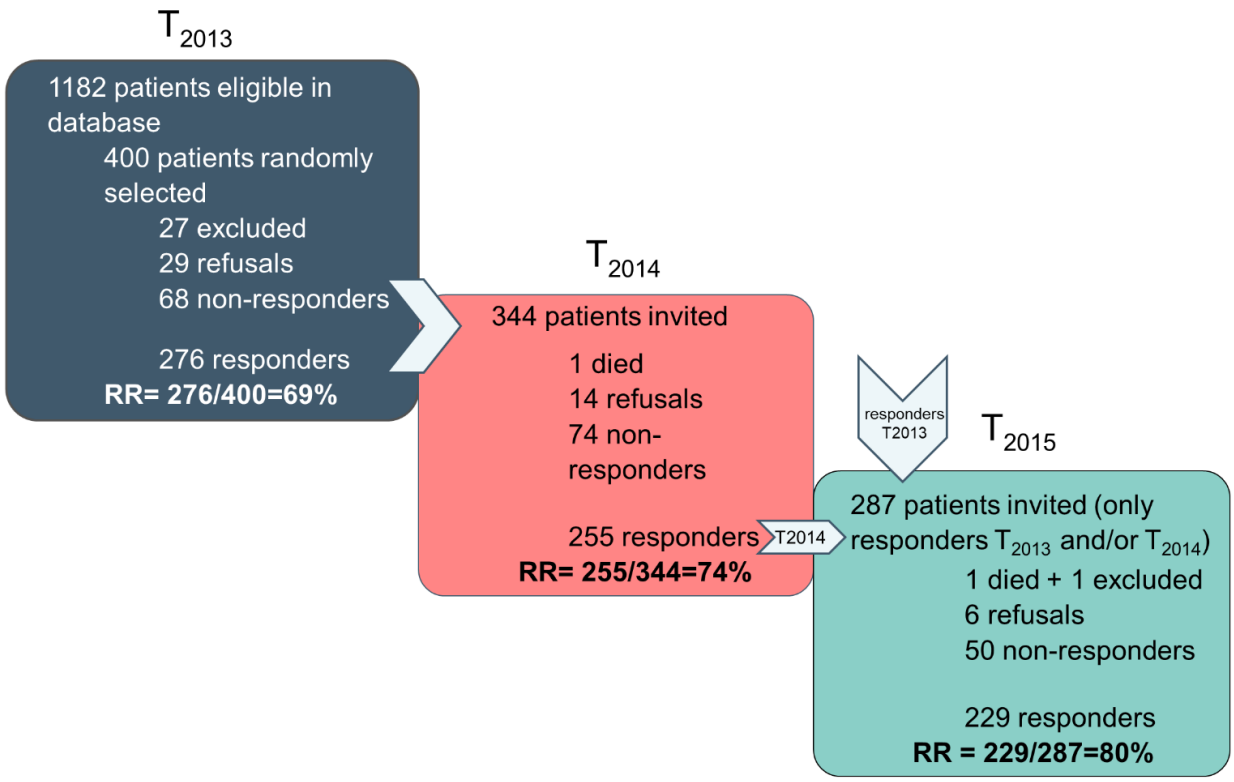

Figure S2. Diagram of the recruitment process and response rates of the Belgian branch of APPROACH-IS, as published by Van Bulck et al.[2]
Legend. RR= response rate

Annex S1. Detailed information on the Latent Class Growth Analysis

The path from the slope to the indicator at T_{2013} was fixed to zero for each model, so that the intercept represented the initial level. Subsequent linear slope pattern coefficients were fixed at 1 and 2 for T_{2014} and T_{2015}, respectively, given the equally spaced measurement intervals of 12 months. The best-fitting model has been indicated based on the Bayesian Information Criterion (BIC), Lo-Mendell-Rubin Loglikelihood Ratio Test (LMR-LRT), entropy (*E*) value) and on the proportion of estimated trajectory groups. Suggesting that adding classes improves the model fit, the BIC value for a solution with *k* classes should be lower than the BIC value for the solution with *k*-1 classes. LMR-LRT was used to obtain p-values to determine whether there is a significant improvement in fit through including an additional class [3]. Entropy is a measure of classification quality. It is a standardized summary measure that indicates the accuracy with which individuals are placed into the classes, based upon the posterior classification probabilities. Entropy ranges from 0.00 to 1.00, with values of ≥0.75 presenting accurate classification of individuals into classes [4]. Finally, the number of patients per class should represent at least 5% of the total sample [5]. A total of 13.0%-13.3% of data of the four illness identity dimensions were missing at T_{2013}-T_{2015}. To handle cases with missing values, we used the full information maximum likelihood (FIML) procedure [6].

Annex S2. Identifying developmental classes of illness identity

Fit indices, mean intercepts, mean slopes and class frequencies that are associated with the models as found in the Latent Class Growth Analysis of the four illness identity dimensions are shown in eTable 2 in Supplementary material.

For engulfment, the model with three classes was selected. The 3-class solution has a lower Bayesian Information Criterion (BIC) value (1374.6), compared to 1-class (1819.3) and 2-class (1481.5) and an entropy value of 0.891. In the 4-class solution, one of the classes represented only 2% of the sample.

Also for rejection, three developmental trajectories were identified. LCGAs favoured a 3-class solution over a 2-class solution as evidenced by a lower BIC value (1682.0 vs 1762.6) and a higher entropy value (0.803 vs 0.749). The 4-class solution had a lower entropy value of 0.742, which suggested worse classification accuracy.

For acceptance, a 2-class solution has been selected. The LCGA identified a group of only three patients (1%) in the 3-class and 4-class solution. The BIC of the 2-class solutions is 1489.1 and the entropy value is 0.823, which indicates good classification accuracy.

For enrichment, the model with three classes was most favourable. Both the 3-class and 4-class solution have an entropy value higher than 0.75. We decided to go for the 3-class solution, because the entropy value is over 0.8 and we wanted to choose the most parsimonious solution. The BIC of this model was 1836.0.

Table S1. Results of Latent Class Growth Analyses to identify the most appropriate developmental trajectories for the four illness identity dimensions

Solution		BIC	Entropy	LMR-LRT	Classes 1	2	3	4
ENGULFMENT								
1-class		1819.3						
	Proportion				276			
	Mean intercept				1.830 ***			
	Mean slope				-0.020			
2-class		1481.5	0.897	p=0.0002				
	Proportion				71 (26%)	205 (74%)		
	Mean intercept				2.980 ***	1.433 ***		
	Mean slope				-0.082	0.008		
3-class		**1374.6**	**0.891**	**p=0.0338**				
	Proportion				**74 (27%)**	**174 (63%)**	**28 (10%)**	
	Mean intercept				**2.409 *****	**1.309 *****	**3.614 *****	
	Mean slope				**-0.069**	**0.027**	**-0.115**	
4-class		1361.6	0.908	p=0.4755				
	Proportion				6 (2%)	70 (25%)	171 (62%)	29 (11%)
	Mean intercept				4.556 ***	2.313 ***	1.285 ***	3.299 ***
	Mean slope				-0.547	-0.056	0.035	-0.071
REJECTION								
1-class		1985.8						
	Proportion				276			
	Mean intercept				2.621 ***			
	Mean slope				-0.036			
2-class		1762.6	0.749	p=0.0002				
	Proportion				109 (40%)	167 (60%)		
	Mean intercept				3.440 ***	2.086 ***		
	Mean slope				-0.023	-0.051		
3-class		**1682.0**	**0.803**	**p=0.0014**				
	Proportion				**124 (45%)**	**130 (47%)**	**22 (8%)**	
	Mean intercept				**3.067 ******	**1.928 *****	**4.294 *****	
	Mean slope				**-0.047**	**-0.036**	**-0.010**	
4-class		1666.7	0.742	p=0.1705				
	Proportion				19 (7%)	117 (42%)	94 (34%)	46 (17%)
	Mean intercept				4.375 ***	2.289 ***	3.213 ***	1.584 ***
	Mean slope				0.007	-0.033	-0.029	-0.072

ACCEPTANCE							
1-class	1658.2						
Proportion				276			
Mean intercept				4.155 ***			
Mean slope				0.056 *			
2-class	**1489.1**	**0.823**	**p=0.004**				
Proportion				**64 (23%)**	**212 (77%)**		
Mean intercept				**3.137 *****	**4.484 *****		
Mean slope				**0.201 ** **	**0.005**		
3-class	1450.0	0.877	p=0.0233				
Proportion				202 (73%)	3 (1%)	71 (26%)	
Mean intercept				4.521 ***	1.405 ***	3.305 ***	
Mean slope				0.002	0.233	0.171 **	
4-class	1448.6	0.817	p=0.352				
Proportion				18 (7%)	69 (25%)	3 (1%)	186 (67%)
Mean intercept				3.027 ***	3.561 ***	1.353 ***	4.574 ***
Mean slope				-0.016	0.180 *	0.250	0.000
ENRICHMENT							
1-class	2233.3						
Proportion				276			
Mean intercept				3.043 ***			
Mean slope				0.021			
2-class	1960.9	0.757	p=0.0009				
Proportion				153 (55%)	123 (45%)		
Mean intercept				3.838 ***	2.057 ***		
Mean slope				-0.027	0.084		
3-class	**1836.0**	**0.839**	**p<0.00001**				
Proportion				**126 (46%)**	**102 (37%)**	**48 (17%)**	
Mean intercept				**2.768 *****	**4.147 *****	**1.448 *****	
Mean slope				**0.067**	**-0.034**	**0.053**	
4-class	1828.3	0.768	p=0.0347				
Proportion				47 (17%)	109 (39%)	42 (15%)	78 (28%)
Mean intercept				1.422 ***	2.617 ***	4.450 ***	3.792 ***
Mean slope				0.037	0.100 +	0.032	-0.082 +

Legend. The selected solution is in bold. BIC= Bayesian Information Criterion. LMR-LRT = Lo-Mendell-Rubin Loglikelihood Ratio Test
+ p<0.1; * p<0.05; ** p<0.01; *** p<0.001

Table S2. Comparison of age, sex and disease complexity of the identified illness identity classes

ENGULFMENT						
Variable (on T_{2013})	**Chronically High (n=28)**	**Intermediate Stable (n=74)**	**Consistently Low (n=174)**	**P-value**	**η^2**	**φ_c**
Median age (in years)	34	35	31.5	**0.013 *** [a]	0.0458	
Sex, %						
Male	61	58	51	0.454 [b]		0.076
Female	39	42	49			
Complexity, %						
Simple	21	33	36	**0.031 *** [b]		0.139
Moderate	61	47	56			
Complex	18	20	8			
REJECTION						
Variable (on T_{2013})	**Chronically High (n=22)**	**Intermediate Stable (n=124)**	**Consistently Low (n=130)**	**P-value**	**η^2**	**φ_c**
Median age	43.5	34	33	**0.019 *** [a]	0.0475	
Sex, %						
Male	50	55	54	0.915 [b]		0.025
Female	50	45	46			
Complexity, %						
Simple	55	33	31	0.235 [b]		0.100
Moderate	36	53	58			
Complex	9	14	11			
ACCEPTANCE						
Variable (on T_{2013})	**Chronically High (n=212)**	**Intermediate Increasing (n=64)**		**P-value**	**η^2**	**φ_c**
Median age	34.0	34.5		0.812 [a]	0.0006	
Sex, %						
Male	54	55		0.898 [b]		0.008
Female	46	45				
Complexity, %						
Simple	36	27		0.376 [b]		0.084
Moderate	53	59				
Complex	11	14				

ENRICHMENT						
Variable (on T_{2013})	**Consistently High (n=102)**	**Intermediate Stable (n=126)**	**Chronically Low (n=48)**	**P-value**	**η^2**	**φ_c**
Median age	42	34	33	0.057 [a]	0.0213	
Sex, %						
Male	49	57	56	0.445 [b]		0.077
Female	51	43	44			
Complexity, %						
Simple	26	33	52	**0.029 *** [b]		0.190
Moderate	58	57	40			
Complex	16	10	8			

Legend. [a] Kruskal-Wallis H [b] Chi-square test; '*' and bold: refer to the significant results, φ_c = Cramer's V, measure of effect size

Table S3. Analyses of variance and post hoc comparisons based upon Gabriel's pairwise test procedure for the classes of the four illness identity dimensions

ENGULFMENT					
Variable (on T_{2015})	**Chronically High (n=28)**	**Intermediate Stable (n=74)**	**Consistently Low (n=174)**	***F* value**	**η^2**
EQ-VAS	66.29 (20.26) [a]	74.07 (12.97) [b]	81.75 (11.07) [c]	22.75	0.143
LAS QOL	62.97 (20.83) [a]	74.8 (11.41) [b]	81.41 (10.77) [c]	30.05	0.180
HADS	14.30 (7.04) [a]	9.8 (5.02) [b]	7.24 (5.18) [c]	23.35	0.146
PCS	56.18 (24.22) [a]	67.97 (20.13) [b]	82.9 (14.50) [c]	40.15	0.227
MCS	55.63 (19.83) [a]	69.71 (14.73) [b]	75.76 (14.80) [c]	21.96	0.139
SWLS	19.67 (6.84) [a]	24.05 (5.28) [b]	27.06 (4.66) [c]	29.59	0.178
REJECTION					
Variable (on T_{2015})	**Chronically High (n=22)**	**Intermediate Stable (n=124)**	**Consistently Low (n=130)**	***F* value**	**η^2**
EQ-VAS	76.43 (13.75) [a]	76.44 (15.04) [a]	80.02 (12.24) [a]	2.362	0.017
LAS QOL	75.37 (14.08) [a, b]	75.89 (14.87) [a]	79.96 (11.75) [b]	3.294	0.024
HADS	9.46 (5.68) [a, b]	9.56 (6.41) [a]	7.63 (4.96) [b]	3.886	0.028
PCS	66.95 (23.77) [a]	74.84 (19.44) [a, b]	79.03 (18.54) [b]	4.193	0.030
MCS	67.75 (19.32) [a]	70.54 (16.87) [a]	74.31 (15.37) [a]	2.516	0.018
SWLS	24.84 (4.90) [a]	24.99 (5.71) [a]	26.10 (5.56) [a]	1.414	0.010
ACCEPTANCE					
Variable (on T_{2015})	**Chronically High (n=212)**	**Intermediate Increasing (n=64)**		***F* value**	**η^2**
EQ-VAS	79.08 (13.26) [a]	74.94 (14.94) [b]		4.521	0.016
LAS QOL	79.09 (12.58) [a]	73.38 (15.61) [b]		9.000	0.032
HADS	8.07 (5.48) [a]	10.52 (6.34) [b]		9.110	0.032
PCS	77.42 (19.54) [a]	72.11 (19.47) [a]		3.639	0.013
MCS	73.13 (16.56) [a]	68.66 (15.86) [a]		3.649	0.013
SWLS	26.21 (5.31) [a]	23.15 (5.89) [b]		15.559	0.054
ENRICHMENT					
Variable (on T_{2015})	**Consistently High (n=102)**	**Intermediate Stable (n=126)**	**Chronically Low (n=48)**	***F* value**	**η^2**
EQ-VAS	77.84 (14.93) [a]	77.03 (13.17) [a]	81.61 (12.27) [a]	1.976	0.14
LAS QOL	77.93 (13.64) [a]	76.67 (13.33) [a]	80.29 (13.76) [a]	1.258	0.009
HADS	7.90 (4.93) [a]	9.68 (5.96) [a]	7.5 (6.56) [a]	3.889	0.028
PCS	72.96 (22.17) [a]	75.94 (18.40) [a]	83.71 (14.67) [b]	5.068	0.036
MCS	73.09 (16.68) [a]	70.39 (16.58) [a]	74.46 (15.65) [a]	1.351	0.010
SWLS	25.78 (5.53) [a]	25.04 (5.85) [a]	26.09 (4.99) [a]	0.820	0.006

Legend. Means and standard deviations (in parentheses) are reported. A class mean is significantly different from another mean if they have different subscripts (i.e., a, b, and c). For example, for the Physical Component Summary (PCS) in the enrichment classes, '*Consistently High'* and '*Intermediate Stable*' share the same superscript (i.e., a) and thus, are not significantly different from each other. Whereas, '*Chronically Low'* and '*Consistently High'* do not share the same superscript, indicating that these classes differ significantly from each other in terms of quality of life. EQ-VAS (EuroQoL-Visual Analogue Scale) ranges from 0 (worst imaginable health status) to 100 (best imaginable health state). LAS QOL (Linear Analogue Scale – Quality of Life) goes from 0 (worst imaginable QOL) to 100 (best imaginable QOL). HADS = Hospital Anxiety and Depression Scale. Higher scores indicate more psychological distress. PCS = Physical Component Summary. Higher score = better perceived physical health. MCS = Mental Component Summary. Higher score = better perceived mental health status. SWLS = Satisfaction With Life Scale. Higher score = higher satisfaction with life. η^2=Eta-squared, measure of effect size

Table S4. Healthcare use (on T_{2015}) for the different classes of illness identity development (n=209)

ENGULFMENT			
Variable	**Chronically High (n=18)**	**Intermediate Stable (n=56)**	**Consistently Low (n=135)**
Hospitalizations	-	0.464 (0.131-1.646)	**0.121 (0.021-0.700) ***
Visits general practitioner	-	0.618 (0.281-1.360)	**0.357 (0.143-0.889) ***
Visits specialist	-	1.175 (0.709-1.948)	0.661 (0.362-1.210)
REJECTION			
Variable	**Chronically High (n=15)**	**Intermediate Stable (n=94)**	**Consistently Low (n=100)**
Hospitalizations	-	0.648 (0.130-3.220)	1.064 (0.187-6.055)
Visits general practitioner	-	2.178 (0.814-5.827)	**3.571 (1.283-9.937) ***
Visits specialist	-	1.206 (0.630-2.309)	1.803 (0.921-3.532)
ACCEPTANCE			
Variable	**Chronically High (n=161)**	**Intermediate Increasing (n=48)**	
Hospitalizations	-	**4.797 (1.394-16.503) ***	
Visits general practitioner	-	**3.991 (2.238-7.117) ***	
Visits specialist	-	**2.737 (1.874-3.999) ***	
ENRICHMENT			
Variable	**Consistently High (n=75)**	**Intermediate Stable (n=95)**	**Chronically Low (n=38)**
Hospitalizations	0.295 (0.059-1.481)	0.251 (0.059-1.065)	-
Visits general practitioner	**3.956 (1.692-9.251) ***	1.186 (0.533-2.642)	-
Visits specialist	1.165 (0.659-2.058)	1.056 (0.628-1.774)	-

Legend. Poisson regression and negative binomial regression with adjustment for age, disease complexity and patient-reported outcomes (HADS, PCS, MCS, LAS-QOL and EQ-VAS). Odds ratios and confidence intervals are reported. Dependent variables are hospitalizations, visits to the general practitioner and specialist over a period of 6 months and for a reason related to the health disease. '*' and bold: refer to the significant results. '–' refers to the reference category.

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PART 2

Healthcare system factors and patient-reported outcomes

Chapter 4

Patient-reported outcomes of adults with congenital heart disease from 8 European countries: scrutinizing the association with healthcare system performance

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Abstract

Background: Inter-country variation in patient-reported outcomes (PROs) of adults with congenital heart disease (CHD) has been observed. Country-specific characteristics may play a role. A previous study found an association between healthcare system performance and PROs. However, it remains unknown which specific components of the countries' healthcare system performance are of importance for PROs.

Aims: The aim of this study was to investigate the relationship between components of healthcare system performance and PROs in a large sample of adults with CHD.

Methods: A total of 1,591 adults with CHD (median age=34y; 51% men; 32% simple, 48% moderate, and 20% complex defects) from eight European countries were included in this cross-sectional study. The following PROs were measured: perceived physical and mental health, psychological distress, health behaviors, and quality of life. The Euro Health Consumer Index (EHCI) 2015 and the Euro Heart Index (EHI) 2016 were used as measures of healthcare system performance. General linear mixed models were conducted, adjusting for patient-specific variables and unmeasured country differences.

Results: Health risk behaviors were associated with the EHCI subdomains about patient rights and information, health outcomes, and financing and access to pharmaceuticals. Perceived physical health was associated with the EHCI subdomain about prevention of chronic diseases. Subscales of the EHI were not associated with PROs.

Conclusion: Several features of healthcare system performance are associated with perceived physical health and health risk behavior in adults with CHD. Before recommendations for policy makers and clinicians can be conducted, future research ought to investigate the impact of the healthcare system performance on outcomes further.

Key words

Healthcare System Performance; Heart Defect, Congenital; Health Services Accessibility; Patient Reported Outcome Measures

Introduction

As a result of an increased life expectancy, the population of adults with congenital heart disease (CHD) is growing exponentially.[1,2] As a consequence, increased healthcare use has been observed, placing additional burden on current healthcare systems worldwide.[3] Hence, healthcare systems across countries are challenged to meet the needs of this patient population, and more specifically, to reach satisfactory outcomes in adults with CHD.[4] Owing to increasing attention for person-centered and comprehensive care, interest in assessing patient-reported outcomes (PROs) is mounting.[5,6] PROs are *"measurements based on a report that comes directly from the patient about the status of a patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else"*.[7, p. 32] PROs have been shown to be of clinical significance, as they are independent predictors of mortality, cardiovascular events, hospitalization, and costs of care in cardiovascular patient populations.[8,9]

Prior research has demonstrated a substantial inter-country variation in PROs of adults with CHD around the world.[10] For example, samples of patients from Australia had a mean quality of life of 82.1 on the Linear Analogue Scale (0-100) and a sample from Japan had a score of 71.6.[11] It has already been demonstrated that patient characteristics, such as sex, age, educational level, and NYHA class partly explain variation in PROs.[10,11] At a country-level, standard of living and healthcare system characteristics are known predictors of PROs in adults with CHD.[10] One of these studies indicated that overall healthcare system performance, as measured by World Health Organization (WHO), was associated with perceived health of adults with CHD. In general, policymakers and healthcare administrators are increasingly interested in assessing the performance of their healthcare systems.[12] Measuring performance is important to identify high- and low-quality service delivery, to design healthcare system reforms, to protect patients and payers, and to decide

on appropriate investments, all with the overarching goal of improving quality of care.[12] Access to care, a component of the overall healthcare system performance, is an important variable that has been associated with healthcare financing and outcomes.[13]

The Andersen behavioral model of health services use is a theoretical framework that was developed in the late 1960s, aiming to facilitate the understanding of which factors influence patients' use of healthcare services.[14] With the growth of supporting empirical evidence, this model has expanded.[15] In the latest version of the model (see Figure 1), healthcare system organization, including performance of the healthcare system, is considered to be a contextual characteristic that determines healthcare use and patient outcomes.[15] Indeed, the model assumes that contextual characteristics at the macro level are both directly and indirectly associated with patient outcomes (i.e., perceived health and quality of life) and that these relationships can be bidirectional. Little research has been undertaken, to date, to confirm this presumed relationship.

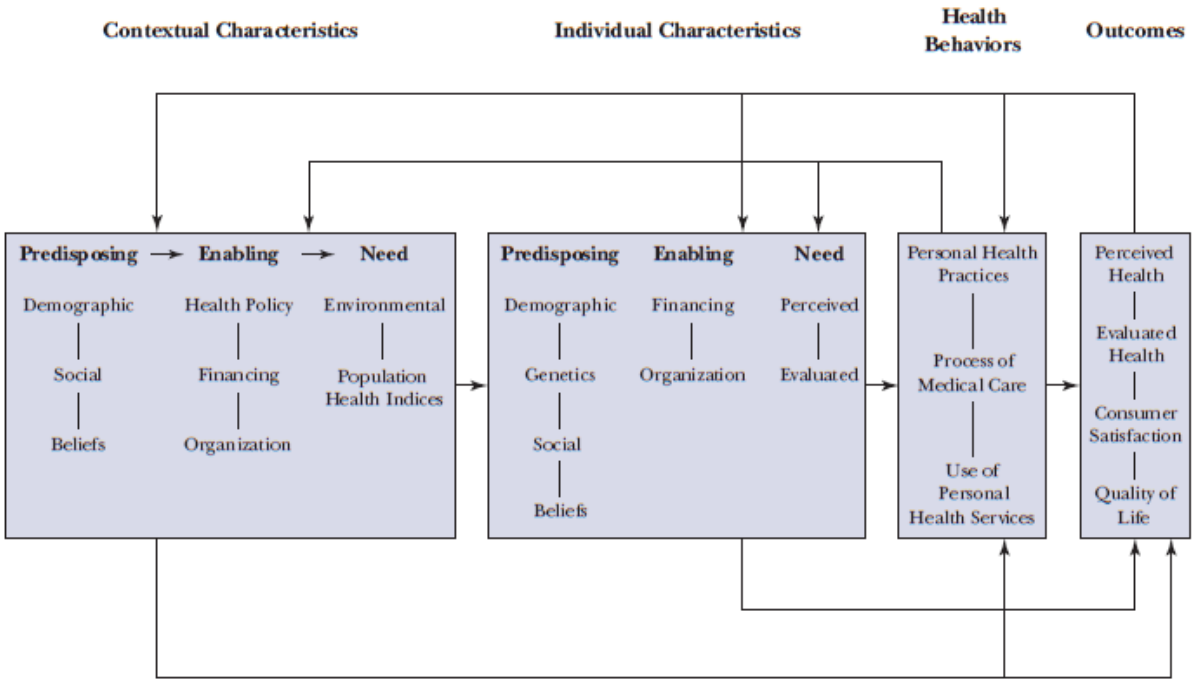

Figure 1. Andersen behavioral model of health services use, sixth revision.[15] Permission for reproduction was obtained from John Wiley and Sons.

In recent decades, international agencies (e.g., WHO, Organization for Economic Co-operation and Development (OECD), and Health Consumer Powerhouse) have made efforts to capture and compare the overall performance of the healthcare systems of different countries. However, it remains unknown which components of countries' healthcare system performance are associated with PROs in adults with CHD. Therefore, in this study we aimed to investigate the relationship between components of healthcare system performance and PROs in adults with CHD.

Methods

The present study is part of a larger project entitled 'Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study' (i.e., APPROACH-IS). This research project included 4,028 adults with CHD from 15 countries comprising five continents around the globe.[10,11,16] For the current analyses, we included all European countries participating in APPROACH-IS: Belgium, France, Italy, Malta, Norway, Sweden, Switzerland, and the Netherlands, because uniform indices of performance of European healthcare systems (i.e., Euro Health Consumer Index [17] and Euro Heart Index [18]) were available for these countries.

Patients were eligible if they met the following criteria: (i) diagnosis of CHD, defined as *"a structural abnormality of the heart and/or intra-thoracic great vessels that is present at birth and of actual or potential functional significance*" [19]; (ii) aged 18 years or older; (iii) CHD diagnosis established before the age of 10 years (i.e., to warrant sufficient experience of living with CHD); (iv) continued follow-up at a CHD center or included in a national/regional CHD registry; and (v) possessing physical, cognitive, and language capabilities required to complete self-reported questionnaires. Exclusion criteria were: (i) prior heart transplantation and (ii) idiopathic pulmonary arterial hypertension.[16] Eligible patients received a questionnaire package by mail or during an outpatient clinic visit. Data collection ran from April 2013 through March 2015. The rationale, design, and methods of APPROACH-IS have been detailed in a previous paper.[16]

The study was approved by the institutional review board of the University Hospitals Leuven/KU Leuven Belgium (the coordinating center) as well as the

local institutional review boards of participating centers when required. All participants provided written informed consent to participate. The investigation confirms with the principles outlined in the Declaration of Helsinki.[20]

Measures

Data on four domains of patient-reported outcomes (PROs) were assessed using self-report questionnaires: (i) perceived physical and mental health status using the 12-item Short Form Health Survey [21]; (ii) psychological distress using the Hospital Anxiety and Depression Scale [22]; (iii) health behaviors using the Health Behavior Scale–Congenital Heart Disease [23]; and (iv) quality of life using a Linear Analog Scale. Further details on the measures and their psychometric properties can be found online in supplementary material (eTable 1).

Healthcare system performance

Healthcare system performance of the participating countries was operationalized using the Euro Health Consumer Index 2015 [17] and the Euro Heart Index 2016 [18], both developed by the Health Consumer Powerhouse.

The Euro Health Consumer Index (EHCI), which is published annually, measures and ranks the performance of healthcare provision of 35 European countries.[17] This index consists of a set of 48 indicators, which are divided in six subdomains: (i) patients' rights and information; (ii) accessibility; (iii) outcomes; (iv) range and reach of services provided; (v) prevention; and (vi) pharmaceuticals. More information about these subdomains can be found in eTable 2. The performance of the respective national healthcare systems were graded on a three-grade scale for each of the 48 indicators (i.e., inadequate, moderate, good) and in line with the grading, scores were assigned (i.e., inadequate/not available = 1, moderate = 2, good = 3). In order to calculate the score of each subdomain, the scores assigned to each indicator were summed up. Afterwards, the subdomain scores were multiplied by fixed weight coefficients and added up to make the final country score. Since data collection ran from 2013 till 2015, we chose to use the Euro Health Consumer Index of 2015.

The Euro Heart Index (EHI), which was published in 2008 and 2016, focuses specifically on the performance of care provided to patients with cardiovascular conditions in 30 European countries.[18] This index was chosen because adults with CHD are primarily treated in cardiovascular care settings. The EHI consists

of a set of 31 healthcare system performance indicators, which are divided in four subdomains: (i) prevention; (ii) procedures; (iii) access to care; and (iv) outcomes (eTable 2). Scores on subdomains and total score were calculated in a similar way as the EHCI. For the present study, we employed the Euro Heart Index of 2016.

Statistical analyses

Demographic and medical background variables were calculated as median and interquartile range in case of non-normally distributed continuous variables, and as absolute numbers and percentages in case of categorical variables.

Multivariable and sensitivity analyses using general linear mixed models were used to estimate the association between the domains and total score of healthcare system performance (i.e., EHCI and EHI) and five PROs (i.e., perceived physical functioning, perceived mental health, psychological distress, health risk behavior, and quality of life). A two-level structured analysis was used, considering that patients were nested within countries. In the multivariable analyses, we controlled for patient characteristics (i.e., age, sex, educational level, employment status, marital status, patient-reported NYHA assessment, and disease complexity) and unmeasured country differences (random effect). Since all domains of the EHCI and EHI were analyzed separately, a total of 60 multivariable analyses were performed. Hence, we adjusted for multiple testing by calculating false discovery rates and reporting Benjamini-Hochberg adjusted p-values. The significance level of the false discovery rate was 0.05. In order to evaluate the robustness of the results, we performed sensitivity analyses in which we left out countries with an outlying value of more than two standard deviations from the mean on one of the subdomains of the EHCI or EHI.

Only patients for whom full data were available for all variables of interest were included in the general linear mixed models, since only a small proportion of patients had missing values for PROs (0.0-2.1%) and patient-related predictors (0.0-2.5%). Euro Health Consumer Index and Euro Heart Index possessed complete data. Data analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp, Armonk, NY, USA).

Results

Sample characteristics

A total of 1,591 adults with CHD with full data from eight European countries were included in the study. The majority of patients were men (50.7%), had a moderate disease complexity (48.0%), and self-reported to be in NYHA Class I (58.8%) (Table 1).

Table 1. Demographic and medical background variables in 1,591 adults with congenital heart disease in Europe

Variables	**n (%)**
Men	806 (50.7%)
Median age in years	34 (Q1=26; Q3=45)
Educational level	
Less than high school	98 (6.1)
High school	778 (48.9)
College degree	270 (17.0)
University degree	445 (28.0)
Employment status	
Part-time or full-time work	1122 (70.5)
Job seeking, unemployed, or disabled	177 (11.1)
Homemaker or retired	112 (7.0)
Full-time student	87 (5.5)
Other	93 (5.9)
Marital status	
Married or living with partner	955 (60.0)
Never married	556 (35.0)
Divorced or widowed	80 (5.0)
Children: yes	735 (46.2)
Patient-reported New York Heart Association assessment	935 (58.8)
Class I	516 (32.4)
Class II	104 (6.5)
Class III	36 (2.3)

Class IV	
Complexity of heart defect	
Simple	511 (32.1)
Moderate	763 (48.0)
Complex	317 (19.9)
Country	
Belgium	261 (16.4)
France	86 (5.4)
Italy	51 (3.2)
Malta	108 (6.8)
Norway	164 (10.3)
Sweden	435 (27.3)
Switzerland	251 (15.8)
the Netherlands	235 (14.8)

Healthcare system performance

Scores on the different domains of the EHCI and EHI for the respective participating countries are presented on the heat map of Figure 2. Looking at the performance of the healthcare system (i.e., EHCI), the healthcare system of the Netherlands was found to have the best total score, followed by Switzerland and Norway. Malta had the lowest total score. When looking at subdomains, Norway and the Netherlands gathered the highest score on ‘patient rights and information’. The lowest waiting times were observed in Belgium and Switzerland. Best health outcomes were measured in the Netherlands, Norway, and Switzerland, whereas ‘range and reach of services’ was found to be best in the Netherlands and Sweden. Norway was leading when looking at indicators about prevention of chronic diseases. Finally, the Netherlands achieved best scores on consumption, financing, and deployment of pharmaceuticals.

Regarding the performance of cardiovascular care and treatment (i.e., EHI) for the respective included countries, France had the highest total score, followed by Norway and Sweden. In line with the Euro Health Consumer Index, the Maltese healthcare system performed lowest on cardiovascular care. When examining subdomains, Italy performed best on ‘prevention for cardiovascular disease’ (CVD). France and the Netherlands were ranked highest with respect

to the subdomain ‘quality and availability of procedures concerning CVD’. Access to cardiovascular care was best in France, the Netherlands, Norway, and Sweden. Finally, Sweden had the best outcomes for CVD patients.

Patient-reported outcomes

Patient-reported outcomes of this patient population were detailed on the heat map (Figure 2). Perceived physical and mental health scores were highest in patients from Malta. Patients from the Netherlands showed lowest symptoms of psychological distress. Participants from Sweden had lowest health risk scores, and patients from Switzerland achieved best results on quality of life.

Association between healthcare system performance and PROs

Adjusting for patient characteristics, unmeasured country differences, and multiple testing, the multivariable general linear mixed models showed that less risky health behaviors were associated with better scores on subdomains ‘patient rights and information’, ‘outcomes’, or ‘pharmaceuticals’, measured by the EHCI (Table 2). Furthermore, perceived physical health was associated with healthcare systems performing high on prevention of chronic diseases, as assessed by the EHCI (Table 2). Components of the Euro Heart Index were not associated with PROs in adults with CHD.

Because Malta had outlying values (> 2 SD) on the EHCI subdomain ‘outcomes’ and the EHI subdomain ‘prevention’, we repeated these analyses while excluding the data from Malta. After correction for false discovery rate, the associations between EHCI subdomain ‘outcomes’ and PROs did not change, since again only the association between the subdomain ‘outcomes’ and the total health risk score was significant. Again, no significant associations were found between the EHI subdomain ‘prevention’ and PROs.



Figure 2. Distribution (heat map) of the patient-reported outcomes and scores on Euro Health Consumer Index and Euro Heart Index of the included European countries. Note. Patient-reported outcomes are described as mean (standard deviation).

Discussion

We examined associations between components of the healthcare system performance and PROs in adults with CHD, in order to further scrutinize geographical differences in PROs that were previously reported.[10] Health risk behaviors of adults with CHD were found to be associated with the EHCI subdomains ‘outcomes’, ‘patient rights and information’, and ‘pharmaceuticals’. Physical health status was associated with the EHCI subdomain ‘prevention’.

The relationship between health risk behaviors and ‘outcomes’ is perhaps unsurprising because the EHCI subdomain ‘outcomes’ comprises indicators particularly relevant for patients with CHD, such as a decrease of CVD deaths, decrease of stroke deaths, and infant deaths.[17] It is well known that a heart-healthy lifestyle is associated with favorable health outcomes, both in the general and in clinical populations.[24]

The subdomain ‘patient rights and information’ pertains to the ability of a healthcare system to provide the patients with a status strong enough to be able to interpret information in an appropriate manner. Hence, a high score on ‘patient rights and information’ reflects the importance that is given to inform and instruct patients in particular countries. In turn, this may have resulted in patients with higher patient activation, who are willing and able to take charge of their own health by performing good health behaviors.[25] Indeed, patient activation and empowerment have been shown to be associated with healthy behavior.[26]

The EHCI subdomain ‘pharmaceuticals’ describes consumption, financing, and access to drugs. It can be presumed that countries with good access and refunds for pharmaceuticals have good access and refunds for other healthcare services as well. Indeed, this might partly explain the found association between the EHCI subdomain ‘pharmaceuticals’ and health risk behaviors.

Table 2. Multivariable General Linear Mixed Models with Euro Health Consumer Index and Euro Heart Index healthcare system performance domains as predictors of PROs, adjusted for patient characteristics and unmeasured country differences (n=1,591)

	Physical health status	Mental health status	Psychological distress	Total health risk score	Quality of life
Euro Health Consumer Index					
Patient rights and information	0.01 (0.05)	-0.01 (0.04)	-0.04 (0.01)	-0.24 (0.06)	0.005 (0.04)
Accessibility	-0.04 (0.01)	-0.01 (0.01)	0.005 (0.007)	0.01 (0.04)	0.0006 (0.01)
Outcomes	0.01 (0.03)	-0.006 (0.02)	-0.02 (0.008)	-0.14 (0.02)	0.01 (0.02)
Range and reach of services provided	0.01 (0.05)	-0.002 (0.04)	-0.01 (0.02)	-0.15 (0.09)	-0.06 (0.04)
Prevention	0.31 (0.04)	0.13 (0.06)	-0.09 (0.03)	-0.38 (0.21)	0.04 (0.08)
Pharmaceuticals	-0.02 (0.07)	-0.05 (0.06)	-0.03 (0.03)	-0.37 (0.09)	-0.02 (0.06)
Total Score	-0.007 (0.01)	-0.006 (0.008)	-0.004 (0.004)	-0.05 (0.01)	-0.0001 (0.008)
Euro Heart Index					
Prevention	-0.03 (0.04)	-0.05 (0.02)	-0.009 (0.01)	-0.10 (0.07)	-0.004 (0.03)
Procedures	-0.02 (0.03)	-0.05 (0.02)	-0.003 (0.01)	-0.08 (0.06)	-0.006 (0.03)
Access to care	0.05 (0.05)	-0.02 (0.04)	-0.02 (0.02)	-0.16 (0.09)	0.03 (0.04)
Outcomes	-0.001 (0.03)	-0.03 (0.02)	0.007 (0.01)	-0.07 (0.05)	-0.02 (0.02)
Total Score	-0.003 (0.01)	-0.02 (0.008)	-0.0007 (0.004)	-0.04 (0.02)	-0.003 (0.009)

Note. Values in table are Estimates (Standard Error); Color-coding refers to significance of estimate after correction for multiple testing (Benjamini-Hochberg adjusted p-value); Physical and mental health status: higher scores reflect better perceived health; Psychological distress: higher scores reflect more symptoms of depression and anxiety; Total health risk score: higher scores reflect unhealthier behavior; Quality of life: higher scores reflect higher quality of life.

N.S.	< 0.05	<0.01	<0.001

The association between perceived physical health and the EHCI subdomain 'prevention' is anticipated given that it is hoped that healthcare systems that focus on prevention would help individuals achieve better health status. Although our study showed an association between these distal concepts, future studies could perhaps add clarity about underlying mechanisms and possible confounders.

Subdomains of the EHCI that were not related to any of the PROs were 'accessibility of care' and the 'range and reach of services provided'. This suggests that the general accessibility of healthcare and a broad offer of public services in the respective countries may not reflect PROs in CHD. Moreover, healthcare system performance only seems to be of importance for physical wellbeing and health risk behaviors. No associations have been found with perceived mental health, psychological distress, and quality of life.

Regarding the EHI, none of the subdomains were associated with PROs of adults with CHD. Even when excluding the outlying value of Malta on the EHI subdomain of prevention in sensitivity analyses, no significant association was found. Since associations with EHI domains were expected, these results are surprising. To the best of our knowledge, this is the first time that the EHI has been used for research. In order to be able to interpret the absence of associations, the relevance of the index for congenital as well as for acquired heart diseases should be investigated.

Methodological issues

First, we performed an explorative ecological cross-sectional study. Hence, no conclusions in terms of the direction of effects or causality can be drawn. Indeed, the field of PRO research would benefit from longitudinal assessment.[27] Moreover, we could not assess the underlying mechanisms, which is why we are unable to provide explanations of observed associations.

Second, we measured the components of healthcare system performance using the EHCI and the EHI.[17,18] These measures deliver very detailed information on the subdomains of healthcare system performance of the participating countries. Although some individuals have criticized these performance measures on their transparency, methodology, and validity [28,29], we are unware of any better measures of components of healthcare system performance.

Third, data of healthcare system performance were gathered on country-level and PROs were gathered on patient-level. However, multilevel analyses were performed to control for unmeasured country differences and to consider that patients are nested in countries.

Fourth, it is difficult to tell to what extent our findings can be generalized. Although the differences in demographic, clinical, and health status characteristics between participants and non-participants appeared to be small,[30] the present study included eight European countries, all of which were high-income countries. It would be interesting to include middle-income European countries (i.e., Albania, Croatia, Macedonia, and Kosovo) in future studies and to investigate the effect of the general healthcare system performance on PROs beyond the European borders. Moreover, the unequal division of participants across the countries might have influenced the results as well, since some countries have been overrepresented with regard to other countries. Furthermore, patients who received the questionnaire where almost all under follow up in a CHD/ACHD centre and it could be that patients who are not under follow up have different characteristics. Finally, it remains unknown whether our results in adults with CHD can be generalized to other patient populations. CHD, as a sample case, represents a broad spectrum of mild, moderate, and complex chronic diagnoses. To increase the generalizability and transferability of findings, it would be interesting to add a healthy control group or general population normative data.

Generally, the findings of this study provide information on which domains of the healthcare system performance are of importance for particular PROs of adults with CHD. However, further research is needed in order to be able to conduct concrete advice for policy makers or for clinical practice. We hope that our present findings may be a trigger for future research to fill these knowledge gaps.

Conclusion

The current study showed that several features of healthcare system performance are associated with perceived physical health and health risk behaviors in adults with CHD. More specifically, the EHCI subdomains ‘outcomes’, ‘prevention’, ‘patient rights and information’, and ‘pharmaceuticals’ were associated with these two PROs, above and beyond patient characteristics. Before recommendations for policy makers can be conducted, future research should further investigate the impact of the healthcare system performance on outcomes of adults with CHD using different indices and should examine the underlying mechanisms of the found associations.

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Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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The study protocol was registered at ClinicalTrials.gov: NCT02150603. https://clinicaltrials.gov/ct2/show/NCT02150603

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Supplementary material – Chapter 4

eTable 1 - Overview of variables and measurements

eTable 2 - Additional information about the Euro Health Consumer Index 2015 and Euro Heart Index 2016

eTable 1. Overview of variables and measurements

Variables	Definition used in this study	Measurement	Interpretation of measurement
Patient-reported health status	The impact of a disease according to the patient, including symptoms, functional status, and health-related quality of life [1]	12-item Short-form Health Survey version 2 (SF-12) [2]	• Physical Component Summary (PCS) and Mental Component Summary (MCS) ranging from 0 to 100; • Higher scores = better perceived health
Psychological distress	The level of internalizing, emotional distress, depressive and anxious symptoms	Hospital Anxiety and Depression Scale (HADS) [3]	• HADS scores ranging from 0 to 21; • Higher scores = more symptoms • Because HADS was found to be accurate when screening psychological distress, a general psychological distress score was used instead of using two subscores for depression and anxiety.[4]
Health behaviors	Activities that a person undertakes to prevent disease or to improve health and well-being [5]	Health-Behavior Scale–Congenital Heart Disease (HBS-CHD) [6]	• Total health risk score ranging from 0 to 100; • Higher scores = unhealthier behavior
Quality of life	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 [7]	Linear Analog Scale (LAS) [8]	• LAS score ranging from 0 (worst imaginable quality of life) to 100 (best imaginable quality of life); • Higher scores = better quality of life

eTable 2. Additional information about the Euro Health Consumer Index 2015 [9] and Euro Heart Index 2016 [10]

Subdomains	Number of indicators	Relative weight	Description of subdomain	Indicator example
Euro Health Consumer Index 2015				
Patients' rights and information	12	150	The indicators concern the ability of a healthcare system to provide the patient with a status strong enough to able to interpret information in an appropriate manner.	➢ Healthcare law based on patients' rights
Accessibility	6	225	The indicators concern accessibility and waiting time for treatment.	➢ Family doctor same day access
Outcomes	8	250	This subdomain reports about the results of all kinds of treatment.	➢ Decrease of CVD death rates
Range and reach of services provided	8	150	The purpose of this subdomain is to give an overview of what is included in public healthcare offering. Before 2009, EHCI called this subdomain 'generosity'.	➢ Equity of healthcare systems
Prevention	7	125	Indicators about modifiable risk factors for chronic diseases (e.g., smoking, obesity) and vaccination can be found in this subdomain.	➢ Infant 8-disease vaccination
Pharmaceuticals	7	100	Indicators concerning the consumption, financing, or deployment of (new) drugs are described in this subdomain.	➢ Antibiotics consumption
Euro Heart Index 2016				
Prevention	10	300	Indicators about modifiable risk factors for CVD can be found in this subdomain.	➢ Prevalence of obesity in adults
Procedures	11	250	This subdomain concerns the provision of well-organized and coordinated services that rely on the knowledge and skills of healthcare professionals.	➢ Rehabilitation program
Access to care/treatment	6	200	The indicators concern accessibility and waiting time for CVD-related treatments.	➢ Waiting time to echocardiography and diagnosis
Outcomes	4	250	This subdomain reports about the outcomes for patients with CVD.	➢ 30-day case fatality rate after admission AMI

Legend. CVD=cardiovascular disease; AMI=acute myocardial infarction

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Chapter 5

Healthcare system inputs and patient-reported outcomes: a study in adults with congenital heart defect from 15 countries

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Abstract

Background: The relationship between healthcare system inputs (e.g., human resources and infrastructure) and mortality has been extensively studied. However, the association between healthcare system inputs and patient-reported outcomes remains unclear. Hence, we explored the predictive value of human resources and infrastructures of the countries' healthcare system on patient-reported outcomes in adults with congenital heart disease.

Methods: This cross-sectional study included 3,588 patients with congenital heart disease (median age=31y; IQR=16.0; 52% women; 26% simple, 49% moderate, and 25% complex defects) from 15 countries. The following patient-reported outcomes were measured: perceived physical and mental health, psychological distress, health behaviors, and quality of life. The assessed inputs of the healthcare system were: (i) human resources (i.e., density of physicians and nurses, both per 1,000 people) and (ii) infrastructure (i.e., density of hospital beds per 10,000 people). Univariable, multivariable, and sensitivity analyses using general linear mixed models were conducted, adjusting for patient-specific variables and unmeasured country differences.

Results: Sensitivity analyses showed that higher density of physicians was significantly associated with better self-reported physical and mental health, less psychological distress, and better quality of life. A greater number of nurses was significantly associated with better self-reported physical health, less psychological distress, and less risky health behavior. No associations between a higher density of hospital beds and patient-reported outcomes were observed.

Conclusions: This explorative study suggests that density of human resources for health, measured on country level, are associated with patient-reported outcomes in adults with congenital heart disease. More research needs to be conducted before firm conclusions about the relationships observed can be drawn.

Trial registration: ClinicalTrials.gov: NCT02150603. Registered 30 May 2014, https://clinicaltrials.gov/ct2/show/NCT02150603

Key words

Congenital Heart Defects; Health Resources; Healthcare workforce; Patient Reported Outcome Measures; Quality of life; Staffing

Background

Healthcare expenditures have never been higher and medical costs are expected to continue to increase in all parts of the world.[1] In 2013, 7.8 trillion US $ were spent on healthcare worldwide, and this number is expected to increase up to 18.3 trillion US $ by 2040.[1] This strong increase can be attributed to an ageing population and medical innovation.[1] Hence, more than ever, it is important to critically evaluate financial investments in health care and appraise the importance of 'inputs', such as human resources and the infrastructure of the healthcare system. Human resources of the healthcare system are *"all people engaged in actions whose primary intent is to enhance health"*.[2] Healthcare system infrastructure refers to *"formal and enduring structures that support health",* such as hospitals and the number of available hospital beds.[3]

In the late 1960s, a behavioral model of healthcare services use was developed by Andersen and colleagues to facilitate an understanding of which factors influenced patients' use of healthcare services.[4] This model has expanded with the growth of supporting empirical evidence.[5] In the latest versions of the model (see eFigure 1), healthcare system inputs are considered part of the organization of the healthcare system and are included as contextual characteristics driving health consumption by patients.[5] The model assumes that contextual characteristics are both directly and indirectly associated with patient outcomes and that these relationships can be bidirectional.

Prior studies have investigated the role of human resources and infrastructure for health in predicting patient outcomes. [6-9] Physician and nurse staffing ratios and the availability of hospital beds per population have been associated with various outcomes including mortality, stage of diagnosis, prognosis, and quality of care.[7-10] However, minimal attention has been devoted to the associations between the human resources and the infrastructure, and outcomes which are particularly relevant from the patients' perspective, namely patient-reported outcomes (PROs).[11-15] Yet, in light of the current priority on patient-centered,

holistic, and comprehensive care, the patient perspective should surely be incorporated in healthcare system evaluations.[16] Therefore, the relationship between country-level healthcare system inputs and PROs warrants investigation in public health and health services research. PROs are *"measurements based on a report that comes directly from the patient about the status of a patient's health condition, without amendment or interpretation of the patient's response by a clinician or anyone else"*.[17] Examples of PROs are self-reported health status or quality of life, these outcomes are included as such in the Andersen behavioral model (see eFigure 1).[5] One study has investigated the association between the density of healthcare workforce (on country-level) and psychosomatic and mental health symptoms (on individual-level), but found no robust relationship.[15] As the Andersen behavioral model presumes a relationship between country-level healthcare system inputs and PROs, such investigations are warranted.

For the present study, we use data of adults with congenital heart disease (CHD). With a birth prevalence up to 9.3 per 1,000 newborns, CHD is the commonest birth defect in neonates.[18] This population is of great interest to investigate the association between healthcare system inputs and PROs, for several reasons. First, in Western countries, due to significant medical advances in recent decades, over 90% of children with CHD now survive into adulthood, thus yielding an exponential growth of the population of adults with CHD.[19] Hence, this population is putting an increased burden on the healthcare system, with exponentially increasing healthcare utilization and costs.[20] From this perspective, CHD can be seen as an exemplar for life-cycle diseases. Second, CHD comprises a range of mild, moderate and complex heart defects. This variability in complexity reflects the broader spectrum of chronic diseases which also differ in complexity and severity. Third, as in other chronic conditions, a comprehensive understanding of adult CHD extends beyond medical outcomes and includes PROs. Inter-country variations in PROs among adults with CHD have previously been observed.[13] It is possible that certain healthcare system characteristics at the national level may play a role in this matter. Indeed, among adults with CHD, total healthcare expenditures per capita and healthcare system performance have been associated with PROs.[13,21] The explained variance of these factors, however, ranged between 0.001% and 0.25%, suggesting that other aspects of the organization of the healthcare system require scrutiny.

When exploring the relationship between healthcare system inputs and PROs in this heterogeneous chronic population, we can obtain valuable information that can be transferred, at least to a certain extent, to other chronic patient populations.

We aimed to test the presumed relationship between the inputs of the overall healthcare system and PROs of the Andersen behavioral model and to obtain a better understanding of the mechanism of inter-country differences in PROs. To achieve this aim, we investigated whether human resources and infrastructure for health on country level, operationalized as physician density, nurse density, and hospital bed density, were predictors of PROs in a large international sample of adults with CHD.

Methods

Study population and procedure

The present study was part of an overarching project entitled 'Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study' (APPROACH-IS). A total of 4,028 adults with CHD from 15 countries, comprising five continents, were included in this project.[13,22,23]

Inclusion criteria were: (i) diagnosis of CHD, defined as *"a structural abnormality of the heart and/or intra-thoracic great vessels that is present at birth and of actual or potential functional significance*";[24] (ii) aged 18 years or older; (iii) diagnosis established before the age of ten years; (iv) continued follow-up at a CHD center or included in a national/regional registry; and (v) possessing physical, cognitive, and language capabilities required to complete self-reported questionnaires. Exclusion criteria were: prior heart transplantation and primary pulmonary hypertension.[22] Data collection was carried out from April 2013 through March 2015. In a previous paper, rationale, design, and methods of APPROACH-IS have been detailed.[22] The study protocol was registered at ClinicalTrials.gov: NCT02150603.

Measures (individual-level data)

For the present study, data on five PROs were analyzed: perceived physical health and mental health status (12-item Short Form Health Survey), psychological distress (Hospital Anxiety and Depression Scale), health behavior

(Health Behavior Scale–Congenital Heart Disease), and quality of life (Linear Analog Scale). Further details on the used set of questionnaires have been reported previously [22] and can be found online in supplementary material (see eTable 1).

Healthcare system inputs (country-level data)

In order to capture inputs of the healthcare system, human resources and infrastructure measurements were assessed. Country-level human resources for health were operationalized in terms of physician density as well as density of nurses. Physician density per 1,000 people was defined as the number of physicians, including generalists and specialist medical practitioners, per 1,000 citizens in the country's population.[25,26] Nurse density per 1,000 people was operationalized as the number of professional nurses, professional midwives, auxiliary nurses, auxiliary midwives, enrolled nurses, enrolled midwives and other associated personnel, such as dental nurses and primary care nurses, per 1,000 people within a country's population.[26] Country-level health infrastructure was expressed as the hospital bed density per 10,000 population, which included the total number of hospital beds excluding labour and delivery beds per 10,000 population.[26] These data were obtained from the World Bank and the World Health Organization (WHO).[25,26] Since data from Taiwan are lacking in the World Health Organization repository, the Taiwan Statistical Data Book was consulted to obtain the required data for Taiwan.[27] For most countries, data from 2015 have been selected. If this score was unavailable, the nearest-to-2015 score has been selected (see eTable 2).

Statistical analyses

Continuous data are presented as medians and interquartile ranges. Categorical variables are presented as absolute numbers and percentages.

The association of healthcare system inputs and PROs was estimated through general linear mixed models (GLMM). GLMM are an extension to the generalized linear model (GLM) with random effects in addition to the usual fixed effects. In the analyses, a 2-level hierarchical structure was taken into account, in which patients were nested within countries. Thereby, random effects were included at the country-level and the model corrects for differences between countries, so called 'unmeasured country differences'. We modeled five PROs as dependent variable with the healthcare system inputs as predictors. Only

patients for whom full data were available for all variables of interest (n=3,588) were included, as only a relatively small proportion of patients had missing data for PROs (0.05-1.89%). Therefore, it was unnecessary to perform multiple imputation. The GLMM analyses were performed in three steps:

First, separate univariable general linear mixed models were applied to estimate the associations between density of physicians, density of nurses and density of hospital beds and the five PROS, being physical health status, mental health status, psychological distress, health behavior, and quality of life.

Second, multivariable general linear mixed models were performed for the three health care system inputs and the five PROs, with adjustments for patient-specific variables that previously have been found to predict PROs (i.e., sex, age, employment status, marital status, highest educational level, complexity of the health disease and the patient's functional ability (New York Heart Association classification) [13]) and unmeasured country differences.

Third, in order to estimate the robustness of the results, we performed sensitivity analyses in which we excluded countries with an outlying density of more than two standard deviations from the mean. The multivariable general linear mixed models were repeated while excluding these centers.

Data analysis was performed using IBM SPSS Statistics for Windows, version 24 (Armonk, NY: IBM Corp.). Tests were two-sided and a $p<0.05$ was considered as statistical significant.

Results

Sample characteristics

In all, 3,588 adults with CHD from 15 countries were included in the analyses. The country with the greatest number of included patients was the USA (666; 18.6%). Most patients had moderate disease complexity (1,740; 48.5%), were women (1,876; 52.3%) and reported no limitations during physical activity (NYHA Class 1) (1,951; 54.4%). Detailed information on the demographic and clinical characteristics of the sample is given in Table 1.

Table 1. Demographic and clinical characteristics of the sample (n=3,588)

Variables	n (%)
Sex: female	1,876 (52.3)
Median age in years	31.0 (IQR: 16.0)
Educational level	
Less than high school	176 (4.9)
High school	1,508 (42.0)
College degree	777 (21.7)
University degree	1,127 (31.4)
Employment status	
Part-time or full-time work	2,343 (65.3)
Job seeking, unemployed, or disabled	424 (11.8)
Homemaker or retired	268 (7.5)
Full-time student	296 (8.2)
Other	257 (7.2)
Marital status	
Married or living with partner	1,831 (51.0)
Never married	1,582 (44.1)
Divorced or widowed	172 (4.8)
Other	3 (0.1)
Children: yes	1,407 (39.2)
Patient-reported functional ability (New York Heart Association)	1,951 (54.4)
Asymptomatic (Class I)	1,255 (35.0)
Slight limitation (Class II)	254 (7.1)
Marked limitation (Class III)	128 (3.5)
Symptoms at rest (Class IV)	
Complexity of heart defect	
Simple	936 (26.1)
Moderate	1,740 (48.5)
Complex	912 (25.4)
Country	
Argentina	145 (4.0)
Australia	125 (3.5)
Belgium	256 (7.1)

Canada	462 (12.9)
France	83 (2.3)
India	184 (5.1)
Italy	49 (1.4)
Japan	235 (6.6)
Malta	100 (2.8)
Norway	162 (4.5)
Sweden	425 (11.8)
Switzerland	219 (6.1)
Taiwan	248 (6.9)
the Netherlands	229 (6.4)
USA	666 (18.6)

Note. IQR= interquartile range

Healthcare system inputs

In Figure 1, we summarize country-level healthcare system inputs data from the different participating countries. Density of physicians was highest in Norway (4.4 per 1,000 people) and lowest in India (0.8 per 1,000 people). Norway had the highest density of nurses (17.9 per 1,000 people), whereas India had the lowest (2.1 per 1,000 people). With 134 beds per 10,000 people, Japan had the highest density of hospital beds, whereas India had the lowest density (7 beds per 10,000 people). For all countries, the mean density of physicians was 3.2 per 1,000 people (SD: 1.0), the mean density of nurses was 9.8 per 1,000 people (SD: 4.4) and the mean density of hospital beds was 48.1 per 10,000 people (SD: 28.9). Hence, two outlying values were noticed, being the density of physicians in India and the density of hospital beds in Japan. In eTable 2 of the supplementary material, a more detailed overview of these data, the year these data were collected, and a brief description of the overall healthcare system, can be found.

Patient-reported outcomes

PROs of this sample are described in eFigure 2 and have been reported and discussed in more detail in a prior publication.[13] Patients from Malta had the best self-reported physical and mental health, whereas patients from India and France had the worst self-reported physical and mental health, respectively. The lowest scores of psychological distress (i.e., depressive and anxiety symptoms)

were found in patients living in the Netherlands, whereas the highest scores were reported by patients from India. Moreover, Indian patients demonstrated higher prevalence of health risk behaviors (i.e., smoking, drinking, drugs, lack of physical activity, and problematic oral care), whereas Swedish patients demonstrated the lowest prevalence of health risk behaviors. Patients from Switzerland demonstrated the best quality of life, and Japanese patients the worst.

Association between healthcare system inputs and PRO

In the univariable general linear mixed models, higher physician density was associated with better self-reported physical and mental health, less psychological distress, and better quality of life (Table 2). A higher number of nurses per population was associated with better physical health status and less risky health behavior. A high hospital bed density was associated with lower quality of life.

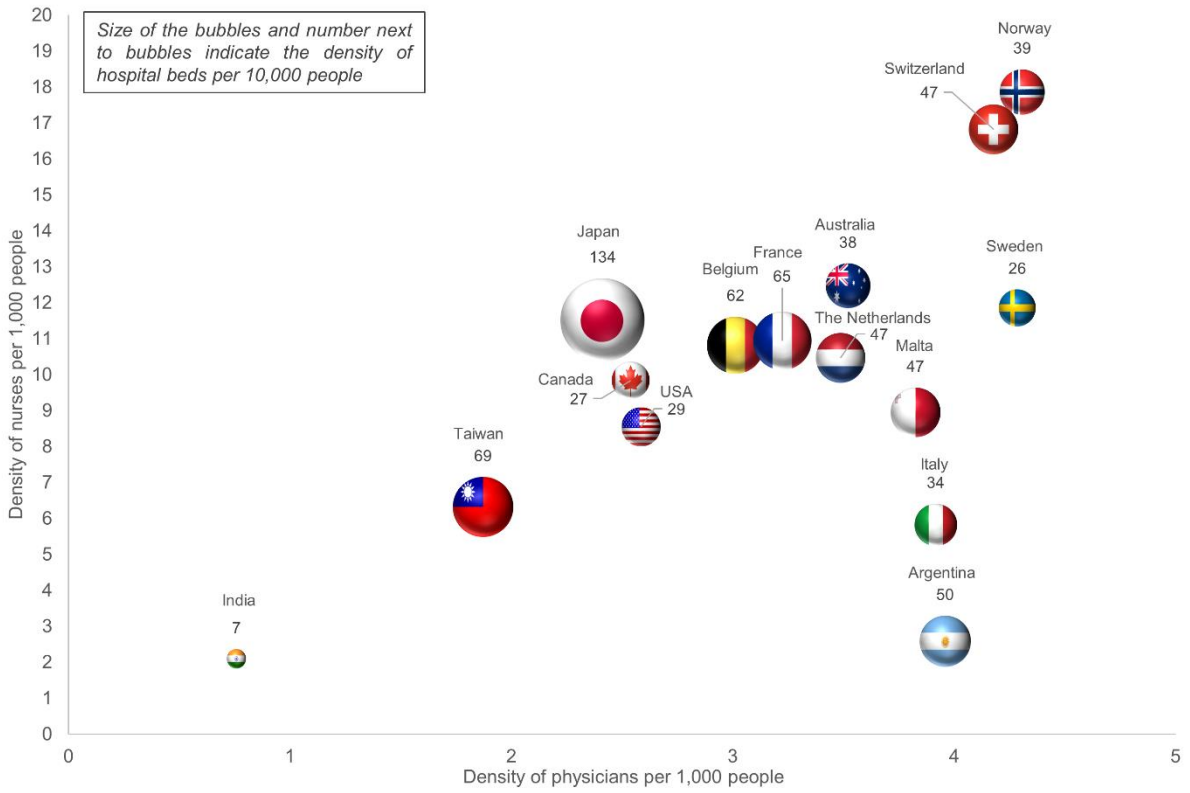

Fig 1. Human resources and infrastructure of the healthcare system of countries included in APPROACH-IS

Legend. Size of the bubbles and number next to bubbles indicate the density of hospital beds per 10,000 people; Sources: World Bank [25], World Health Organization [26] and Taiwan Statistical Data Book 2016 [27]

Multivariable general linear mixed models, adjusted for patient characteristics and unmeasured country differences, showed very similar results (Table 2). However, the association between density of physicians and quality of life was no longer significant and the association between density of nurses and psychological distress turned significant in the multivariable analyses.

Because the density of physicians in India and the density of hospital beds in Japan deviated more than two standard deviations from the mean in the sample, we performed sensitivity analyses excluding these countries on an individual basis (Table 2). After removing India, higher density of physicians remained associated with better self-reported physical and mental health status, less psychological distress, and better quality of life. When Japan was excluded from the analyses, no associations between bed density and PROs were observed.

Discussion

We explored the relationship between healthcare system inputs and PROs, as proposed in the Andersen behavioral model. The results of the present study demonstrated that country-level density of physicians and nurses were associated with PROs among adults with CHD. Although replication in future studies is needed, our results suggested that human resources for health might directly or indirectly affect PROs and might partly explain the inter-country variations in PROs reported previously.[13]

Table 2. General Linear Mixed Models with healthcare system inputs as predictors of PROs (n=3,588)

	Physical health status	Mental health status	Psycho-logical distress	Total health risk score	Quality of life
Univariable analyses					
Density physicians	3.16 (0.78) **	1.90 (0.71) *	-0.84 (0.20) **	-2.31 (1.30)	1.59 (0.69) *
Density nurses and midwifes	0.50 (0.23) *	0.22 (0.19)	-0.13 (0.06)	-0.73 (0.27) *	0.07 (0.18)
Density beds	0.03 (0.04)	-0.01 (0.03)	-0.0008 (0.01)	0.04 (0.05)	-0.06 (0.02) *
Multivariable analyses					
Density physicians	3.11 (0.84) **	1.51 (0.59) *	-0.72 (0.20) **	-2.41 (1.26)	1.33 (0.69)
Density nurses and midwifes	0.51 (0.23) *	0.15 (0.16)	-0.12 (0.05) *	-0.77 (0.25) **	0.05 (0.18)
Density beds	0.05 (0.04)	0.002 (0.02)	-0.002 (0.01)	0.04 (0.05)	-0.06 (0.02) *
Sensitivity analyses					
Density physicians *(without India)*	2.54 (1.14) *	2.00 (0.77) *	-0.79 (0.27) *	-1.31 (1.66)	2.09 (0.90) *
Density beds *(without Japan)*	-0.01 (0.07)	-0.04 (0.04)	-0.008 (0.02)	-0.006 (0.09)	-0.02 (0.04)

Legend. Values in the table are Estimates (Standard Error) of the General Linear Mixed Models; * refers to significance of estimate (see below); Multivariable analyses are adjusted for patient characteristics (sex, age, employment status, marital status, highest educational level, complexity of the health disease and the patient's functional ability) and unmeasured country differences (since country has been seen as random effect in the analyses). Physical and mental health status: higher scores reflect better perceived health; Psychological distress: higher scores reflect more symptoms of depression and anxiety; Total health risk score: higher scores reflect unhealthier behaviour; Quality of life: higher scores reflect higher quality of life; Density of physicians per 1000 people; Density of nurses per 1000 people; Density of beds per 10,000 people.

*	**	***
< 0.05	<0.01	<0.001

Physician density

In the current study, univariable, multivariable, and sensitivity analyses indicated that a higher country-level physician density was associated with favourable PROs in adults with CHD. More precisely, we found that a higher number of physicians was associated with better self-reported health, less psychological distress, and better quality of life. This is not in line with the study of Riehm and colleagues, in which no association between the density of physicians and psychiatrists (on country-level) and better mental health of adolescents was found.[15] However, most previous research, which investigated the relationship between the density of physicians and outcomes at a national level, both patient-reported and other patient outcomes, are in line with our findings. In Canada, the variation of physician density within the country determined self-reported general health status.[12] It was estimated that adding an additional family physician per 10,000 population would yield a 2% to 4% increase in self-reported general health.[12] Similarly, an American study demonstrated that a higher supply of primary care physicians was associated with a higher probability of reporting good self-rated health.[28] In addition, a study from Hungary showed that more physicians per 100,000 inhabitants was associated with better recognition of depression and a lower suicide rate.[29] It can be hypothesized that earlier diagnosis and timely treatment of health problems may explain the associations between higher physician density with better health status and less psychological distress. Indeed, greater physician density has been shown to be associated with lower mortality rates, earlier stage of diagnoses, and better prognosis.[7-9] As yet another example, the geographical variation in breast cancer mortality in the United States was shown to be partly explained by the number of physicians.[8] Our study suggested that improved outcomes do not only pertain to mortality and morbidity, but also to PROs.

Nurse density

We also found that a higher country-level nurse density was associated with better perceived physical health, less psychological distress, and less risky health behaviors. A higher nurse density is likely to yield more absolute hours available for direct nursing care. A prior study in the United States showed that more hours of provision of direct nursing care on a shift was related to lower levels of pain and better self-reported health status of patients.[30] Hence, the time that a nurse has for direct patient care is probably a mediator for the association

between nurse density and self-reported health, as it can be assumed that when the nurse density increases, the patient-to-nurse ratio decreases. Our finding that a higher density of nurses was associated with less psychological distress may initially seem to contradict those of an American study conducted in nursing homes, in which optimal staffing ratios were related to higher levels of depression.[11] However, this finding was determined to be due to the fact that higher nurse density led to improved recognition (i.e., diagnosis) of depression and anxiety.[11] This was confirmed in another study in which the predicted probability of a diagnosis of depression or anxiety increased from 14% to 16% when the ratio changed from over five patients per nurse to under three.[31]

Hospital bed density

Higher hospital bed density was associated with lower quality of life in uni- and multivariable analyses. However, the hospital bed capacity of Japan (i.e., 134 per 10,000 people) is by far the highest in the world [32], and is an outlier in our sample. In addition, we previously showed that Japanese patients enrolled in APPROACH-IS had the lowest average quality of life. We thus suspected that the association between bed density and quality of life could be fully explained by the outlying hospital bed capacity of Japan. This was confirmed by sensitivity analysis, which showed no associations between bed density and PROs after Japan was excluded. The number of hospital beds is an indicator for the capacity and availability of hospital infrastructure. But, it does not seem to be of great importance for patients with CHD. It could be that hospital beds are not the best indicator for this population, as most patients make use of the outpatient clinics. Therefore, in future studies in patients with CHD, it could be interesting to bring PROs of adults with CHD in association with the number of outpatient clinics or outpatient clinic visits.

Methodological considerations

To date, most research on the association between health system inputs and PROs have been performed on a national level.[8,11,12] These studies investigated regional or institutional variance, but did not allow us to appraise variability between countries. Hence, the unique contribution of our study was the examination of healthcare system inputs (on country level) and PROs (on individual level) from an international perspective. Nonetheless, there are some methodological limitations to consider.

First, we used healthcare input data at country level and PROs at the level of individual patients, who were recruited from one or more centers in the respective countries. Although we performed multilevel analyses to control for unmeasured country differences and to take into account that patients are nested in countries, it would have been interesting to investigate human resources and PROs both measured at country or center level.

Second, although we included data from 15 countries around the globe, all but two (i.e., India and Argentina) were high income countries. To gain a richer understanding of the impact of healthcare system inputs at the international level, it will be important that future studies include more low- and middle-income countries. Furthermore, in most countries, there is regional variation in healthcare system inputs. Hence, it could be that the results have been influenced by the fact that some centers are located in high resources areas. Also this issue should be examined in future studies.

Third, although the Andersen behavioral model suggested both a direct and indirect link between contextual organization of the healthcare system and PROs (see eFigure 1) [5], the variables are distal from each other. Indeed, it is highly unlikely that the associations are direct. It can be assumed that other healthcare system characteristics (e.g., accessibility to care, including aspects of financing and insurance) or country specific characteristics (e.g., educational level or overall wealth of the population) might be confounding the association. The present study, therefore, warrants future research in which the underlying mechanisms and the intermediate variables are investigated thoroughly.

Fourth, the Andersen behavioral model assumes that the relations are bidirectional.[5] Because our study used an ecological cross-sectional design [22], we cannot draw conclusions in terms of the direction of effects, nor could causality be tested. Since this cross-sectional study provided strong indications about this association, subsequent studies should investigate the associations longitudinally by using multiple time points to confirm the presumed bidirectional association of the Andersen behavioural model.

Fifth, it is unknown whether our results pertaining to adults with CHD may be generalized to adults with other health conditions. As a sample case, CHD does represent a broad spectrum of mild, moderate, and complex chronic diagnoses. However, it would be interesting to investigate whether our observations could

be replicated among patients with other chronic health conditions. Furthermore, there was no control group available for this study, in which the same patient-reported outcomes were measured using a similar methodology. But, it would be interesting in future studies to add a healthy control group or general population normative data to increase the generalizability and transferability of the findings.

In addition, this study focused on the density of physicians, nurses, and hospital beds. These are important indicators of the healthcare system, since they have been shown to be associated with the national performance of the system.[33] However, other aspects of the comprehensive organization of the healthcare system, such as the overall performance, accessibility to care and quality of care metrics should also be considered in future studies. Moreover, for the population of adults with CHD, it would be interesting to study the association between PROs and the density of human resources that is most relevant to them, namely the density of congenital cardiologists or specialised nurses. Additionally, it would be interesting to subsequently look at the combination of these professions and their impact on PROs, since they interact highly with each other and are both needed in the provision of good care.

Moreover, it is contradictory that midwives have been included in the nurse density and maternity beds have been excluded in the bed density. However, this is how the data were represented by the World Health Organization and the World Bank. Leaving out certain data for our analyses would have impacted the comparability and reliability of the data, since the available information on the number of midwives was incomplete or outdated for several countries.

Finally, valid and reliable self-reported instruments were used to measure PROs. Consequently, patients with cognitive impairment and learning difficulties were excluded in the study, which might also influence the generalizability of the findings. However, a study on the Swedish data of APPROACH-IS has shown that differences between participants and non-participants in demographic, clinical, and health status characteristics were small.[34]

Understanding the influence of density of human resources and infrastructure on outcomes is an important consideration for health policy and planning.[12] Indeed, the study should be seen as a preliminary step for researchers to investigate the influence of healthcare system inputs on PROs. It is likely only

with the availability of such scientific data that we will be able to advise policy makers about aspects of the healthcare system impacting PROs.

Conclusion

This explorative study provides a first indication that country-level density of healthcare system inputs are associated with PROs in adults with CHD. More specifically, higher physician density was associated with better self-reported physical and mental health, less psychological distress, and better quality of life. Higher density of nurses was associated with better physical health status, less psychological distress, and less risky health behaviors. Density of hospital beds was not associated with PROs. Before firm conclusions about the relationships observed can be drawn and before recommendations for policy-making can be made, more research ought to be conducted in order to replicate the present findings and to scrutinize the mediating mechanisms between characteristics of the healthcare system and outcomes as perceived by the patients.

Declarations

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare to have no conflicts of interest regarding this manuscript.

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Supplementary material - Chapter 5

eTable 1 - Overview of variables and measurements

eTable 2 - Detailed overview of the healthcare system inputs and other healthcare system characteristics of countries included in APPROACH-IS

eFigure 1 - Andersen behavioral model of health services use, sixth revision.[13]

eFigure 2 - Mean and standard deviation of patient-reported outcomes in 3588 adults with congenital heart disease

eTable 1. Overview of variables and measurements

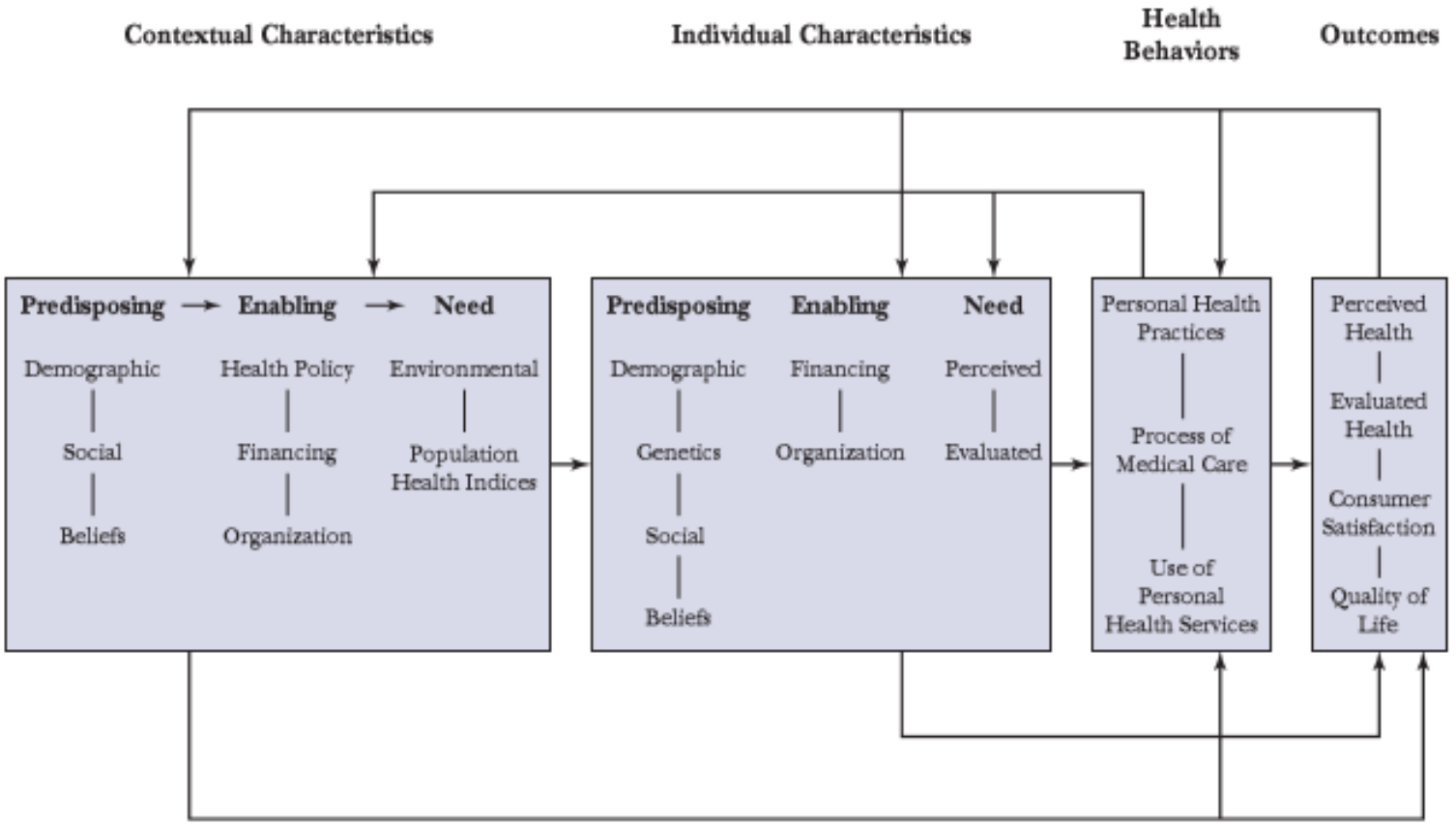
Variables	Definition used in this study	Measurement	Interpretation of measurement
Patient-reported health status	The impact of a disease according to the patient, including symptoms, functional status, and health-related quality of life [1]	12-item Short-form Health Survey version 2 (SF-12) [2]	Physical Component Summary (PCS) and Mental Component Summary (MCS) ranging from 0 to 100; Higher scores = better perceived health
Psychological distress	The level of internalizing, emotional distress, depressive and anxious symptoms	Hospital Anxiety and Depression Scale (HADS) [3]	HADS scores ranging from 0 to 21; Higher scores = more symptoms Because HADS was found to be accurate when screening psychological distress, a general psychological distress score was used instead of using two subscores for depression and anxiety [20].
Health behaviors	Activities that a person undertakes to prevent disease or to improve health and well-being [4]	Health-Behavior Scale–Congenital Heart Disease (HBS-CHD) [5]	Total health risk score ranging from 0 to 100; Higher scores = unhealthier behavior
Quality of life	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 [6]	Linear Analog Scale (LAS) [7]	LAS score ranging from 0 (worst imaginable quality of life) to 100 (best imaginable quality of life); Higher scores = better quality of life

eTable 2. Detailed overview of the healthcare system inputs and other healthcare system characteristics of countries included in APPROACH-IS

Healthcare system inputs Countries	Density of physicians (per 1,000 population)	Measured in (year)	Density of nurses (per 1,000 population)	Mea-sured in (year)	Density of hospital beds (per 10,000 population)	Measured in (year)	Brief description of the healthcare system	
							Model of health system financing [8, 9]	Health expenditure as a % of the GDP in 2015
Argentina	3.96	2017	2.58	2017	50	2014	Universal public-private insurance system	6.8
Australia	3.5213	2015	12.4667	2015	38	2014	Universal government-funded health system	9.4
Belgium	3.0138	2015	10.8193	2015	62	2014	Universal public insurance system	10.5
Canada	2.5388	2015	9.8398	2015	27	2012	Universal government-funded health system	10.4
France	3.2237	2015	10.9403	2015	65	2013	Universal public insurance system	11.1
India	0.759	2016	2.0981	2016	7	2011	Non-universal insurance system	3.9
Italy	3.9174	2015	5.8184	2015	34	2012	Universal government-funded health system	9
Japan	2.412	2016	11.518	2015	134	2012	Universal public insurance system	10.9
Malta	3.826	2015	8.95	2015	47	2014	Universal government-funded health system	9.6
Netherlands	3.4875	2015	10.4675	2015	47	2009	Universal private health insurance system	10.7

Norway	4.394	2015	17.8622	2015	39	2013	Universal government-funded health system	10
Sweden	4.2861	2015	11.8503	2015	26	2013	Universal government-funded health system	11
Switzerland	4.1782	2015	16.8152	2015	47	2013	Universal private health insurance system	12.1
Taiwan	1.873	2015	6.316	2015	69	2015	Universal government-funded health system	5.9
USA	2.5858	2015	8.55	2015	29	2013	Non-universal insurance system	16.8

Sources. World Bank Open Data [10], World Health Organization [11] and Taiwan Statistical Data Book 2016 [12]



eFigure 1. Andersen behavioral model of health services use, sixth revision (Reproduced from Andersen et al.[13]). Permission to reuse figure was obtained from John Wiley and Sons.

Patient-reported outcomes	Physical health status (0-100)	Mental health status (0-100)	Psychological distress (0-42)	Total health risk score (0-100)	Quality of life (0-100)
Countries					
Argentina (n=145)	79.3 (18.2)	72.1 (18.5)	8.8 (6.0)	28.4 (16.4)	80.0 (14.5)
Australia (n=125)	76.7 (19.2)	71.2 (18.3)	8.1 (6.2)	26.0 (16.4)	82.5 (14.2)
Belgium (n=256)	78.9 (19.5)	74.5 (17.9)	8.5 (6.4)	23.0 (16.4)	77.7 (13.4)
Canada (n=462)	79.1 (17.8)	69.8 (16.8)	10.2 (5.3)	18.8 (17.2)	76.0 (15.7)
France (n=83)	73.4 (22.5)	66.4 (20.7)	10.6 (6.7)	30.2 (16.3)	78.2 (15.0)
India (n=184)	66.9 (20.6)	68.6 (19.8)	10.7 (6.5)	34.8 (13.2)	76.3 (17.8)
Italy (n=49)	79.5 (17.8)	76.9 (17.3)	7.5 (7.0)	25.4 (16.4)	80.9 (15.1)
Japan (n=235)	81.3 (17.6)	72.8 (19.3)	9.1 (8.0)	30.1 (16.7)	70.7 (21.6)
Malta (n=100)	85.8 (15.8)	77.2 (17.1)	8.0 (6.6)	32.8 (16.3)	81.2 (13.3)
Norway (n=162)	77.8 (20.5)	70.1 (20.0)	7.7 (6.2)	18.5 (18.2)	76.9 (17.3)
Sweden (n=425)	84.3 (19.9)	76.8 (19.5)	7.6 (6.5)	16.8 (16.0)	79.6 (17.4)
Switzerland (n=219)	82.6 (19.0)	76.4 (16.6)	7.1 (5.9)	17.9 (16.3)	83.1 (14.2)
Taiwan (n=248)	71.1 (18.3)	67.0 (16.9)	9.1 (5.7)	22.0 (15.2)	75.5 (14.1)
the Netherlands (n=229)	78.1 (18.9)	76.0 (17.0)	6.8 (5.1)	19.2 (16.9)	80.2 (12.1)
USA (n=666)	75.6 (23.1)	71.9 (20.5)	9.3 (6.8)	21.7 (16.5)	80.6 (17.0)
All countries (n=3588)	**78.1 (20.3)**	**72.5 (18.8)**	**8.8 (6.4)**	**22.5 (17.1)**	**78.4 (16.3)**



Score reflecting worst status within this sample

50th percentile

Score reflecting best status within this sample

eFigure 2. Mean and standard deviation of patient-reported outcomes in 3588 adults with congenital heart disease

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PART 3

Development of the APPROACH-IS II project

Chapter 6

Rationale, design and methodology of APPROACH-IS II: International study of patient-reported outcomes and frailty phenotyping in adults with congenital heart disease

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Abstract

Background: In recent years, patient-reported outcomes (PROs) have received increasing prominence in cardiovascular research and clinical care. An understanding of the variability and global experience of PROs in adults with congenital heart disease (CHD), however, is still lacking. Moreover, information on epidemiological characteristics and the frailty phenotype of older adults with CHD is minimal. The APPROACH-IS II study was established to address these knowledge gaps. This paper presents the design and methodology of APPROACH-IS II.

Methods/design: APPROACH-IS II is a cross-sectional global multicentric study that includes Part 1 (assessing PROs) and Part 2 (investigating the frailty phenotype of older adults). With 53 participating centers, located in 32 countries across six continents, the aim is to enroll 8,000 patients with CHD. In Part 1, self-report surveys are used to collect data on PROs (e.g., quality of life, perceived health, depressive symptoms, autonomy support), and explanatory variables (e.g., social support, stigma, illness identity, empowerment). In Part 2, the cognitive functioning and frailty phenotype of older adults are measured using validated assessments.

Discussion: APPROACH-IS II will generate a rich dataset representing the international experience of individuals in adult CHD care. The results of this project will provide a global view of PROs and the frailty phenotype of adults with CHD and will thereby address important knowledge gaps. Undoubtedly, the project will contribute to the overarching aim of improving optimal living and care provision for adults with CHD.

1. Background

Congenital heart disease (CHD) is the most common form of congenital defect among newborns, with a global birth prevalence of 9.4 per 1,000.[1] As the life expectancy of patients with CHD is increasing, the population is substantially growing and aging, especially in higher-income countries.[2] Because patients with CHD remain at increased risk for comorbidities, they require lifelong follow-up to optimize outcomes. The epidemiological characteristics and healthcare needs of the 'emerging' group of older adults with CHD should be identified for optimal care planning. In addition, the focus has expanded from improving longevity to also enhancing patient-reported outcomes.[3]

It is essential to understand the outcomes and experiences from patients' perspectives, namely via patient-reported outcomes (PROs). PROs are defined as *"any report of the status of a patient's health condition, health behaviour, or experience with health care that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"*.[4] PROs are related to a broad range of patient outcomes, such as mortality and resource use.[5,6] The original APPROACH-IS study, which ran from 2013 until 2015, investigated PROs among adults with CHD around the globe.[7-9] This earlier study identified intercountry variation in PROs and detected associations both at the individual and contextual level.[10] Most variance in PROs could be explained by individual medical, demographic, behavioral, psychological, and social factors. Little variance could be explained by country-level characteristics. Indeed, APPROACH-IS has already answered some important initial questions.

However, gaps in our knowledge base remain.[9] Although a broad list of PROs and explanatory factors were included in the original APPROACH-IS study, only part of the variation in PROs could be explained, indicating a need to investigate the association between PROs and additional explanatory factors.[10] Moreover, a particular type of PRO, experiences with health care, remain largely uninvestigated in adults with CHD, leaving questions unanswered about the quality of care, the geographical variation and predictors of patient-reported experiences with care. Furthermore, the initial APPROACH-IS study included patients from 13 high-income and two middle-income countries.[7] An understanding of PROs in patients living in low- and middle-income countries, in comparison to high-income countries, is still lacking.

Furthermore, as adults with CHD are ageing, many will encounter disability, morbidity and a state of frailty, thereby increasing susceptibility for adverse outcomes and premature mortality.[11] To maintain longevity and quality of life, an understanding of variables associated with prognosis, comorbidity and mortality will enable us to map specific healthcare needs.[11] Frailty phenotype refers to a distinct clinical syndrome that classifies patients as non-frail, pre-frail, or frail based upon the assessment of five criteria: weakness, slow walking speed, unintentional weight loss, exhaustion, and low physical activity.[12] Growing evidence suggests that independent of age and comorbidity, frailty phenotyping can guide risk prediction in chronically ill patients.[13] Unfortunately, our current knowledge about epidemiological characteristics, frailty phenotype and healthcare needs of ageing adults with CHD is very limited.[13]

These factors led to the decision to proceed with a second APPROACH-IS study, with an expanded list of PROs and explanatory variables and for which data from patients living in low- and middle-income countries are included. Moreover, APPROACH-IS II will also deliver much-needed empirical data describing the clinical and epidemiological characteristics of the emerging population of older adults with CHD. The paper aims to describe the design and methodology of the APPROACH-IS II study.

2. Study objectives

The aims of APPROACH-IS II are (i) to increase our understanding of PROs in adults with CHD by enrolling adults with all types of CHD from low-, middle-, and high-income countries and including a novel set of potential explanatory variables; and (ii) to assess the profile and healthcare needs of older adults with moderate to complex CHD, with a particular focus on frailty.

3. Design and methods

The project has a cross-sectional global multicentric design and consists of Part 1 (PROs) and Part 2 (frailty phenotype) (see Figure 1). All participating centers contribute data to Part 1, and data collection for Part 2 is optional (and likely depends upon local research resources).

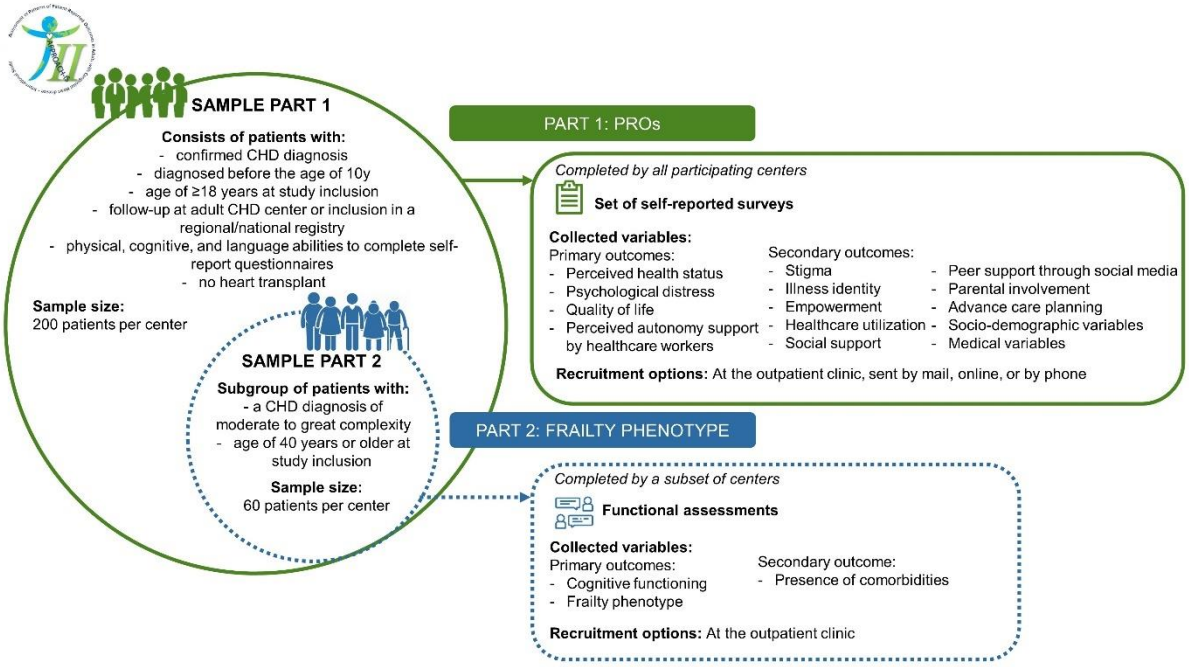

Figure 1. Structure of the APPROACH-IS II project

3.1 Part 1: PROs

Data collection procedures

In Part 1 of the study, patients are asked to complete a set of self-reported surveys. Participating centers can recruit patients using one of four recruitment strategies:

1. Eligible patients can be approached consecutively at outpatient clinics for adults with CHD. Consecutive sampling is a technique in which every eligible case is selected until the required sample size is achieved. Following informed consent, patients may complete surveys while in the clinic (on paper or online) or at home (online or by returning paper surveys in a pre-addressed and pre-stamped envelope).
2. Eligible patients can be randomly selected from the institution's database and receive a study package, including an information letter, two copies of the informed consent form, surveys, and an addressed envelope, by mail. Reminders can be sent out to non-responders.
3. Eligible patients can be identified from the institution's database and receive an email with a link to the online survey (i.e., REDCap). Informed consent can be obtained at an outpatient clinic, over the telephone, or

online before the completion of the surveys. Reminders can be used to increase the response rate.

4. Eligible patients can be identified from the institution's database and receive a phone call to complete the survey. Informed consent can be obtained at an outpatient clinic visit, by phone or online. The option to collect data over the phone is limited to centers with a population with low (written) health literacy levels.

In addition to study surveys, clinical medical data are collected from the medical records of each study participant, overseen by a member of the medical team. The anatomic complexity and current physiological stage are measured and categorized according to the ACHD anatomical and physiological classification (see Table 1).[14]

Participating centers are responsible for the local data collection process. Data collection began in August 2019, was paused in all centers from March 2020 until June 2020 due to the COVID-19 pandemic, and will be completed by August 2022. In some centers, data collection was paused longer or again at a later date, depending on the local pandemic situations. Details regarding decision-making to pause the data collection process due to COVID-19 have been published elsewhere.[15]

Sample

Participants are eligible if they fulfill the following criteria: (i) diagnosed with CHD, defined as: "*a gross structural abnormality of the heart and/or intra-thoracic great vessels that is actually or potentially of functional significance (including mild, moderate, and complex heart defects)*"[16]; (ii) aged 18 years or older at the date of study entry; (iii) diagnosed with CHD before the age of 10 years; (iv) followed at an adult CHD center or included in a national/regional registry; (v) demonstrated physical, cognitive and language abilities required to complete self-report questionnaires. Patients are excluded if they received a heart transplantation before study participation.

The recruitment goal is 200 patients per center. This goal is determined based on a survey sample size calculation and feasibility for all participating centers. The survey sample size calculation takes into account the margin of error (measure of accurateness), size of the population and alpha level.[17] With a recruitment goal of 200 patients per center and an alpha level of 5%, the margin

of error is around 7 percentage points for analyses of the PROs, which is acceptable. In addition, in the previous APPROACH-IS study, the sample size of 200 per center proved feasible for larger and smaller centers.[7] Although 53 centers are participating in APPROACH-IS II, we realize that centers located in low- and middle-income countries might have difficulties achieving this recruitment goal due to fewer patients in adult CHD care; as such, we estimate a total sample size of 8,000 patients for Part 1 of the project.

Variables

An overview of the core battery of questionnaires included in Part 1 of the study, their interpretation and psychometric properties are presented in Table 1.

Four patient-reported outcomes are included: perceived health status, psychological distress, quality of life, and patients' perception of providers' autonomy support. Perceived health status is measured using the 12-item shortened and adapted version of the RAND-36.[18] It is a disease-generic measure of eight health domains: physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems, and mental health. Psychological distress is assessed using the Patient Health Questionnaire-8 (PHQ-8) for depression [19] and the General Anxiety Disorder-7 (GAD-7) for anxiety.[20] The PHQ-8 includes eight of the nine criteria of the DSM–IV (Diagnostic and Statistical Manual of Mental Disorders-IV) diagnosis of depressive symptoms; it does not include the item about suicidal or self-injurious ideation.[19] Quality of life is determined using a 0 – 100 linear analog scale.[21] Our experience measure is the brief Health Care Climate Questionnaire, which has been modified for use with adults with CHD and assesses patients' perceptions of the degree to which their team of healthcare providers is supporting their autonomy (versus them taking control).[22] The questionnaire is based on self-determination theory, which proposes that individuals tend to feel more competent when they are autonomously motivated.[23]

The survey packet includes additional explanatory variables. The Stigma Scale for Chronic Illnesses measures multifaceted (both enacted and internalized) stigma.[24] The Illness Identity Questionnaire assesses four illness identity dimensions (i.e., engulfment, rejection, acceptance and enrichment).[25] Empowerment, the capacity of individuals to become responsible for their

health,[26] is assessed by the Gothenburg Empowerment Scale,[27] which has five dimensions: identity, knowledge and understanding, personal control, shared-decision making, and enabling others (i.e. peers with similar conditions).[28] Healthcare use (i.e., hospitalizations, visits to the general practitioner, medical specialist or emergency department in the last 12 months) was captured using a healthcare measure that has previously been used with adults with CHD; a distinction is made between healthcare use related to CHD vs. other diseases/symptoms.[29] The Multidimensional Perceived Social Support Scale (MSPSS) assesses perceived social support, which refers to how individuals perceive family, friends and significant others as sources available to provide psychosocial, materialistic and overall support during times of need.[30] Parental involvement is measured using a modified version of the MSPSS, in which the items reflect perceived social support by parents. Social media and advance care planning are measured using survey items developed by the Steering Committee based on existing surveys.[31] Information about basic demographic variables are also collected. Surveys for Part 1 were carefully selected based on their validity, reliability and availability in different languages.

Table 1. Details and psychometric properties of the surveys used in Part 1 of APPROACH-IS II

Variable	Source	Measurement tool	# items	Validity	Reliability	Use in cardiac population	Interpretation
Socio-demographic variables - Age - Sex - Marital status - Number of children - Cultural background/ethnicity - Educational level - Employment status - Religion	Self-report	Survey developed by Steering Committee	13	NA	NA	NA	NA
Medical variables - New York Heart Association functional class - Height and weight	Self-report	Survey developed by Steering Committee	3	NA	NA	NA	NA
- Diagnosis of CHD - History of cardiac surgeries / interventions - Number of cardiac admissions (over past 5 years) - Number of cardiac outpatient visits (over past 5 years)	Chart review	Form developed by Steering Committee	12	NA	NA	NA	NA

- Aortopathy - Arrhythmia - Concomitant valvular heart disease - End-organ dysfunction - Exercise capacity - Hypoxemia/hypoxia/cyanosis - NYHA functional classification system (physician assessment) - Pulmonary hypertension - Shunt (hemodynamically significant shunt) - Venous and arterial stenosis	Chart review	Form based on the ACHD Anatomical and Physiological Classification System [14]	21	NA	NA	NA	NA
Primary outcomes							
Perceived health status	Self-report	12-item shortened version of the RAND-36 [18]	12	Supported [32]	Supported [32]	Yes, in adults with CHD [7]	Composite physical (PCS) and mental health (MCS) scores are computed. Scores range from 0 (lowest health level) to 100 (highest health level).
		Linear Analogue Scale Health Status (LAS HS) [21]	1	Supported [21]	Supported [21]	Yes, in adults with CHD [21]	Scores range from 0 (worst imaginable health state) to 100

							(best imaginable health state).
Psychological distress	Self-report	Patient Health Questionnaire 8 [19]	8	Supported [33]	Supported [33]	Yes, in adults with CHD [34]	Scores range from 0 to 24. Scores of ≥10 indicate depression.
		General Anxiety Disorder 7 [20]	7	Supported [33]	Supported [33]	Yes, in adults with CHD [34]	Scores range from 0 to 21. Scores of 5, 10, and 15 are taken as cut-off points for mild, moderate and severe anxiety.
Quality of life	Self-report	Linear Analog Scale Quality of Life (LAS QOL) [21]	1	Supported [21]	Supported [21]	Yes, in adults with CHD [21]	Scores range from 0 (worst imaginable quality of life) to 100 (best imaginable quality of life)
Perceived autonomy support by health workers	Self-report	Modified Health Care Climate Questionnaire [22]	6	Supported [35]	Supported [35]	Yes, in patients with cardiovascular disease [36]	Each of the 6 items is scored from 1 to 7. Scores are calculated by averaging the individual item scores. Higher average score

							represents a higher level of perceived autonomy support.
Secondary outcomes							
Stigma	Self-report	Chronic Illness Stigma Scale (CISS) [24]	8	Supported [24]	Supported [24]	No, used in patients with chronic disease, but not yet used in cardiac populations	Scores range from 8 to 40. Higher scores indicate higher levels of perceived stigma.
Illness identity	Self-report	Illness Identity Questionnaire (IIQ) [25]	25	Supported [37]	Supported [37]	Yes, in adults with CHD [25]	Consists of five-item rejection scale, seven-item enrichment scale, five-item acceptance scale and eight-item engulfment scale. A mean score is calculated per subscale. Higher scores indicate more rejection, enrichment, acceptance or engulfment.

Empowerment	Self-report	Gothenburg Empowerment Scale (GES generic v1.1) [27]	15	Supported [38]	Supported [38]	Yes, in adolescents with CHD [38]	Scores range from 15 to 75. Higher score reflects a higher level of empowerment.
Healthcare utilization	Self-report	Patient-Reported In- and outpatient Utilization Scale (PRIUS) [29]	16	NA	NA	Yes, in adults with CHD [29]	Higher numbers indicate more healthcare use.
Perceived Social Support	Self-report	Multidimensional Perceived Social Support Scale (MSPSS) [30]	12	Supported [39]	Supported [39]	Yes, in adults with CHD [40]	Scores range from 12-84. Higher score indicates greater social support perceived by an individual.
Social media to connect with peers	Self-report	Survey developed by the Steering Committee	3	NA	NA		NA
Parental Involvement	Self-report	Adapted version of the items, retrospectively reflecting perceived social support by parents of the MSPSS [30]	5	NR	NR		Scores range from 5-35. Higher score indicates greater parental support in childhood and adolescence.
Thinking about the future (advance care planning)	Self-report	Survey developed by the Steering Committee	5	NA	NA		NA

Legend. CHD: congenital heart disease, NA: not applicable, NR: not reported

3.2 Part 2: Healthcare needs of older CHD patients

Sample

For Part 2, additional inclusion criteria are (i) age of 40 years or older, and (ii) CHD diagnosis of moderate or great complexity.[14] Patients who meet these additional inclusion criteria can complete study procedures for both Part 1 and Part 2. Centers that are collecting data for Part 2 are asked to aim to enroll (i) 20 adults aged 40-50 years, (ii) 20 adults aged 51-60 years, and (ii) 20 adults older than 60 years. The estimation of the sample size for Part 2 was 800 patients; 21 centers are participating in Part 2 of the project, but we realize that many centers will encounter difficulties enrolling patients in the older cohorts.

Data collection procedure

In Part 2 of the study, patients participate in several assessments carried out by a research assistant during a patient visit at an outpatient clinic.

Variables

Two primary outcomes, namely cognitive functioning and frailty phenotype, are included. Cognitive functioning is assessed using the Montréal Cognitive Assessment (MoCA).[41] The MoCA assesses different cognitive domains, including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation. Frailty phenotype is assessed using the Fried method.[12] This method consists of five parts: self-report questions about unintentional weight loss, exhaustion and physical activity, an assessment of weakness performed using a handgrip dynamometer, and a walk test. In addition, the Charlson Comorbidity Index is determined based on medical files for every participant to provide information on the presence and burden of comorbidities.[42] Table 2 contains an overview of the included variables in Part 2.

Table 2. Variables included in Part 2 of APPROACH-IS II

Variable	Source	Measurement tool	# items	Validity	Reliability	Use in cardiac population	Interpretation
Cognitive functioning	Assessment by research assistant	Montréal Cognitive Assessment [41]	30	Supported [41]	Supported [41]	Yes, in adolescents and young adults with CHD [43]	Scores range from 0 to 30. Scores of <26 indicate cognitive dysfunction.
Frailty phenotype (i.e., non-frail/pre-frail/frail)	Assessment by research assistant	Fried method [12]: 1. Unintentional weight loss: self-reported 2. Exhaustion: self-reported 3. Low physical activity level: self-reported 4. Weakness: test performed using a handgrip dynamometer, assessment performed by a research assistant and adjusted for sex and body mass index 5. Slow walking speed: based on time to walk 15 feet, assessment performed by a research assistant and adjusted for sex and standing height	5	Supported [12,44,45]	Supported [44]	Yes, in patients with cardiac disease [45]	Frail: when ≥3 criteria are positive Pre-frail: 1 or 2 criteria are positive Robust or non-frail: no criterion is positive

Presence and burden of comorbidities	Chart review	Charlson Comorbidity Index [42]	19	Supported [46]	Supported [46]	Yes, in adults with CHD [47]	Comorbidities range from 1 to 6 points. The final score is obtained via the summation of applicable points and ranges from 0 (no disease burden) to 29 (maximal disease burden).

Legend. CHD: congenital heart disease.

4. Data analysis

Descriptive statistics (means, standard deviations, medians and interquartile ranges) will be calculated and compared between participating centers. Multilevel analyses will be performed because the data have a hierarchical nature. More specifically, data will be organized at the level of (1) the individual patient, (2) the center, and (3) the country. Data of individual patients are nested within the center and country levels (i.e., aggregate units). General and generalized linear mixed models will be used to analyze continuous, and binomial or count variables, respectively. Additional analyses will be performed to determine the psychometric properties of the surveys. Frailty phenotypes will be calculated based on the Fried method. Multilevel multivariable analyses will be performed by grouping patients with comparative phenotypes and exploring trends and associations in terms of frailty phenotype, comorbidity burden, and healthcare consumption.

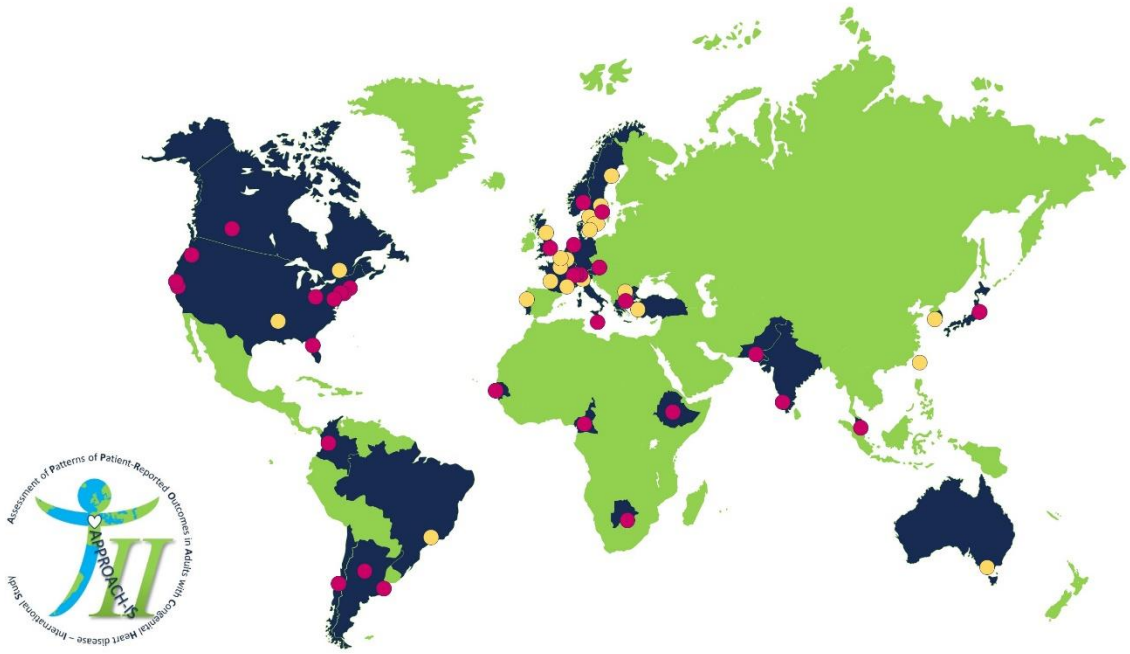

Figure 2. Geographic distribution of the APPROACH-IS II participating centers
Legend. Yellow dots indicate centers that are participating in Part 1 and Part 2 of the study (n=21). Pink dots indicate centers that are participating in Part 1 only (n=32).

5. Participating centers

Centers are eligible to take part if (i) participation is feasible in terms of infrastructure and clinical research resources, and (ii) patient volume is sufficient to support the recruitment of an adequate number of patients. As shown in Figure 2, 53 centers across 32 countries are participating in Part 1 of the study. A total of 21 centers, across 15 countries, are also participating in Part 2 of the study. The full list of participating centers is available in the supplementary material (eTable 1).

6. Project management

The University of Leuven (KU Leuven, Belgium) is the coordinating center of APPROACH-IS II and is responsible for the general management and administration, as carried out by the international project coordinator (LVB). All aspects of this international study are overseen by the Steering Committee (PM, EG, KL, AK) that makes substantive decisions and has final responsibility for scientific conduct. All participating centers have a local principal investigator, responsible for the study execution in their center.

Standard Operating Procedures (SOPs) were developed to standardize processes during the preparatory phase, data collection and data management, and to ensure the use of a uniform methodology. The Open Science Framework (https://osf.io/) is used as a platform to store and share relevant documents about the project. For survey distribution, data entry and data hosting, REDCap (Research Electronic Data Capture) was used, which is a secure, web-based software platform designed to support data capture for research studies.[48] The use of REDCap for the APPROACH-IS II project has been described in more detail elsewhere.[48] Project information, updates, and data collection progress are available on the study website (www.approach-is.net), and via information flashes regularly distributed to the consortium.

7. Translations

Given the global geographic distribution of this project, survey documents were required in 22 different languages. If there was no available translation for a

measure, the local team undertook this process using a standardized academic translation protocol, based on WHO guidelines.[49] This protocol includes a forward translation, a backward translation, pre-testing in a few patients, proofreading, finalization and documentation. No substantial changes to the English version of the survey were permitted.

8. Ethical issues

The Institutional Review Board of the University Hospitals Leuven/KU Leuven (i.e., the coordinating center) approved the main study protocol of APPROACH-IS II and each participating center obtained local ethics approval for study execution. Written informed consent is obtained from all participants as required; in some regions, legislation stipulates that written informed consent is unnecessary for survey studies. The project is conducted in accordance with the declaration of Helsinki. The protocol is registered at ClinicalTrials.gov (NCT04902768).

Data management is conducted in accordance with current worldwide privacy regulations. Participant confidentiality is a priority in this project. The coordinating center did not collect patient names, medical record numbers, or dates of birth. Only non-identifiable information was made available to other participating centers.

9. COVID-19

The APPROACH-IS II study has faced unexpected challenges and made several adaptations due to the COVID-19 pandemic.[15] Enrollment was paused during the first months of the coronavirus outbreak in all participating centers, because of a potential risk of biased results (March till June 2020). Data collection was also paused locally by many participating centers during outbreaks of the virus, as this typically entailed a shift in clinical care and research priorities as well as a reduction in routine outpatient visits.

As increased levels of anxiety and depression have been documented in the general population during the pandemic, we realized that data collected peri-pandemic could be at risk of bias.[50] Therefore, in three participating centers, namely Leuven (Belgium), Oslo (Norway) and Seoul (South Korea) in which

data collection was completed before the first COVID-19 outbreak, a second measurement wave was set up one year after the first measurement wave.[50] Published results revealed that, fortunately, differences between pre- and peri-pandemic PROs were very small and clinically negligible on a group level and no differences were observed between patients who had and had not been infected with COVID-19.[50] Hence, we may be relatively confident that the results of this project will not be biased by the pandemic.

10. Discussion

Optimization of quality of life remains a healthcare priority for the growing and ageing population of patients with CHD. However, important questions remain unresolved. International variation in PROs is only partly understood [10] and an elucidation of PROs in patients living in low- and middle-income countries is currently lacking. In addition, our field currently lacks data on the frailty phenotype and healthcare needs of ageing adults with CHD.[13] The APPROACH-IS II project will contribute to addressing these respective issues. With 53 participating centers located in 32 countries, APPROACH-IS II will be one of the largest collaborations on PROs worldwide and will generate a large study sample of around 8,000 patients. As high-, middle- and low-income countries from six continents are represented, the data will reflect cultural and regional diversities of the adult CHD population. The project employs a robust and uniform methodology, which will generate and safeguard reliable data.

This project has some limitations. First, the project has a cross-sectional research design, which will not allow to determine the direction of effects. Using advanced techniques, it will be possible to make causal inferences on this large database. Moreover, in three centers a second measurement wave has been set-up that generated longitudinal data. Second, only patients who are physically or mentally capable of completing surveys are included. Indeed, this impacts the generalizability of the results. Third, although high-, middle- and low-income countries are represented in this study, still a larger number of high-income countries are included, leading to their overrepresentation.

Despite these limitations, we are confident that APPROACH-IS will address knowledge gaps about PROs and the frailty phenotype of adults with CHD worldwide.

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12. Acknowledgements

We want to thank all APPROACH-IS II participants and all individuals at the participating centers who are making substantial contributions to this project.

13. Declaration of interest

Declarations of interest: none

14. APPROACH-IS II Consortium

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Supplementary material

eTable 1. List of participating centers

Country	City	Center
ASIA		
India	Kochi	Amrita Institute of Medical Sciences
Japan	Chiba	Chiba Cerebral and Cardiovascular Center
Malaysia	Kuala Lumpur	Paediatric & Congenital Heart Centre, IJN (National Heart Institute)
Pakistan	Karachi	Aga Khan University Hospital
South-Korea	*Seoul*	*Samsung Medical Center*
Taiwan	*Taipei City*	*National Taiwan University Hospital*
Turkey	*Bornova/İzmir*	*Ege University Health Application and Research Center, Cardiology Department*
AFRICA		
Botswana	Gaborone	Princess Marina Hospital
Cameroon	Yaoundé	Clinique Medical Le Jourdain
Ethiopia	Addis Ababa	College of Health sciences, Addis Ababa University
Senegal	Thiés	Centre Hospitalier Régional de Thiès
EUROPE		
Austria	Vienna	Vienna General Hospital
Belgium	*Leuven*	*University Hospitals Leuven*
Belgium	*Ghent*	*Ghent University Hospital*
Bulgaria	*Sofia*	*National Heart Hospital*
Denmark	*Copenhagen*	*Copenhagen University Hospital*
France	*Paris*	*Hôpital Européen Georges Pompidou*

France	*Bordeaux*	*Hôpital cardiologique Haut-Leveque*
France	*Montpellier*	*Montpellier University Hospital*
Greece	Thessaloniki	AHEPA University Hospital
Italy	*Milan*	*Policlinico San Donato (IRCCS)*
Malta	L-Imsida	Mater Dei Hospital
Norway	Oslo	Oslo University Hospital, Rikshospitalet
Portugal	*Porto*	*Reference Center of Congenital Heart Disease , University Hospital Center of São João*
Sweden	*Gothenburg*	*Sahlgrenska University Hospital*
Sweden	*Uppsala*	*Uppsala University Hospital*
Sweden	*Lund*	*Skånes Universitetssjukhus*
Sweden	Stockholm	Karolinska Universitetssjukhuset
Sweden	*Umea*	*Umea University Hospital*
Switzerland	Bern	University Hospital Bern
Switzerland	Lausanne	Centre hospitalier universitaire vaudois
Switzerland	Genève	Hôpitaux Universitaires de Genève
The Netherlands	Groningen	Centrum voor Congenital Hartafwijkingen
United Kingdom	London	Royal Brompton Hospital, Royal Brompton & Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust
United Kingdom	*Newcastle upon Tyne*	*Freeman Hospital, Newcastle Upon Tyne Hospitals NHS Foundation Trust*
NORTH-AMERICA		
Canada	*Montreal*	*Montreal Heart Institute, Université de Montréal*
Canada	Edmonton	Mazankowski Alberta Heart Institute
USA, CA	Stanford	Lucile Packard Children’s Hospital and Stanford Health Care
USA, CA	San Francisco	University of California

USA, FL	Gainesville	University of Florida Health
USA, MD	Baltimore	Taussig Heart Center of Johns Hopkins Hospital
USA, MA	Boston	Boston Children's / Brigham and Women's
USA, NY	New York	Mount Sinai Heart
USA, OH	Columbus	Nationwide Children’s Hospital
USA, OR	Portland	Oregon Health and Science University
USA, PA	Philadelphia	Philadelphia Penn Medicine
USA, TX	*Dallas*	*University of Southwestern Medical Center*
SOUTH-AMERICA		
Argentina	Cordoba	Hospital de Niños
Argentina	Buenos Aires	Hospital San Juan De Dios De La Plata
Brazil	*Ribeirão Preto*	*Hospital das Clinicas da Faculdade de Medicina de Ribeirão Preto*
Chile	Santiago	Intituto Nacional Del Torax
Colombia	Manizales	Meintegral Clinic
OCEANIA		
Australia	*Melbourne*	*Melbourne Children's Cardiology*

Legend. Centers in *italics* participate in both Part 1 and Part 2 of the study.



PART 4

Palliative and end-of-life care

Chapter 7

Advance Care Planning in Adults with Congenital Heart Diseases: current practices, preferences and needs of 8,285 adults from 32 countries

Manuscript almost ready for submission as:

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Abstract

Background

Adults with congenital heart diseases (CHD) are at high risk of premature death. To help prepare for the end of life, advance care planning (ACP) discussions are important. Previous studies have only examined ACP preferences and practices in adults with CHD in the United States and Canada. A global investigation is imperative.

Aims

The paper aims to describe the ACP practices, needs and preferences of adults with CHD around the globe and to investigate associations with patient-related factors.

Methodology

The present cross-sectional study is part of the APPROACH-IS II project. ACP preferences, needs and practices were measured using patient-reported surveys. Descriptive and multilevel analyses were used to describe the ACP variables around the globe and the associations with patient-related variables. A total of 8,285 patients with CHD (median age: 32 years, 54% women, 15% mild CHD, 58% moderate CHD, 27% complex CHD) from 53 centres, located in 32 countries across 6 continents, were included in the study.

Results

Overall, 55% of the participants reported having spoken with their doctor about how their health will be in the future and 9% had advance directives. According to 66% of the patients, the best time to initiate ACP is early in the disease trajectory. Most patients indicated being relatively comfortable talking about how their health will be in the future with their physician and about death. ACP varied widely across the different countries. Age, sex, CHD complexity and NYHA class were found to predict ACP factors.

Conclusion

Large differences in ACP factors were noticed around the world. More research is needed on the preferences of patients with regard to how and by whom ACP conversations should be initiated, what topics should be discussed and how family members can be involved in these discussions.

Introduction

Adults with a congenital heart disease (CHD) represent a remarkable success story in the field of cardiovascular disease management and cardiac surgery.[1] Survival of children with CHD was only around 15% in the 1950s.[1] As a result of improvements in the diagnosis and treatment of CHD, infant mortality survival has greatly improved, and nowadays, over 90% of children born with CHD reach adulthood.[2,3] However, behind this success story, many challenges still persist for these patients.

A large fraction of patients with CHD remain symptomatic and at risk for comorbidities, reduced exercise capacity, and need for further interventional or surgical procedures, although the majority of patients had surgery for their CHD in childhood.[1,4] They are not cured, but rather palliated, and therefore remain considered patients with a chronic disease for the rest of their lives.[1]

Moreover, the improved life expectancy has led to changes in the demographic profile of these patients.[1,5] The population is not only growing in absolute numbers, but also aging.[6] The number of adults with CHD of 60 years or older has increased 10-fold from 2000 to 2013 and is now estimated to comprise about 5-10% of the overall CHD population.[6,7] This also means that many patients now also develop typical age-related comorbidities.[8] More than half of the CHD patients were found to have at least one acquired comorbidity and almost 25% had two or more comorbidities.[9]

Furthermore, patients with CHD remain at high risk of premature death, with the median age at death being 55 years.[10] The most common causes of death are sudden cardiac death and heart failure, with sudden death being more prevalent in young people with CHD and heart failure more predominant in the aging population.[10,11] Consequently, patients and their families should be prepared for both unexpected and predictable deaths, which are sometimes preceded by a period of declining health.[5]

To help prepare for the end of life, advance care planning (ACP) is needed. ACP can be defined as *"a process that supports and empowers individuals at any stage of their lives or disease process to consider, communicate, and document preferences for future health care"*.[5] ACP aims to identify personal values and goals in an effort to align future medical treatment and care with these personal

beliefs and convictions.[5,12] ACP is often seen as part of palliative care. In ACP discussions, patients can indicate which treatments and measures they would prefer in specific situations.[5] These discussions can take place early in the disease course or at the end of life.[13]

Different international organisations, such as the American Heart Association[14], the European Society of Cardiology [15], and the European Association for Palliative Care [16], have recommended palliative care, including ACP, for people with advanced cardiac diseases. Ideally, ACP should be an integral part of routine care for adults with CHD, reviewed annually and in accordance with disease progression.[5] Previous studies have shown that ACP discussions can positively affect the quality of life, spiritual well-being, number of hospitalisations, amount of inappropriate care, the chance of dying at the preferred place and costs in general.[17-19] Indeed, the benefits of ACP for patients, family members, healthcare systems and societies are clear.[5]

In adults with CHD, only a few studies have investigated the use and preferences with regard to ACP, and all these studies were conducted in Canada or the United States.[20-24] Indeed, information about ACP from adults with CHD beyond North America is completely lacking. It is very likely that there are differences in end-of-life decision-making around the world, as there are many cultural differences in coping with death and bereavement.[25,26] Some researchers have even stated that choices around end-of-life decision making might be more related to ethnicity and culture than to patient-related factors, such as age, educational level and other socio-demographic variables.[26,27] Hence, a global investigation of ACP needs and preferences of adults with CHD, in which associations with geographic and patient-related factors are investigated, is imperative. This will help to understand the needs of patients and tailor care to these specific needs.

Therefore, the aim of this paper is to describe the ACP current practices, needs and preferences of adults with CHD around the globe and to investigate associations with patient-related factors.

Methods

Design

The present study is part of the larger 'Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study II' (APPROACH-IS II). APPROACH-IS II is a cross-sectional descriptive global multicentric study in which 53 centres have participated, located in 32 countries across 6 continents. It is the follow-up project of APPROACH-IS.[28] The study consists of two parts: one part aims to understand patient-reported outcomes and one part examines frailty and cognitive functioning in older patients with CHD. More information with regard to the methodology of the APPROACH-IS II project can be found elsewhere.[29] The study protocol of APPROACH-IS II is recorded at ClinicalTrials.gov (NCT04902768).

Participants

The recruitment goal for each participating centre was 200 patients. Patients were eligible to be included in APPROACH-IS II if they fulfilled the following criteria: (i) diagnosed with CHD, defined and *" a gross structural abnormality of the heart and/or intra-thoracic great vessels that is actually or potentially of functional significance (including mild, moderate, and complex heart defects)"* [30], (ii) aged 18 years or older at the start of the study, (iii) diagnosed with CHD before the age of 10 years (to have at least 8 years of experience of living with CHD), (iv) being in follow-up at an adult CHD centre, and (v) demonstrated physical, cognitive and language abilities required to complete self-report questionnaires. Patients who had heart transplantation were excluded from the study. Especially for this sub-study, one inclusion criterion was added: patients had to complete at least one question from the 'advance care planning'-questionnaire.

A total of 8,285 patients with CHD were included in the study. The sample characteristics are described in Table 1. The median age was 32 years. Most participants (54%) were women. A total of 7 patients indicated that their gender was non-binary. Almost half of the study population (48%) was married or lived with their partner and 42% of patients had a high school degree as the highest level of education. With 1,161 patients (14%) included, the United States were best represented in the sample, followed by Sweden (801; 10%) and Belgium

(676; 8%). Over half of the patients (58%) had a moderate CHD and most patients (54%) reported having NYHA Class I.

Data collection

Medical data were collected from the electronic health records and patients were asked to complete self-reported surveys at one moment in time. The data collection procedure varied in the different participating centres. Most patients were approached consecutively at the outpatient clinic of the hospital. The remaining patients were randomly selected from the institution's database and were asked to fill out the survey on paper, via a link to an online survey (on REDCap), or, in case of low literacy, over the phone.

Variables and instruments

ACP practices, preferences and needs were measured through seven self-reported questions. These questions were set up by the Steering Committee of APPROACH-IS II, which based themselves on a survey of Tobler and colleagues.[31,32] The questions and response options can be found in Table 2 and eTable 1 in the Supplementary Material.

Demographic variables and the New York Heart Association (NYHA) classification were patient-reported. Classification of the CHD was based on the Adult Congenital Heart Disease Anatomical and Physiological Classification system of Stout and colleagues.[33]

Ethics

The main study protocol was approved by the Institutional Review Board of the University Hospitals Leuven/KU Leuven (i.e., the coordinating centre). Furthermore, each participating centre obtained local ethics approval for the study execution in their centre. Written informed consent from patients was obtained if required by the local legislation. The legislation in certain regions specifies that written informed consent is unnecessary for survey studies. The study is conducted in accordance with the declaration of Helsinki.

The data management is in line with current worldwide privacy regulations and participant confidentiality was assured. Only non-identifiable data were shared across centres and outside the APPROACH-IS II consortium.

Data analyses

Descriptive statistics (medians, interquartile ranges and proportions) of the ACP current practices, preferences and needs were calculated for the overall sample and for the participating countries individually. Medians and interquartile ranges were reported, because the continuous variables were not normally distributed.

To increase the interpretability of the findings, the categorical variables (questions 1-6) have been dichotomized. For variables concerning how comfortable patients are, answers were dichotomized into ‘at least somewhat comfortable’ and ‘in the middle or uncomfortable’. With regard to (knowledge of) advance directives (ADs), the categories were ‘yes’ and ‘no or I don’t know’. Regarding the preference of patients on when to receive ACP, the categories were ‘before the patient gets sick, while still healthy’ (because most patients chose this answer possibility) and ‘other’.

The associations between patient-related variables (e.g., age, sex, marital status, complexity, and NYHA Class) and ACP practices, preferences and needs were estimated through multivariable general linear mixed models for the continuous variable (i.e., question 7: ‘how concerned are you about how your health will be’) and through generalised linear mixed models with a binomial distribution for the dichotomous variables. Doing so, a two-level structure in which patients were nested within centres could be modelled. The fixed variables were age, sex, complexity and NYHA class. The random variable was the centre in which they were under follow up. For the continuous variable, R^2 statistics were reported. These estimates can be used to express the percentage of explained variance by the model. For the dichotomous variables, only pseudo R^2 can be obtained, which is hard to interpret and difficult to compare with the R^2 of continuous variables. Therefore, pseudo R^2 values were not reported. For the general and generalised linear models, only patients for whom full data was available were included and the patients with a non-binary sex were left out (n=7,602; 92%). The assumptions of the general and generalised linear models were checked and were not found to be violated. The variance inflation factors (VIF) were all below 1.4, indicating that there was no collinearity between the included variables. Statistical analyses were performed in IBM SPSS Statistics for Windows version 27.

Table 1. Demographic and clinical characteristics of included patients (n=8,285)

Median age	32 years (IQR: 18) (available for 8,265 patients)
Sex	
Male	3797/8265 (45.9%)
Female	4461/8265 (54.0%)
Other	7/8265 (0.1%)
Marital status	
Never married	3823/8250 (46.3%)
Married or living with partner	3988/8250 (48.3%)
Divorced or widowed	415/8250 (5.0%)
Other	24/8250 (0.3%)
Highest level of education	
Did not complete high school	1224/8184 (15.0%)
High school	3431/8184 (41.9%)
Bachelors/college degree	2327/8184 (28.4%)
Master's degree or higher	1202/8184 (14.7%)
Country	
Argentina	142/8285 (1.7%)
Australia	184/8285 (2.2%)
Austria	313/8285 (3.8%)
Belgium	676/8285 (8.2%)
Botswana	17/8285 (0.2%)
Brazil	200/8285 (2.4%)
Bulgaria	200/8285 (2.4%)
Cameroon	42/8285 (0.5%)
Canada	151/8285 (1.8%)
Chile	191/8285 (2.3%)
Colombia	200/8285 (2.4%)
Denmark	198/8285 (2.4%)
Ethiopia	77/8285 (0.9%)
France	527/8285 (6.4%)
Greece	228/8285 (2.8%)

India	125/8285 (1.5%)
Italy	201/8285 (2.4%)
Japan	270/8285 (3.3%)
Malaysia	204/8285 (2.5%)
Malta	58/8285 (0.7%)
Netherlands	107/8285 (1.3%)
Norway	143/8285 (1.7%)
Pakistan	244/8285 (2.9%)
Portugal	244/8285 (2.9%)
Senegal	179/8285 (2.2%)
South Korea	209/8285 (2.5%)
Sweden	801/8285 (9.7%)
Switzerland	319/8285 (3.9%)
Taiwan	300/8285 (3.6%)
Turkey	41/8285 (0.5%)
United Kingdom	333/8285 (4.0%)
United States of America	1161/8285 (14.0%)
Disease complexity	
Simple	1164/7962 (14.6%)
Moderate	4630/7962 (58.2%)
Complex	2168/7962 (27.2%)
Self-reported limitations (NYHA Class)	
I	4417/8217 (53.8%)
II	2704/8217 (32.9%)
III	819/8217 (10.0%)
IV	277/8217 (3.4%)

Legend. NYHA=New York Heart Association; IQR=interquartile range

Results

Current practices

A total of 55% reported having had a conversation with their doctor about what their health might be like in the future (Table 2). This proportion is highest in the United States (73%) and Canada (70%) and lowest in Turkey (24%) (Figure 1A and eTable 1). Almost 9% indicated that they did not want to discuss with their physician how their health would be in the future. This is highest in Pakistan (31%) and Colombia (25%) and lowest in Ethiopia (1%) and Japan (1%) (eTable 1). Females and patients with a higher CHD complexity were more likely to have spoken with their physician about how their health will be in the future (Table 3).

When asking patients whether they had heard of the existence of ADs in their country, 42% of patients reported having heard about it, 33% of patients reported not having heard about it, while 24% of patients did not know (Table 2). The proportion of patients that heard about ADs was highest in the United States (80%) and lowest in Senegal (1%) (Figure 1B and eTable 1). Older patients, females, patients with great CHD complexity, and patients with NYHA class I were more likely than their counterparts to have heard about ADs in their country, above and beyond centre differences (Table 3).

A small proportion (9%) of patients reported having written down information about which care they would want in case they become seriously ill. Of these, 5% wrote it down in an official or legal document and 3% in an unofficial document. More than half of the participants (55%) did not tell anyone which care they wanted and 25% did not write down information but told at least one person which care they would want (Table 2). The proportion of patients with ADs was highest in the United States (24%) and Canada (21%) and lowest in Malta and Botswana, where no patients reported having ADs (Figure 1C and eTable 1). Older patients, patients with simple CHD complexity and high NYHA class are more likely to have advanced directives (Table 3).

Preferences

As the best time for healthcare providers to start talking about ACP, 66% of patients indicated that this is before the patient gets sick while still healthy (Table 2). A total of 28% thought these conversations should happen when a patient is

diagnosed with a life-threatening illness or complication. A tiny proportion (1%) reported that this should never happen. Except for patients from Turkey, Italy, and Colombia, more than 50% of the patients preferred to have these conversations while still feeling healthy (Figure 1D). In Colombia, most patients (62%) preferred to have these conversations when diagnosed with a life-threatening illness or complications. Patients with males and patients with a lower NYHA score were more likely to think that the best moment to provide ACP is before the patient gets sick while still healthy, when controlling for centre differences (Table 3).

When asking patients how comfortable they are talking with their doctor about their health in the future, most patients were at least somewhat comfortable (76%) (Table 2). Again, the United States (88%) and Canada (87%) scored highest, whereas only 57% of patients in Norway reported being somewhat comfortable talking about death (Figure 1E and eTable 1). Patients with NYHA I were more comfortable talking about what their health might be like in the future than their counterparts, when taking into account unmeasured centre differences (Table 3).

Less than half of the patients (42%) indicated that they are at least somewhat comfortable talking about death in general (Table 2). Brazil had the highest proportion of patients (63%) who felt at least somewhat comfortable talking about death, followed by Canada (62%), and the United States (57%) (Figure 1F and eTable 1). In Cameroon, only 21% of patients reported being comfortable talking about death, followed by Austria (22%) and Ethiopia (24%). Above and beyond centre influences, older patients, male patients and patients with CHD of simple complexity were more comfortable talking about death (Table 3).

Needs – concerned about the future

When asking patients how concerned they are about their health in the future on a scale from 0 to 10, 10 being the most concerned, the median overall response was 6 (Table 2). Large differences could be observed between different countries worldwide (Figure 1G). People from Sweden were the least concerned, with a median of 4, whereas people from Senegal, Botswana and Malaysia were the most concerned (median of 9). Above and beyond centre differences, older patients, females, patients with a great CHD complexity, and

with a higher NYHA class, were more likely to be more concerned about how their health will be in the future (Table 3). The entire model, including fixed and random efforts, explained 24.1% of the variance in how concerned patients were. Country differences explained 19.0% of the variance, whereas patient-related characteristics explained 7.9%.

Table 2. ACP preferences of adults with congenital heart diseases (n=8,285)

CURRENT PRACTICES	
Have you ever talked to a doctor about what your health might be like in the future (for example, symptoms that you might get or whether your health might worsen)?	
Yes	4534/8248 (55.0%)
No, but I want to talk about this with my doctor	2014/8248 (24.4%)
No, I don't want to talk about this with my doctor	711/8248 (8.6%)
I don't know	989/8248 (12.0%)
In your country, have you heard of a process in which people can write down information ahead of time about the care they want if they become seriously ill?	
Yes	3496/8238 (42.4%)
No	2735/8238 (33.2%)
I don't know	2007/8238 (24.4%)
Have you personally written down information about the care you would want in case you become seriously ill in the future? (n=8195)	
Yes, I have written down information in an official/legal document	431/8249 (5.2%)
Yes, I have written down information, although not in an official/legal document	279/8249 (3.4%)
No, but I have told at least one person what I would want	2048/8249 (24.8%)
No, and I have not told anyone what I would want	4522/8249 (54.8%)
I don't know	969/8249 (11.7%)
PREFERENCES	
In general, when is the best time for health providers (like doctors or nurses) to start talking with patients with congenital heart disease about planning in advance for care they would want if they become seriously ill?	
Before the patient gets sick, while healthy	5363/8186 (65.5%)
When diagnosed with a life-threatening illness or complication from heart disease	2311/8186 (28.2%)
When hospitalised with a life-threatening illness or complication from heart disease	309/8186 (3.8%)
When it is known that the patient does not have long to live	90/8186 (1.1%)
Never	113/8186 (1.4%)

How comfortable do you think you would be talking with your doctor about what your health might be like in the future?	
Very comfortable	3966/8260 (48.0%)
Somewhat comfortable	2276/8260 (27.6%)
In the middle (neither comfortable, nor uncomfortable)	1403/8260 (17.0%)
Somewhat uncomfortable	485/8260 (5.9%)
Very uncomfortable	130/8260 (1.6%)
In general, how comfortable are you talking about death?	
Very comfortable	1632/8227 (19.8%)
Somewhat comfortable	1799/8227 (21.9%)
In the middle (neither comfortable, nor uncomfortable)	2478/8227 (30.1%)
Somewhat uncomfortable	1298/8227 (15.8%)
Very uncomfortable	1020/8227 (12.4%)
NEEDS – CONCERNED ABOUT THE FUTURE	
On a scale from 0 to 10, how concerned are you about your health in the future? (10 being extremely concerned)	Median: 6 (IQR: 5) (n=8228)

Legend. IQR=interquartile range

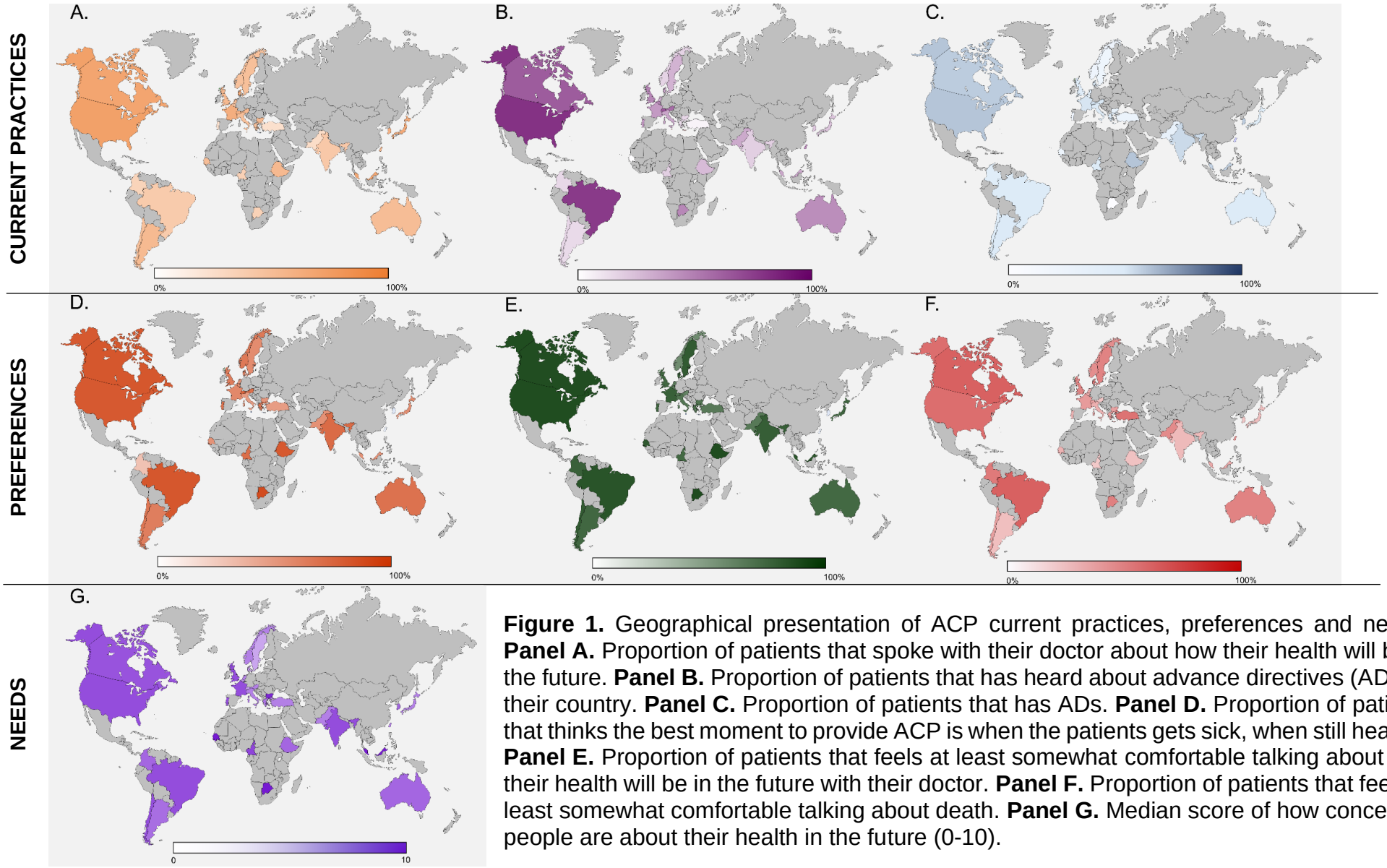

Figure 1. Geographical presentation of ACP current practices, preferences and needs. **Panel A.** Proportion of patients that spoke with their doctor about how their health will be in the future. **Panel B.** Proportion of patients that has heard about advance directives (ADs) in their country. **Panel C.** Proportion of patients that has ADs. **Panel D.** Proportion of patients that thinks the best moment to provide ACP is when the patients gets sick, when still healthy. **Panel E.** Proportion of patients that feels at least somewhat comfortable talking about how their health will be in the future with their doctor. **Panel F.** Proportion of patients that feels at least somewhat comfortable talking about death. **Panel G.** Median score of how concerned people are about their health in the future (0-10).

Table 3. Multilevel analyses of ACP current practices, preferences and needs (n=7,602)

	CURRENT PRACTICES			PREFERENCES			NEEDS
	Patients that have talked to their doctor about how their health will be in the future ‡	Patients that heard about advance directives in their country ‡	Patients that had advanced directives ‡	Patients that think the best moment to provide ACP is when the patients gets sick ‡	Patients that feel at least somewhat comfortable talking with their doctor about their health in the future ‡	Patients that feel at least somewhat comfortable talking about death ‡	Concerned about health in the future (0-10) *
Age	1.00 (0.99-1.00)	1.02 (1.01-1.02)	1.04 (1.03-1.04)	1.00 (0.99-1.00)	1.00 (0.99-1.01)	1.01 (1.00-1.01)	0.02 (0.002)
Sex							
Male	0.91 (0.82-0.99)	0.72 (0.64-0.79)	1.05 (0.88-1.25)	1.11 (1.00-1.22)	1.03 (0.92-1.14)	1.44 (1.31-1.59)	-0.29 (0.06)
Female	#	#	#	#	#	#	#
Complexity							
Simple	0.84 (0.71-0.99)	0.82 (0.69-0.99)	0.81 (0.59-1.10)	0.93 (0.79-1.11)	1.10 (0.91-1.33)	1.29 (1.09-1.52)	-0.42 (0.10)
Moderate	0.95 (0.85-1.07)	0.90 (0.79-1.01)	0.80 (0.66-0.98)	1.00 (0.89-1.13)	1.09 (0.96-1.24)	1.06 (0.95-1.19)	-0.06 (0.07)
Great	#	#	#	#	#	#	#
NYHA							
I	1.28 (0.98-1.68)	1.48 (1.09-2.01)	0.61 (0.40-0.93)	1.61 (1.22-2.13)	1.62 (1.21-2.22)	1.31 (0.99-1.73)	-1.77 (0.17)
II	1.12 (0.85-1.47)	1.17 (0.86-1.59)	0.72 (0.47-1.09)	1.28 (0.97-1.69)	1.19 (0.88-1.61)	1.29 (0.98-1.72)	-0.78 (0.17)
III	1.09 (0.81-1.48)	1.05 (0.75-1.47)	0.82 (0.52-1.31)	1.10 (0.81-1.49)	1.08 (0.77-1.50)	1.15 (0.84-1.56)	-0.29 (0.19)
IV	#	#	#	#	#	#	#
R^2	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*23.8%*
Semipartial R^2 centre differences	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*19.0%*
Semipartial R^2 patient characteristics	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*7.8%*

Legend. # = reference category; ‡ Values in table are Odds Ratios (95% Confidence Intervals); * Values in table are Estimates (Standard Error); Random effect = centre. Colour coding refers to significance of estimate, ACP=advance care planning, NYHA=New York Heart Association

N.S.	< 0.05	<0.01	<0.001

Discussion

Overall, we found that nearly half of the sample did not speak with their physician about their future health and only a small proportion of patients had ADs. According to patients, the best time to initiate ACP is early in the disease trajectory and most patients indicated being rather comfortable talking about how their health will be in the future with their physician and about death. Big differences were found around the world and age, sex, CHD complexity and NYHA classification were found to predict ACP preferences, current practices and needs.

ACP practices, preferences and needs of the overall sample

Nearly half of the sample did not have conversations with their physician about their future health, although most of these patients indicated they wanted to have such conversations. This proportion is, however, still much larger than the proportions from previous Canadian and American studies that indicated that only 1%-29% of patients had end-of-life or ACP discussions with their providers.[22,31,32,34] A possible explanation for the different proportions is that slightly different concepts were measured. Indeed, discussing future health is not necessarily the same as having an ACP conversation, in which patients' wishes regarding end-of-life care are discussed. Moreover, the prior Canadian studies were executed more than 10 years ago.[31,32] It is clear that ACP has gained increasing attention over the past years.[35] Moreover, in our study, only 9% reported to have written information about the care they would want. Altogether, this shows that there is room for improvement of ACP provision in adults with CHD worldwide. This is not surprising as earlier studies from the United States and Belgium showed that provision of end-of-life care to adults with CHD is still very much focused on intense and potentially avoidable care at the end of life.[10,36] ACP conversations and ADs could help to reduce inappropriate and unnecessary healthcare provisions at the end of life.

Globally, a large majority of patients indicated that ACP discussions should occur early in the disease course. This is in line with earlier American studies.[34,37] Strangely enough, another study indicated that the most common barrier to ACP was not feeling sick enough to discuss end-of-life care with a physician (42% of participants).[22] When looking at healthcare providers'

perspective on the best timing for the initiation of ACP conversations, a different story emerges. About 63% of clinicians thought that patients were not ready for end-of-life discussions if the estimated life expectancy was over 5 years and 79% of providers thought that ACP conversations with patients with a life expectancy of over 10 years was not appropriate.[38] With regard to the timing, 12% of providers indicated that discussions should be initiated when the patient is first diagnosed with a life-threatening illness or complication, 2% thought this should occur when the patient is hospitalised with a life-threatening illness or complication, and 8% preferred to wait until multiple complications or hospitalisations have occurred.[21]

In general, patients do not seem to be very concerned about how their health will be in the future (median: 6/10). For patients who are very concerned, this can imply that they need ACP conversations or that they had ACP conversations and are more aware of how their health will be like in the future. When looking at the R^2, country differences explained 19% of the variance, whereas patient-related characteristics explained only 8% of the variance. This confirms the hypothesis that cultural or geographic factors impact ACP more than patient-related factors.[26,27]

The results described above should be interpreted with care, because there are important restrictions to the representativeness and the generalisability of the findings to the entire CHD population. Many countries are not represented in this sample and there is an overrepresentation of high-income and catholic and protestant countries. Additionally, selection bias might have taken place since patients who are physically or mentally unable to fill out surveys have not been included in this sample. Hence, the sample does not entirely represent the global ACHD population.

Country differences in ACP practices, preferences and needs

ACP provision seems to be a step ahead in the United States and Canada. Patients from Canada and the United States had the highest scores on most items. These were also the countries where all research regarding ACP in adults with CHD has taken place so far.[21,31,32,36] The great attention for ACP is probably the result of numerous large-scale campaigns about the importance of ADs and ACP that the general population and chronic patients were exposed to over the past years.[35,39] Indeed, also in the general population of the United States and

Canada, much attention is provided to ACP. Approximately 37% of all US citizens have an AD[39] and 59% of Canadians talked to a family member about the care they want to receive at the end of life.[35] In our study, 73% of Americans and 70% of Canadians had conversations with regard to their future health with their physicians. These proportions are in line with the 69% of adults with CHD that indicated to be willing to have ACP discussions in a previous American study.[22] In our study, 24% of Americans and 21% of Canadians had ADs. These numbers are still rather low, as previous studies from US and Canada have shown that both providers and patients recognised ADs as important.[21,40] A broad range (5% to 42%) of proportions with regard to the completion of ADs in adults with CHD was found in previous studies.[24,34,36,40]

Conversely, in some countries, such as Pakistan and Turkey, there seems to be only limited attention to ACP. Respectively 27% and 24% of patients from Pakistan and Turkey reported having had conversations about ACP, and 3% and 2% had ADs, respectively. Moreover, it is remarkable that patients from Cameroon and Ethiopia have difficulties talking about death, as we observed that only a small proportion (<25%) feels at least somewhat comfortable talking about death. It can be assumed that this is due to influences of culture and religion, as we know that the view on the end and end-of-life decisions are influenced by culture and religion.[41] The dimensions of Inglehart and Welzel, survival versus self-expression values or the traditional versus secular-rational values, could explain part of the differences.[42] Pakistan, as well as Turkey and Ethiopia are part of the African-Islamic cluster, which means that they share cultural values.[42] These countries are focused rather on traditional values (e.g., the importance of religion, parent-child ties, often no acceptance of euthanasia) and survival values (e.g., emphasis on the economic and physical security). Future research should investigate in more detail the obtained geographical differences and the role of cultural values. The geographic and cultural differences indicate that local preferences should be taken into account and diverse approaches are needed across countries when trying to improve or implement ACP practices.

The results with regard to country differences are novel and shed light on the differences between the included countries. However, the results should be interpreted with caution. A non-random selection of centres was made. Hence, the included patients might not be entirely representative for the CHD population

in this country. The results were generalised for the entire country to facilitate interpretation, but, therefore, the data should be interpreted with care.

Individual characteristics associated with ACP practices, preferences and needs

Older patients were more likely to have heard about ADs and to have ADs. A possible explanation is that, for these patients, the life expectancy is shorter, compared to their counterparts, and therefore, they could be more concerned with the end of life. Participants with a simpler CHD complexity and patients with a lower NYHA class were more comfortable talking about how their health will be in the future and about death. This could be because they are still healthy and the end of life seems very far away. However, these hypotheses could not be investigated in more detail in this study. Hence, they need to be studied further. The investigation of the associations with patient-related factors will facilitate the understanding of variation in ACP preferences, practices and needs and will help to identify the patients who are the most in need of ACP. Since the study is cross-sectional, causality within the found associations cannot be determined.

Implications for practice and research

We found that 9% did not want to discuss future health with their physician and that 1% indicated they never wanted to have these conversations. As these proportions are relatively low, this should be seen as an encouragement for healthcare workers to have such conversations with their patients. As it was found that older patients, females, and patients with a higher CHD complexity and NYHA Class were more concerned about their health, healthcare providers should pay additional attention trying to measure and intervene upon their ACP needs. Indeed, the identified personal factors associated with ACP factors will help to identify the patients who are the most in need of ACP.

Large differences in ACP practices, preferences and needs were noticed around the world. This indicates that different approaches with regard to the implementation of ACP practices might be needed across different countries.

Although some information with regard to ACP was measured in this study, more research is needed on patients' preferences worldwide. Indeed, it remains unknown how and by whom such conversations should be initiated, which topics should be discussed and how family members can be involved in these discussions. Furthermore, future studies should focus on the identification of

appropriate outcome measures of ACP and make sure such outcome measures are truly patient-specific. Meanwhile, intervention studies on how ACP practices can be improved and good measurement tools to investigate the effects of ACP interventions should be developed.

Methodological considerations

This is the first study to shed light on variables related to ACP in adults with CHD worldwide. The study has a large sample of over 8,000 adults with CHD and has included centres from all continents. There are also a couple of important limitations that should be mentioned. First, readers should keep in mind that selection bias might have influenced the generalisability of the findings, both for the data reported for the overall sample and for the data reported on country level. A second limitation is that the questionnaire has not been tested in the different countries in advance to see whether the questions and concepts were interpreted in the same way in all participating countries. No country-specific operationalization was performed. This could have created issues of linguistic, conceptual and semantic equivalence. Third, the COVID-19 pandemic might have impacted the data, as the data reported in this study are measured partly before the start of the COVID-19 pandemic and partly during the pandemic. However, Moons and colleagues have investigated the impact of the COVID-19 pandemic on the data of APPROACH-IS II in three centres and found that the pre- to peri-pandemic changes were negligibly small.[43] More specifically, the pre-pandemic and post-pandemic difference in how concerned patients were about their health remained approximately the same and was not significantly different.[43] Fourth, the data on ACP practices and preferences could be subject to socially desirable responses. Indeed, it could be that patients do not dare to indicate that they do not feel comfortable to discuss ACP with their physician. In Pakistan, the responses were gathered over the phone, because of low literacy levels of the study population. Certainly, in these patients, the risk of socially desirable answers should be kept in mind.

Conclusion

This is the first study to provide an overview of ACP practices, preferences and needs of adults with CHD worldwide. Overall, nearly half of the sample did not speak with their physician about their future health and only a small proportion of patients had advance directives. According to patients, the best time to initiate ACP is early in the disease trajectory. Most patients indicated being rather comfortable talking about how their health will be in the future with their physician and about death. Large differences in ACP practices were noticed around the world. Furthermore, age, sex, complexity and NYHA class were found to predict ACP factors. More research is needed on the global differences in ACP practices, on the preferences of patients with regard to how and by whom ACP conversations should be initiated, which topics should be discussed and how family members can be involved in these discussions.

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Declaration of interest

The authors do not have declarations of interest with regard to this study.

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Supplementary material

eTable 1. ACP preferences of adults with CHD in the participating countries (n=8,285)

	CURRENT PRACTICES											PREFERENCES														NEEDS
	Have you ever talked to a doctor about what your health might be like in the future (for example, symptoms that you might get or whether your health might worsen)? N (%) *Missing = 37*				In your country, have you heard of a process in which people can write down information ahead of time about the care they want if they become seriously ill? N (%) *Missing=47*			Have you personally written down information about the care you would want in case you become seriously ill in the future? N (%) *Missing=36*					In general, when is the best time for health providers (like doctors or nurses) to start talking with patients with congenital heart disease about planning in advance for care they would want if they become seriously ill? N (%) *Missing = 99*					How comfortable do you think you would be talking with your doctor about what your health might be like in the future? N (%) *Missing = 25*					In general, how comfortable are you talking about death? N (%) *Missing = 58*					On a scale from 0 to 10, how concerned are you about your health in the future? (10 being extremely concerned) Median (IQR) *Missing=57*
	Yes	No, but I want to talk about this with my doctor	No, I don't want to talk about this with my doctor	I don't know	Yes	No	I don't know	Yes, in an official/legal document	Yes, although not in an official/legal document	No, but I have told at least one person	No, and I have not told anyone	I don't know	Before the patient gets sick, while healthy	When diagnosed with a life-threatening illness or complication	When hospitalised with a life-threatening illness	When it is known that the patient does not have long to live	Never	Very comfortable	Somewhat comfortable	In the middle	Somewhat uncomfortable	Very uncomfortable	Very comfortable	Somewhat comfortable	In the middle	Somewhat uncomfortable	Very uncomfortable	
Total (N=8285)	**4534 (55)**	**2014 (24)**	**711 (9)**	**989 (12)**	**3496 (42)**	**2735 (33)**	**2007 (24)**	**431 (5)**	**279 (3)**	**2048 (25)**	**4522 (55)**	**969 (12)**	**5363 (66)**	**2311 (28)**	**309 (4)**	**90 (1)**	**113 (1)**	**3966 (48)**	**2276 (28)**	**1403 (17)**	**485 (6)**	**130 (2)**	**1632 (20)**	**1799 (22)**	**2478 (30)**	**1298 (16)**	**1020 (12)**	**6 (5.0)**
Argentina	76 (54)	33 (23)	16 (11)	17 (12)	21 (15)	58 (41)	63 (44)	5 (4)	2 (1)	38 (27)	67 (47)	30 (21)	90 (63)	42 (30)	4 (3)	1 (1)	5 (4)	87 (61)	19 (13)	23 (16)	10 (7)	3 (2)	16 (11)	20 (14)	63 (44)	21 (15)	22 (15)	6 (4.8)
Australia	94 (51)	45 (25)	19 (10)	25 (14)	82 (45)	58 (32)	44 (24)	6 (3)	2 (1)	37 (20)	125 (68)	14 (8)	127 (69)	49 (27)	3 (2)	2 (1)	2 (1)	94 (51)	42 (23)	34 (18)	11 (6)	3 (2)	31 (17)	58 (32)	50 (27)	30 (16)	14 (8)	6 (4.0)
Austria	169 (55)	61 (20)	33 (11)	46 (15)	176 (57)	14 (5)	117 (38)	7 (2)	11 (4)	97 (31)	157 (51)	36 (12)	214 (71)	62 (20)	13 (4)	5 (2)	9 (3)	105 (34)	84 (27)	80 (26)	34 (11)	6 (2)	28 (9)	42 (14)	122 (39)	66 (21)	51 (17)	5 (5.0)
Belgium	304 (45)	154 (23)	92 (14)	122 (18)	325 (48)	221 (33)	127 (19)	9 (1)	13 (2)	183 (27)	413 (61)	54 (8)	369 (56)	239 (36)	37 (6)	5 (1)	10 (2)	285 (42)	168 (25)	146 (22)	69 (10)	6 (1)	102 (15)	118 (18)	211 (31)	150 (22)	89 (13)	4 (4.0)

Botswana	6 (35)	8 (47)	3 (18)	0 (0)	8 (47)	8 (47)	1 (6)	0 (0)	0 (0)	3 (18)	13 (76)	1 (6)	15 (88)	2 (12)	0 (0)	0 (0)	0 (0)	12 (71)	3 (18)	1 (6)	1(6)	0 (0)	6 (38)	2 (13)	1 (6)	2 (13)	5 (31)	9 (2.0)
Brazil	81 (41)	91 (46)	24 (12)	4 (2)	155 (78)	35 (18)	10 (5)	1 (1)	3 (2)	35 (18)	154 (77)	7 (4)	165 (83)	24 (12)	4 (2)	0 (0)	7 (4)	148 (74)	20 (10)	22 (11)	9 (5)	1 (1)	89 (45)	35 (18)	39 (20)	20 (10)	17 (9)	7 (4.0)
Bulgaria	109 (55)	39 (20)	24 (12)	28 (14)	33 (17)	88 (44)	79 (40)	4 (2)	2 (1)	33 (17)	133 (67)	28 (14)	105 (53)	67 (34)	11 (6)	7 (4)	10 (5)	101 (51)	37 (19)	47 (24)	13 (7)	2 (1)	43 (22)	32 (16)	48 (24)	28 (14)	49 (25)	9 (2.9)
Cameroon	15 (36)	22 (52)	1 (2)	4 (10)	8 (19)	22 (52)	12 (29)	1 (2)	1 (2)	7 (17)	23 (55)	10 (24)	30 (71)	10 (24)	1 (2)	0 (0)	1 (2)	23 (55)	8 (19)	4 (10)	6 (14)	1 2)	6 (14)	3 (7)	10 (24)	9 (21)	14 (33)	7 (4.4)
Canada	104 (70)	23 (15)	7 (5)	15 (10)	97 (64)	27 (18)	27 (18)	21 (14)	11 (7)	65 (43)	49 (32)	5 (3)	124 (83)	19 (13)	6 (4)	0 (0)	1 (1)	88 (58)	44 (29)	9 (6)	9 (6)	1 (1)	48 (32)	46 (30)	17 (11)	23 (15)	17 (11)	7 (3.8)
Chile	93 (49)	66 (35)	5 (3)	25 (13)	31 (16)	75 (40)	82 (44)	5 (3)	3 (2)	55 (29)	85 (45)	42 (22)	126 (68)	48 (26)	6 (3)	2 (1)	3 (2)	106 (56)	46 (24)	28 (15)	7 (4)	2 (1)	45 (24)	26 (14)	60 (32)	35 (18)	24 (13)	7 (4.0)
Colombia	67 (34)	49 (25)	50 (25)	33 (17)	31 (16)	98 (49)	71 (36)	4 (2)	4 (2)	67 (34)	57 (29)	67 (34)	60 (30)	123 (62)	13 (7)	2 (1)	2 (1)	81 (41)	75 (38)	28 (14)	8 (4)	8 (4)	37 (19)	66 (34)	60 (30)	20 (10)	14 (7)	6 (4.0)
Denmark	131 (66)	34 (17)	13 (7)	19 (10)	65 (33)	79 (41)	51 (26)	7 (4)	7 (4)	38 (19)	125 (63)	20 (10)	118 (61)	66 (34)	7 (4)	2 (1)	1 (1)	101 (51)	55 (28)	27 (14)	13 (7)	1 (1)	43 (22)	63 (32)	47 (24)	28 (14)	15 (8)	4 (5.0)
Ethiopia	41 (54)	21 (28)	1 (1)	13 (17)	20 (27)	21 (28)	34 (45)	6 (8)	13 (17)	6 (8)	17 (22)	35 (45)	62 (82)	5 (7)	4 (5)	1 (1)	4 (5)	48 (63)	19 (25)	3 (4 (5)	2 (4)	(3)	5 (7)	13 (17)	13 (17)	18 (24)	26 (35)	6 (3.0)
France	328 (62)	96 (18)	33 (6)	69 (13)	208 (40)	172 (33)	144 (27)	19 (4)	22 (4)	131 (25)	275 (52)	77 (15)	303 (59)	184 (36)	25 (5)	0 (0)	5 (1)	312 (59)	100 (19)	74 (14)	33 (6)	7 (1)	124 (24)	81 (16)	146 (28)	81 (16)	88 (17)	7 (3.0)
Greece	111 (49)	76 (33)	17 (7)	24 (11)	32 (14)	115 (50)	81 (36)	5 (2)	9 (4)	36 (16)	153 (67)	25 (11)	154 (68)	68 (30)	3 (1)	2 (1)	1 (0)	74 (32)	88 (39)	46 (20)	16 (7)	4 (2)	45 (20)	42 (18)	68 (30)	21 (9)	52 (23)	6 (4.4)
India	53 (42)	39 (31)	11 (9)	22 (18)	24 (19)	55 (44)	46 (37)	10 (8)	7 (6)	23 (18)	44 (35)	41 (33)	91 (73)	22 (18)	5 (4)	1 (1)	6 (5)	75 (60)	24 (19)	19 (15)	3 (2)	4 (3)	20 (16)	14 (11)	45 (36)	11 (9)	35 (28)	7 (4.0)
Italy	101 (50)	27 (13)	23 (11)	50 (25)	70 (35)	41 (21)	87 (44)	5 (3)	5 (3)	45 (23)	108 (54)	36 (18)	98 (49)	91 (46)	5 (3)	0 (0)	4 (2)	68 (34)	69 (34)	54 (27)	7 (3)	3 (1)	21 (11)	41 (21)	81 (41)	30 (15)	26 (13)	5 (5.0)
Japan	176 (66)	56 (21)	3 (1)	33 (12)	63 (23)	123 (46)	84 (31)	4 (1)	7 (3)	36 (13)	170 (63)	52 (19)	150 (56)	100 (37)	11 (4)	4 (1)	2 (1)	128 (48)	76 (28)	58 (22)	5 (2)	2 (1)	21 (8)	48 (18)	132 (49)	34 (13)	33 (12)	5 (4.0)
Malaysia	140 (69)	35 (17)	6 (3)	23 (11)	70 (34)	36 (18)	97 (48)	17 (8)	19 (9)	71 (35)	42 (21)	55 (27)	109 (53)	80 (39)	10 (5)	0 (0)	5 (2)	93 (46)	76 (37)	27 (13)	7 (3)	1 (0)	25 (12)	43 (21)	87 (43)	32 (16)	14 (7)	9 (3.0)
Malta	31 (53)	9 (16)	7 (12)	11 (19)	11 (19)	22 (38)	25 (43)	0 (0)	0 (0)	12 (21)	34 (59)	12 (21)	41 (73)	11 (20)	1 (2)	2 (4)	1 (2)	33 (57)	18 (31)	6 (10)	1 (2)	0 (0)	9 (16)	14 (24)	24 (41)	6 (10)	5 (9)	7 (3.3)
Netherlands	53 (50)	30 (28)	10 (9)	14 (13)	33 (31)	50 (47)	23 (22)	2 (2)	2 (2)	30 (28)	66 (62)	7 (7)	54 (51)	44 (42)	4 (4)	0 (0)	3 (3)	35 (33)	34 (32)	24 (22)	12 (11)	2 (2)	12 (11)	22 (21)	33 (31)	22 (21)	17 (16)	5 (4.7)
Norway	69 (48)	49 (34)	16 (11)	9 (6)	25 (18)	94 (66)	23 (16)	1 (1)	2 (1)	23 (16)	104 (73)	13 (9)	80 (57)	58 (41)	3 (2)	0 (0)	0 (0)	53 (37)	28 (20)	30 (21)	26 (18)	6 (4)	35 (25)	28 (20)	38 (27)	25 (18)	16 (11)	5 (4.0)
Pakistan	65 (27)	93 (38)	74 (31)	10 (4)	82 (34)	145 (59)	17 (7)	4 (2)	3 (1)	40 (16)	184 (76)	12 (5)	131 (54)	80 (33)	14 (6)	3 (1)	13 (5)	130 (53)	31 (13)	62 (25)	6 (2)	15 (6)	81 (33)	30 (12)	81 (33)	16 (7)	36 (15)	5 (7.5)
Portugal	126 (52)	55 (23)	39 (16)	24 (10)	100 (41)	126 (52)	18 (7)	2 (1)	3 (1)	61 (25)	151 (62)	26 (11)	171 (70)	62 (26)	6 (2)	3 (1)	1 (0)	117 (48)	68 (28)	47 (19)	7 (3)	5 (2)	32 (13)	43 (18)	88 (36)	40 (16)	40 (16)	7 (4.0)
Senegal	91 (51)	71 (40)	14 (8)	3 (2)	1 (1)	164 (92)	14 (8)	2 (1)	2 (1)	35 (20)	140 (78)	0 (0)	96 (54)	44 (25)	24 (13)	15 (8)	0 (0)	38 (21)	108 (60)	14 (8)	16 (9)	3 (2)	9 (5)	45 (25)	18 (10)	64 (36)	43 (24)	9 (2.0)
South Korea	124 (60)	58 (28)	5 (2)	21 (10)	46 (22)	112 (54)	51 (24)	13 (6)	30 (14)	55 (26)	64 (31)	47 (22)	164 (78)	33 (16)	3 (1)	7 (3)	2 (1)	41 (20)	94 (45)	58 (28)	13 (6)	3 (1)	15 (7)	32 (15)	87 (42)	39 (19)	36 (17)	6 (2.0)
Sweden	392 (49)	216 (27)	62 (8)	127 (16)	238 (30)	353 (45)	201 (25)	8 (1)	8 (1)	104 (13)	633 (80)	42 (5)	522 (66)	228 (29)	29 (4)	7 (1)	6 (1)	341 (43)	304 (38)	106 (13)	43 (5)	7 (1)	154 (19)	235 (30)	236 (30)	122 (15)	47 (6)	4 (4.3)

Switzer-land	192 (60)	61 (19)	22 (7)	44 (14)	213 (67)	34 (11)	72 (23)	24 (8)	8 (3)	105 (33)	149 (47)	33 (10)	242 (77)	58 (18)	13 (4)	2 (1)	1 (0)	135 (42)	83 (26)	77 (24)	16 (5)	7 (2)	54 (17)	62 (19)	112 (35)	59 (19)	31 (10)	4 (4.0)
Taiwan	163 (54)	74 (25)	21 (7)	42 (14)	144 (48)	41 (14)	115 (38)	10 (3)	8 (3)	77 (26)	153 (51)	51 (17)	187 (63)	94 (31)	15 (5)	2 (1)	1 (0)	110 (37)	77 (26)	91 (30)	19 (6)	2 (1)	63 (21)	69 (23)	121 (40)	35 (12)	11 (4)	5 (4.0)
Turkey	10 (24)	23 (56)	3 (7)	5 (12)	2 (5)	21 (51)	18 (44)	1 (2)	0 (0)	0 (0)	10 (24)	30 (73)	20 (49)	15 (37)	3 (7)	0 (0)	3 (7)	9 (22)	18 (44)	10 (24)	2 (5)	2 (5)	11 (28)	11 (28)	4 (10)	9 (23)	5 (13)	5 (4.0)
United Kingdom	181 (54)	85 (26)	27 (8)	40 (12)	157 (47)	128 (38)	48 (14)	5 (2)	9 (3)	83 (25)	218 (65)	18 (5)	216 (65)	103 (31)	10 (3)	3 (1)	1 (0)	152 (46)	96 (29)	55 (17)	23 (7)	7 (2)	68 (20)	92 (28)	84 (25)	44 (13)	44 (13)	7 (3.1)
United States	838 (73)	215 (19)	30 (3)	67 (6)	925 (81)	99 (9)	125 (11)	223 (19)	63 (5)	417 (36)	406 (35)	43 (4)	929 (81)	180 (16)	16 (1)	12 (1)	3 (0)	743 (65)	264 (23)	92 (8)	37 (3)	14 (1)	334 (29)	323 (28)	252 (22)	158 (14)	84 (7)	7 (3.3)

Legend. IQR=interquartile range

Chapter 8

Last year of life of adults with congenital heart diseases: causes of death and patterns of care

This chapter is published as:

Van Bulck L, Goossens E, Morin L, et al. Last year of life of adults with congenital heart diseases: causes of death and patterns of care. European Heart Journal. 2022; 43(42):4483–4492. Peer reviewed.

Abstract

Background and aims**:** Although the life expectancy in adults with congenital heart diseases (CHD) has increased dramatically over the past five decades, still a substantial number of patients dies prematurely. To gain understanding in the trajectories of dying in adults with CHD, the last year of life warrants further investigation. Therefore, our study aimed to 1) define the causes of death and 2) describe the patterns of healthcare utilisation in the last year of life of adults with CHD.

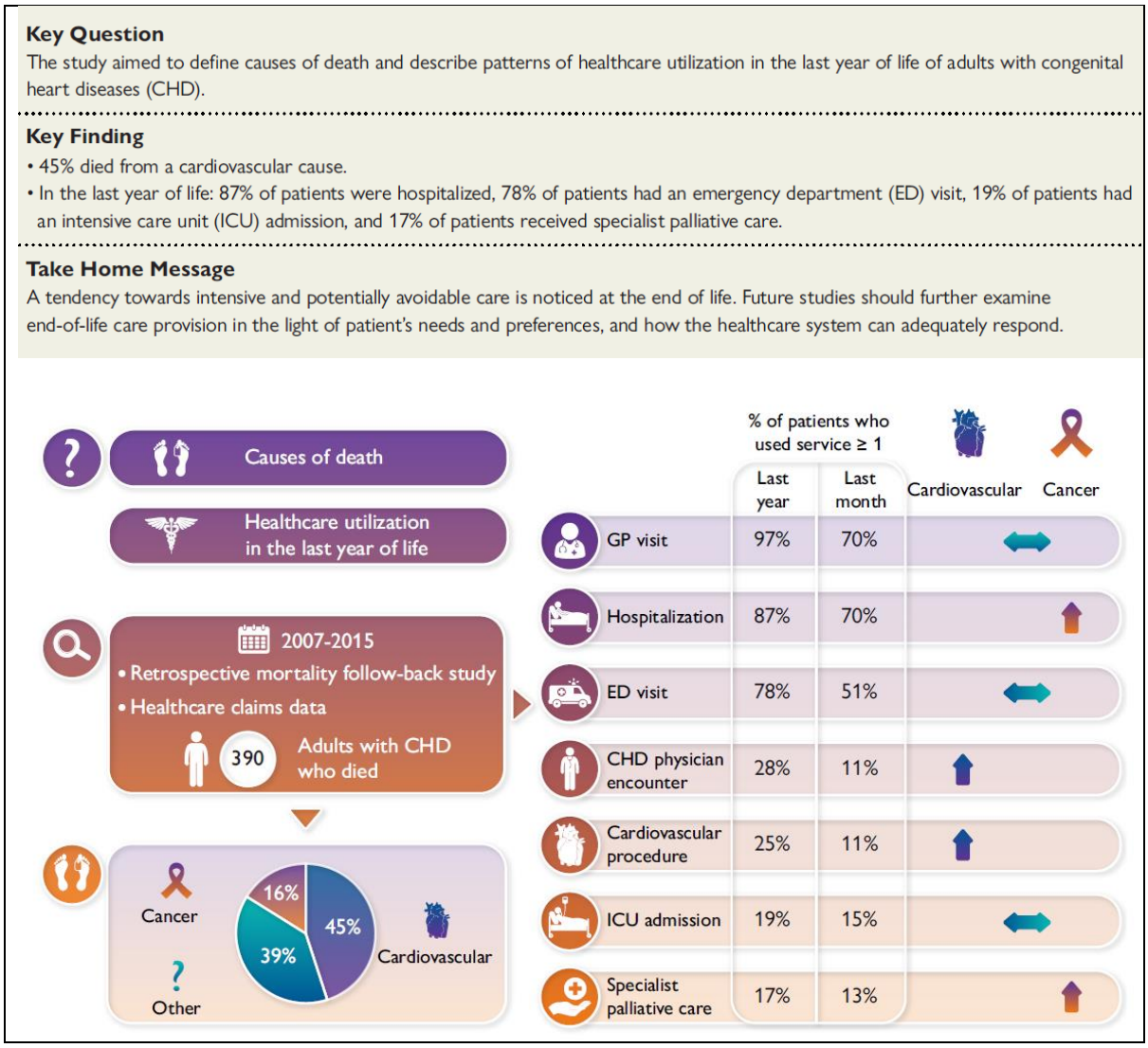
Methods and Results: This retrospective mortality follow-back study used healthcare claims and clinical data from BELCODAC, which includes patients with CHD from Belgium. Healthcare utilisation comprises cardiovascular procedures, CHD physician contacts, general practitioner visits, hospitalisations, emergency department (ED) visits, intensive care unit (ICU) admissions, and specialist palliative care and was identified using nomenclature codes. Of the 390 included patients, almost half of the study population (45%) died from a cardiovascular cause. In the last year of life, 87% of patients were hospitalised, 78% of patients had an ED visit, and 19% of patients had an ICU admission. Specialist palliative care was provided to 17% of patients, and to only 4% when looking at the patients with cardiovascular causes of death.

Conclusions: There is a high use of intensive and potentially avoidable care at the end of life. This may imply that end-of-life care provision can be improved. Future studies should further examine end-of-life care provision in the light of patient's needs and preferences, and how the healthcare system can adequately respond.

Keywords

Cause of death, Congenital Heart Disease, End-of-life, Healthcare utilization, Hospitalisations, Palliative Care

Structured graphical abstract



Legend. CHD=congenital heart disease; ED=emergency department; GP=general practitioner; ICU=intensive care unit; A horizontal arrow indicates no significant difference between the two groups and a vertical arrow indicates significantly more healthcare use for this group in the last year of life.

Introduction

Over the past five decades, patients with congenital heart disease (CHD) have experienced a considerable increase in their life expectancy.[1] For instance, nowadays, 97% of children with CHD reach adulthood, compared to 85% two decades ago.[2,3] Despite these improvements, a large fraction of adults with CHD remains symptomatic and at high-risk for premature death (median age at death is still below 50 years).[4] Long term sequalae, such as heart failure and arrhythmias, become increasingly frequent as patients age, with a negative impact on the quality of life and overall survival.[5]

Indeed, the trajectories that patients follow towards death depend upon the cause of death and presence of long term sequalae or comorbidities.[6,7] It is likely that there will be a group of patients characterized by sudden death, a group with a rapid decline (typically for cancer patients), and a group of patients with intermittent serious episodes of complications (typically for patients with some form of organ failure).[8] Prior studies that have reported the causes of death of adults with CHD have used historical cohorts [9-11], were single centre studies [12], or have been performed outside of Europe [13].

Given the burden of symptoms and risk of premature death of adults with CHD, it is argued that there is a need for adequate palliative and end-of-life care.[5] Palliative care can be defined as *"an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering"*.[14] Palliative care can be complementary to standard medical care and can be introduced at any stage of the illness.[15] In contrast, end-of-life care can be defined as *"the process of supporting patients who are in their final months of life and their relatives"*.[16]

There are well-documented reasons to believe that adults with CHD have specific needs as they near the end of life, which are not comparable with the needs of patients who die from acquired heart diseases.[17] They not only die at a younger age [4], the presentation of symptoms and cardiac deterioration of CHD patients is also diverse and often atypical because of the heterogeneity of the heart disease and subsequent surgical and transcatheter interventions.[18]

Therefore, it is challenging to define a prognosis and identify the triggering event for deterioration of the situation.[18,19]

Although the implementation of palliative care in cardiology has gained substantial traction in recent years [20] and recommendations for advance care planning and end-of-life care for adults with CHD were discussed in guidelines by ESC working groups [21,22], palliative and end-of-life care for adult CHD patients still is an understudied area. Up to now, the existing empirical studies mainly focus on preferences regarding advance care planning.[19,23-26] One study has investigated healthcare utilisation at the end of life and showed that many patients were admitted to an intensive care unit during their last month of life, hinting at a lack of adequate end-of-life care.[27] To date, no empirical studies have described the current outpatient healthcare utilisation or specialist palliative care of adults with CHD. Given these gaps in the body of knowledge, the present study aimed to (1) identify the causes of death and (2) describe the patterns of healthcare utilisation in the last year of life of adults with CHD.

Methods

Data source

We used the BELgian COngenital heart disease Database combining Administrative and Clinical data (BELCODAC), which includes administrative and clinical data of patients with CHD in Flanders and Brussels. More details about this database have been described previously.[28] In short, BELCODAC comprises data on healthcare utilisation from 2006–2015 and clinical data (e.g., information about diagnosis, comorbidities, and interventions) from the same period and before. Data were derived from five organizations, namely three Belgian hospitals (i.e., University Hospital Leuven, Saint-Luc University Hospital and Ghent University Hospital), the national statistical office (i.e., Statistics Belgium) and the authority in charge of maintaining all healthcare claims from the seven health insurance funds in the country (i.e., InterMutualistic Agency). These different datasets were linked at the patient level under the supervision of the Belgian Data Protection Authority, and included a four-layer pseudonymization system to safeguard the identity of all patients. Overall, BELCODAC comprises 18,510 children and adults with CHD.[28]

Study design and population

For the purpose of the present study, we conducted a mortality follow-back study in adult patients who died between January 1, 2007 and December 31, 2015, and who had lived in Belgium during their last year of life. The timeline and flowchart of this study are presented in eFigure 1 and 2 in the Supplementary Material.

A total of 390 patients died in the observation period, 51% of which were women, and the median age at the time of death was 55 years (Table 1). Most patients had a CHD of moderate complexity (46%), followed by mild complexity (43%) and severe complexity (11%), as defined by Stout et al.[29] The most common heart defect in patients who died was Type 2 atrial septum defect (n=88; 23%). In eTable 1, the variables and codes used to identify clinical characteristics in BELCODAC are described.

Outcome definitions

Causes of death were derived from the *International Classification of Diseases and Related Health Problems, 10th revision* (ICD-10) codes reported as the underlying cause of death on the death certificates of patients, which are filled out by a certifying doctor for every death that takes place in Belgium. The categories and corresponding ICD-10 codes are reported in eTable 2.

Sudden death, defined as "*a death, non-violent and not explained otherwise, occurring less than 24 hours from the onset of symptoms*"[30], was identified by LVB based on the clinical interpretation of available data. For patients who had no healthcare utilisation in the last 10 days of life, except for the day of death, the underlying cause of death, the clinical profile, and the provision of care in the last year of life was checked to evaluate whether or not death was most likely sudden and unexpected. Reasons to believe that a patient did not die suddenly were a registered chronic disease, residence in a nursing home, use of incontinence equipment, regular hospitalisations in the last year of life, or regular visits at the general practitioner or specialist in the last 6 months of life. Ambiguous cases were discussed within the team (LVB, PM, EG) until an agreement was made.

Healthcare utilisation includes contacts with a general practitioner (GP), contacts with a CHD physician, hospitalisations, visits to the emergency

department (ED), cardiovascular procedures, admissions to the intensive care unit (ICU), and specialist palliative care, which can be both inpatient and outpatient. Healthcare utilisation was based on nomenclature codes derived from healthcare claims data. Detailed information about the variables and nomenclature codes used are described in eTable 3.

Statistical analysis

Sample characteristics and causes of death of all patients who died (n=390) were analyzed descriptively and were presented as median and quartiles for continuous variables and as frequencies and percentages for categorical variables.

Healthcare utilisation was analysed for the 327 patients who had a cause of death and died non-suddenly and non-accidently, as these patients could have had end-of-life care needs and death could have been expected. Healthcare utilisation in the last 12 months of life was analysed descriptively and logistic regression analyses were used to examine differences between patients who died due to either a malignant or a cardiovascular cause of death. For contacts with a GP, hospital days, and ED visits, the mean monthly days with an event were reported for every month in the last year of life and modelled using binomial regressions with generalized estimating equations. For the analyses of GP and ED visits, only the days that patients were not hospitalised (starting from the second day of the hospital admission) were taken into account, as patients usually do not have GP contacts or ED visits during a hospital admission. For contacts with CHD physicians, cardiovascular procedures, admissions to the ICU, and specialist palliative care, it was considered inappropriate to calculate the mean monthly days for each item, because of excessive zeros in the data. Therefore, for these types of healthcare utilisation, the proportions of patients using this healthcare service at least once per month for the last 12 months of life were reported, together with exact confidence limits for the proportions.

Ethical approval

Approval of the ethics committee from University Hospitals Leuven (file numbers S59859 and S59858), Ghent University Hospital (file numbers 2017/0436 and 2017/0437), and Saint-Luc University Hospitals (file numbers 2017/26JUI/333 and 2017/26JUI/332) was obtained. At this governmental level, approval was obtained from the Statistical Supervisory Committee (SA2/STAT-MA-2017-021), the Sectoral Committee of Social Security and of Health (CSSSS/17/184 and SCSZG/17/184), and the Sectoral Committee of the National Register. The study is legally exempt from the obligation to obtain written informed consent from each patient. More information can be found elsewhere.[28]

Results

Causes of death

The distribution of causes of death is depicted in Figure 1. While 55 (14%) patients died due to a sudden, accidental or violent cause of death, most patients (n=327; 84%) had a non-sudden death. A total of 28 (7%) patients had an accidental or violent cause of death (including 14 deaths due to intentional self-harm), 15 (4%) patients had a sudden cardiac death and 12 (3%) patients died suddenly with a noncardiac cause of death reported. For 8 patients (2%), the cause of death was missing or unclear (for 6 patients due to death outside of Belgium).

Almost half of the study population (n=174; 45%) died from a cardiovascular cause, of which 15 (4%) patients had a sudden cardiac death. Of the patients who died due to a cardiovascular cause, 30% (n=51/174) had the CHD as reported cause of death and 14% (n=25/174) died due to a stroke.

In addition, 64 (16%) patients died from cancer, with the most common cancers being lung cancer (n=13/64; 20%) and breast cancer (n=7/64; 11%). The remaining 104 patients died from respiratory diseases (n=24; 6%), non-cardiovascular congenital malformations (n=19; 5%), digestive diseases (n=12; 3%), endocrine, nutritional and metabolic disorders (n=12; 3%), infectious and parasitic diseases (n=9; 2%), diseases of the nervous system (n=7; 2%) and other reasons (n=21; 5%).

As reported in Table 2, a large majority of patients with severe CHD lesions (n=32/43; 74%) died from a cardiovascular cause of death, compared with only half of patients (n=88/174; 50%) with moderate lesions and only 31% (n=54/173) of the patients with mild lesions. A quarter of the patients (n=41/173; 24%) with mild lesions died due to a malignant cause of death. These proportions were lower for patients with moderate (n=21/174; 12%) and severe (n=2/43; 5%) CHD lesions. The causes of death for each CHD diagnosis can be found in eTable 4. For patients with an atrioventricular septum defect, Ebstein malformation, a valve abnormality, aortic abnormality, left ventricular outflow tract obstruction, atrial septum defect type 2, ventricular septum defect, and pulmonary vein abnormality, proportionally more patients died due to a malignant or other cause of death than to a cardiovascular cause of death.

Healthcare utilisation

Contacts with general practitioner (GP)

Almost all patients (97%) had a GP encounter in the last year of life and 70% had a GP encounter in the last month of life. The proportions of patients having had GP visits in the last year were not significantly different for the two groups (Figure 2). However, the number of GP visits in the last month of life significantly differed for the two groups, with patients with a malignant cause of death reporting twice as many visits (Figure 3).

The number of GP encounters significantly increased in the last months of life (Figure 3). The patterns of GP contacts over time were different for patients who died due to a cardiovascular or malignant cause of death (Figure 3).

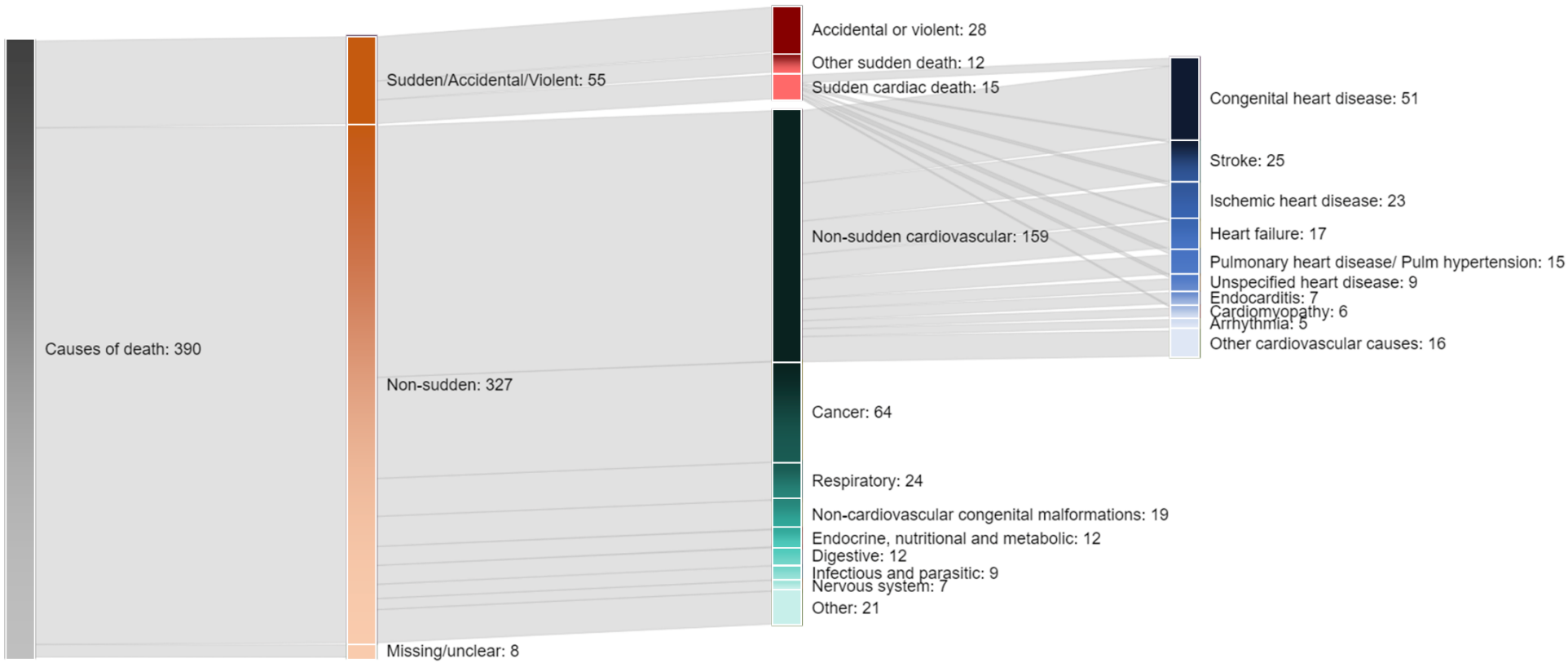


Figure 1. Causes of death of adults with CHD (n=390)

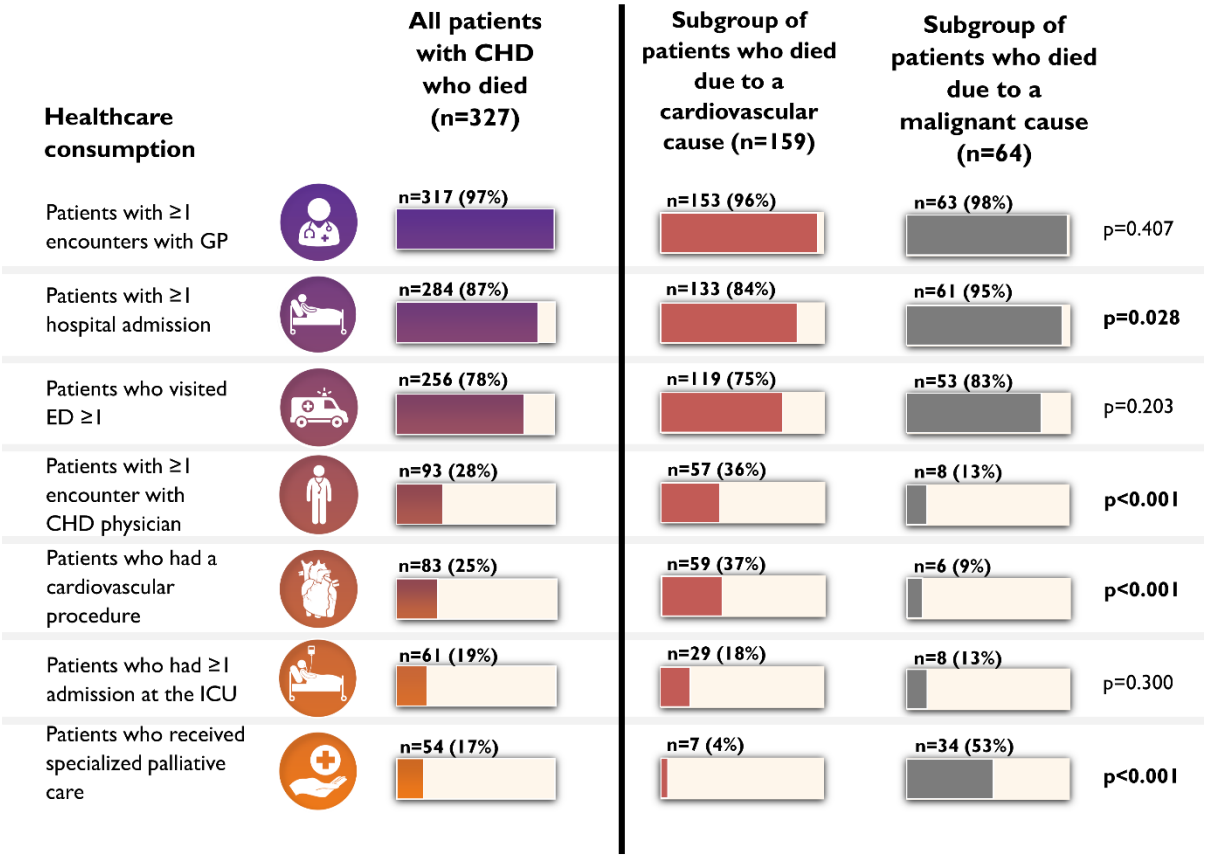


Figure 2. Healthcare utilisation in the last year of life of adults with CHD (n=327) and of subgroups of patients with a cardiovascular cause of death (n=159) and malignant cause of death (n=64)

Legend. CHD=congenital heart disease; ED=emergency department; GP=general practitioner; ICU=intensive care unit

Hospitalisations

A total of 815 hospital admissions in the last year of life were found for all patients, of which almost half (374; 46%) were preceded by an ED visit. Respectively, 87% and 70% of patients were hospitalised at least once in the last year and month of life. The proportion of patients who were hospitalised in the last year of life was significantly higher for patients who died due to a malignant cause of death compared to patients with a cardiovascular cause of death (Figure 2). However, the number of hospital days in the last month of life was not significantly different for these two groups.

Patients spent more days hospitalised towards the end of life (Figure 3). The patterns of mean monthly hospital days over the last year were similar for

patients who died due to cardiovascular and malignant causes of death (Figure 3).

Visits to emergency department (ED)

In the last year and month of life, 78% and 51% of the patients had at least one ED visit. The proportion of patients who had an ED visit in the last year of life and the mean number of ED visits in the last month were not different for patients who died due to a cardiovascular or malignant cause of death (Figure 2 and 3).

In the last month of life, the number of ED visits increased (Figure 3). Patients who died from a malignant or cardiovascular disease followed different patterns throughout the last year of life (Figure 3), that were characterized by a mean monthly number of ED visits of 0.5 for patients with a malignant deaths and 0.1 for cardiovascular deaths.

Contact with a congenital heart disease physician

The proportions of patients with at least one CHD contact in the last year and month of life were respectively 28% and 11% (Figure 2 and 3). A significant difference between the proportion of patients with CHD physician contacts during the last year and last month of life was found for patients with cardiovascular and malignant causes of death (Figure 2 and 3).

The proportion of patients having a CHD physician contact was higher in the last month of life compared to one year before death, but an increase around the 5th and 6th month before death could be noticed as well (Figure 3).

Cardiovascular procedures

Respectively 25% and 11% of patients had a cardiovascular procedure (e.g., heart surgery or catheter-based heart intervention) in the last year and month of life (Figure 2 and 3). Compared to patients with a malignant cause of death, significantly more patients who died from a cardiovascular disease had procedures in the last year and month of life (Figure 2 and 3).

There was an increase in patients receiving a cardiovascular procedure towards the end of life, for all patients and for patients who died due to a cardiovascular cause (Figure 3).

Admissions to the intensive care unit (ICU)

A total of 19% had an ICU admission in the last year of life and 15% had an ICU admission in the last month of life (Figure 2 and 3). These proportions were not significantly different for patients who died due to a malignant or cardiovascular cause.

When looking at the proportion of patients with admissions to the ICU, an increase in the last months of life was noticed. The trajectory over time was similar for patients who died due to a cardiovascular or malignant cause of death (Figure 3).

Specialist palliative care

A total of 17% and 13% of patients received specialist palliative care in the last year and month of life, respectively (Figure 2 and 3). Significantly more palliative care in both the last year and month of life was provided to patients with a malignant cause of death, as compared to patients with a cardiovascular cause of death. Of the latter group, 4% received specialist palliative care in the last month, whereas 41% of patients with a malignant cause of death received specialist palliative care in the last month of life.

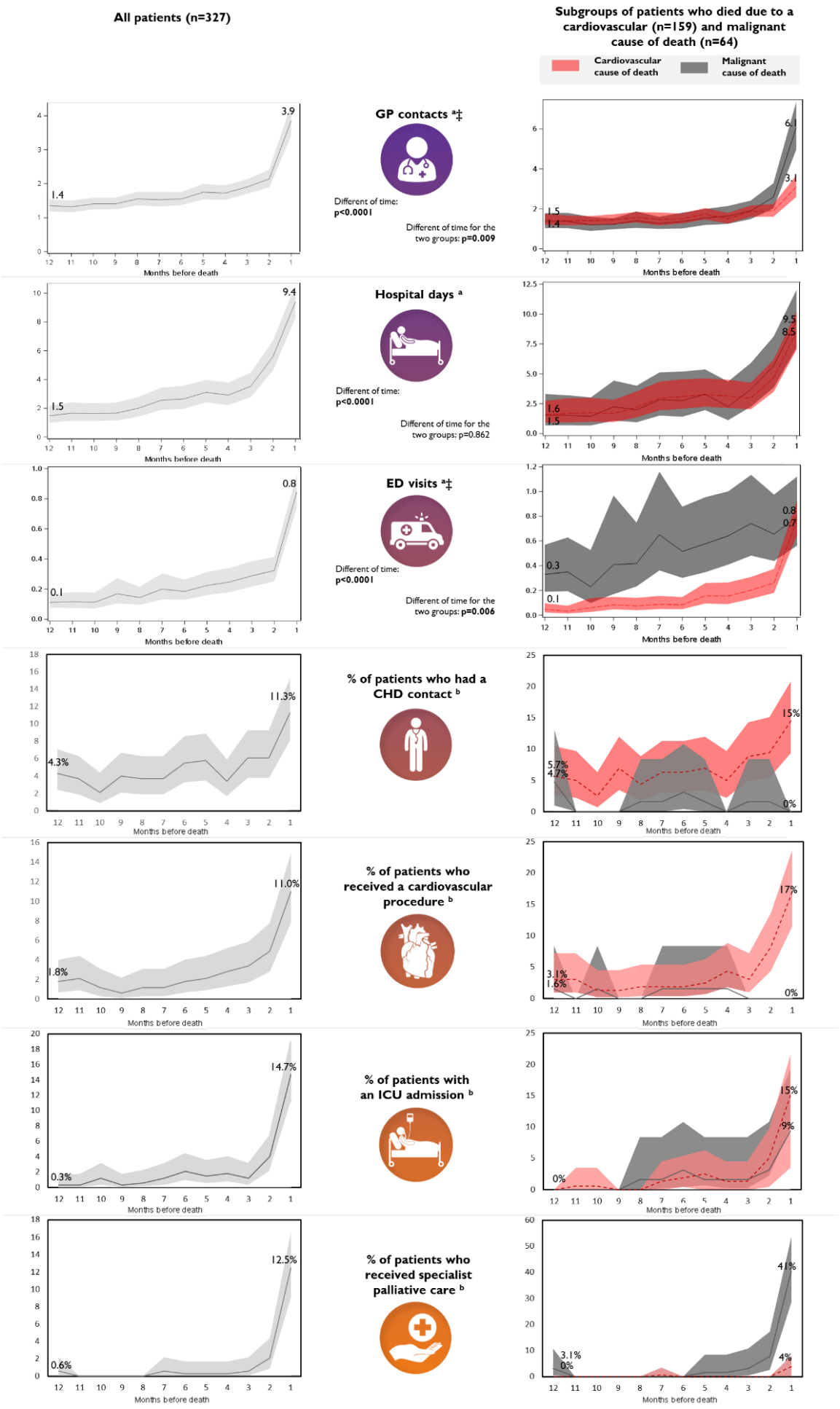


Figure 3. Healthcare utilisation patterns of the last year of life in adults with CHD (n=327)

Legend. *a* Binomial regression model with generalized estimating equations (mean numbers of days with event per month over the last 12 months are shown); *b* Exact confidence limits for the proportion (proportions of patients who used health service at least once per month over the last 12 months are shown); Lighter coloured area represents the 95% confidence interval. ‡ Calculations are based on days that patients were not hospitalised. CHD=congenital heart disease; ED=emergency department; GP=general practitioner; ICU=intensive care unit

Discussion

The last year of life of adults with CHD is an understudied domain. The present study had several notable findings. First, less than half of people with CHD died due to cardiovascular diseases. Second, we found high healthcare utilisation in terms of hospital admissions, ED visits, cardiovascular procedures, and ICU admissions, which increased towards the last months of life. Third, use of specialist palliative care seemed very limited, especially for patients with a cardiovascular cause of death (Structured Graphical Abstract).

Our finding that less than half (45%) of the study population died due to a cardiovascular cause of death is in line with a recent study from the USA.[13] However, older studies reported markedly higher proportions of death due to cardiovascular causes. In studies from 2000 and 2007, it was stated that cardiovascular death accounted for 65%[9] and 67%[31] of all deaths of patients with CHD, respectively. Earlier studies have reported that the causes of death differ by CHD complexity, with more cardiovascular death for those with severe lesions.[13] This was also confirmed in our study. The different proportions of cardiovascular deaths found in the literature could be due to subjectivity in reporting the causes of death, or by the changing profile of patients with mild and moderate CHD lesions in the last decade. For instance, a study published in 2010 described that over 70% of patients with a ventricular septum defect died due to a cardiovascular cause of death [4], whereas in our study, only 32% of the patients with a ventricular septum defect died due to a cardiovascular cause. The changing profile is also noticeable when looking at the median age of the decedents. The median age in this study was 55 years, which is remarkably higher than the mean ages at death reported in previous

studies.[4,9,32] Only in the recent study of Goldstein and colleagues, a higher median age of 64.2 years was reported.[13] The shifting cause of death from cardiovascular death to other causes and increasing ages could be the result of improved management of long-term sequelae and a better follow-up of patients with mild and moderate CHD during child- and adulthood.[13] The changing profiles might also have implications for the end-of-life and palliative care needs, which may be different to date than in the past. Care at the end of life should go beyond cardiovascular care, and interdisciplinary collaborations are increasingly needed, as patients with CHD do not exclusively die from their heart disease and many patients have comorbidities. Developing best practice models with an interdisciplinary approach regarding the CHD and comorbid conditions such as cancer and respiratory diseases could improve outcomes for this patient population.

It was also remarkable that 14/382 patients (3.6%) died due to intentional self-harm, of which at least 12 were confirmed suicides (12/382; 3.1%). The prevalence of psychiatric disorders is higher in adults with CHD than in the general population.[33] However, the suicide rate found in this study is much higher than the 0.56% suicide proportion found among all deaths in a Danish cohort of CHD patients.[34] The suicide rate per 100,000 inhabitants is higher in Belgium (18.3) than in Denmark (10.7)[35]. However, that does not explain the 5-fold higher percentage of suicides as cause of death in the patients in BELCODAC and hence, this finding requires further investigation.

We observed potentially avoidable resource use in terms of (unplanned) hospital admissions, ED visits, cardiovascular procedures, and ICU admissions at the end of life, mainly in the last three months. This was in line with the existing literature. The only published study to date about end-of-life care for adults with CHD, which included 65 patients from the USA with moderate or severe CHD lesions, reported high healthcare utilisation in the last month of life.[27] In that study, Steiner and colleagues described that 39% of patients were hospitalised, 39% had an admission to the ICU, and 3% had a visit to the ED in the last month of life.[27] In our study, a much higher number of patients (70%) were found to be hospitalised and to have had an ED visit (51%) in the last month of life. A lower proportion (15%) was admitted to the ICU in the last month of life. These discrepancies might originate in the differences between healthcare systems in Europe and United States or could be due to differences

in the study methodologies and sample sizes, with the American study having a much smaller sample. Furthermore, the high resource use at the end of life was also not surprising because adults with CHD already use a lot of healthcare during their lives, much more than people from the general population.[36-38] A previous BELCODAC study reported that, in 2015, 21% of patients visited an ACHD physician, 86% had a GP visit, 17% of patients had an ED visit, and 17% were hospitalised at least once.[38] On top of that, we know from studies in other chronic patient populations that healthcare utilisation increases in the last months of life, mainly as a response to the presence of comorbidities and exacerbations at the end of life.[39] Referral to palliative care has shown to decrease the number of inpatient stays and ICU admissions at the end of life.[40] Indeed, to lower unnecessary healthcare utilisation, such as hospital admissions and ED visits at the end of life, properly implementing palliative care for adults with CHD could be an important strategy.

Patients with CHD, especially those with a cardiovascular cause of death, seem to have received only little specialist palliative care. In contrast to hospitalisations, ED visits, and ICU admissions, which may not necessarily be appropriate at the end of life, palliative care is typically seen as desirable at the end of life. Although palliative care is gaining recognition as a critical component of comprehensive care for adults with CHD early in the disease trajectory[41], the actual implementation of palliative care in routine clinical practice remains limited. In a study in adults with CHD, who were not necessarily in the terminal phase of their lives, 91% had indicated that they were at least moderately willing to speak to a clinician specialised in palliative care and 3% indicated to have met one.[19] A qualitative study showed that adults with CHD are rather unfamiliar with the definition and elements of palliative care.[24] Palliative care was often related to the terminal phase and described as “giving up”.[24] In a survey study among CHD healthcare providers, the providers reported low levels of personal palliative care knowledge.[25] Moreover, only 14% to 32% of CHD providers indicated that they would initiate referral to palliative care.[25] Furthermore, although the importance of early advance care planning has been described for adults with CHD[21,42], CHD providers seem to be worried about the readiness of their patients for these discussions, particularly for patients who are still in good health.[25,43] When advance care planning is not routinely addressed, this may cause lack of referral to palliative care.[44] Compared to patients who died from

a cardiovascular disease, a much higher proportion of patients who died from cancer received specialist palliative care. This is not surprising as end-of-life care needs of cancer patients have been studied thoroughly and receive much more attention.[45] A Western Australian study reported that, during the last year of life, 69% of decedents with cancer and only 14% of non-cancer decedents accessed specialist palliative care.[45] Compared to decedents with heart failure, decedents with cancer were 10 times more likely to receive specialist palliative care.[45]

Only one in four patients saw a CHD physician in the last year of life and 11% in the last month of life. When looking at the patients who died due to a cardiovascular disease, still only 36% and 15% had a CHD physician encounter in the last year of life and month of life, respectively. This finding raises the question whether CHD physicians are adequately involved in the final stage of life and whether the cardiovascular needs and symptoms are sufficiently taken into account at the end of life. It would be interesting to examine whether a closer engagement of CHD physicians at the end of life could reduce potentially avoidable resource use and improve referral to palliative care.

Hence, the findings of this study suggest that healthcare utilisation at the end of life of adults with CHD requires more attention. Future studies should further examine the changing end-of-life care needs and trajectories towards death, and investigate how the healthcare system can adequately respond to these needs. Improving the quality of end-of-life care provision for adults with CHD will be an important health challenge for the upcoming years.

The present study has several strengths. First, this is the first study to report on healthcare utilisation of outpatient healthcare services, cardiovascular procedures, and specialist palliative care in the last year of life of adults with CHD. Second, the study included data of a large number of patients who died in an 9-year period. Third, the study used data of a population-level database. The database included patients without preselection. As a result, the level of ascertainment bias is much lower than in registries that include only a subgroup of patients and this database also includes patients that are often missed. Fourth, whereas most existing databases use ICD diagnosis to identify patients, BELCODAC patients were selected in the hospital database and their diagnosis was confirmed by expert clinicians.

However, our results should also be interpreted with a number of limitations in mind. First, we could not distinguish whether a healthcare service was used for a reason related to the CHD or not, because this information was not available. In future studies, it would be interesting to look into more detail whether the high potentially avoidable resource use was related to the heart disease or not. Second, the underlying causes of death should be interpreted with caution. Unfortunately, only the primary cause of death was available in BELCODAC, and the accuracy and reliability of ICD-10 codes are known to be limited.[10,46] The disease profile of adults with CHD is often complicated at the end of life and, therefore, might be hard to interpret by the physician without CHD background who fills out the death certificate. Moreover, the investigators had to use proxies to pinpoint potentially sudden and unexpected deaths, without having access to the full electronic medical records. Inaccuracies may also occur due to incomplete death certificates, diagnostic issues, or when the death had multiple causes.[10] Also, we did not have information about the place of death. Third, it is likely that the reported findings are not entirely generalizable to other countries and healthcare systems, as the study only uses data of patients from Belgium. Fourth, the data are subject to limitations because they are not collected for research purposes, but primarily for clinical and reimbursement purposes. As a consequence, some clinical data are not comprehensive enough, and the reliability of the data mainly depends on its impact on reimbursements. Finally, no data on patient-reported outcomes, preferences, or on the reasoning behind certain end-of-life care decisions was available.

Conclusion

High healthcare utilisation in terms of hospital admissions, ED visits, ICU admissions, and cardiovascular procedures, was found, whereas the use of specialist palliative care was limited. This intensive and maybe sometimes avoidable care, especially for patients with a cardiovascular cause of death, suggest that the care provision at the end of life for adults with CHD can be improved. Care at the end of life for adults with CHD should go beyond cardiovascular care, as less than half of the study population died due to a cardiovascular disease. Future studies should further examine the changing end-of-life care needs, patient's preferences, and investigate how the healthcare system can adequately respond.

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Authors' contributions: LVB conceived and designed the study, performed the statistical analysis, interpreted the data, drafted, and critically revised the manuscript. EG, PM, LM, and KL interpreted the data and critically revised the manuscript. FO, RW, WB, MdH, KDG, LA, JDB, and SM acquired, analysed interpreted the data, and critically revised the manuscript. AM was essential while setting up the database and critically revised the manuscript. All authors gave approval for the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no conflict of interest regarding this article.

Ethical approval: Approval of the ethics committee from University Hospitals Leuven (file numbers S59859 and S59858), Ghent University Hospital (file numbers 2017/0436 and 2017/0437) and Saint-Luc University Hospitals (file numbers 2017/26JUI/333 and 2017/26JUI/332) was obtained. At this governmental level, approval was obtained from the Statistical Supervisory Committee (SA2/STAT-MA-2017-021), the Sectoral Committee of Social Security and of Health (CSSSS/17/184 and SCSZG/17/184), and the Sectoral Committee of the National Register.

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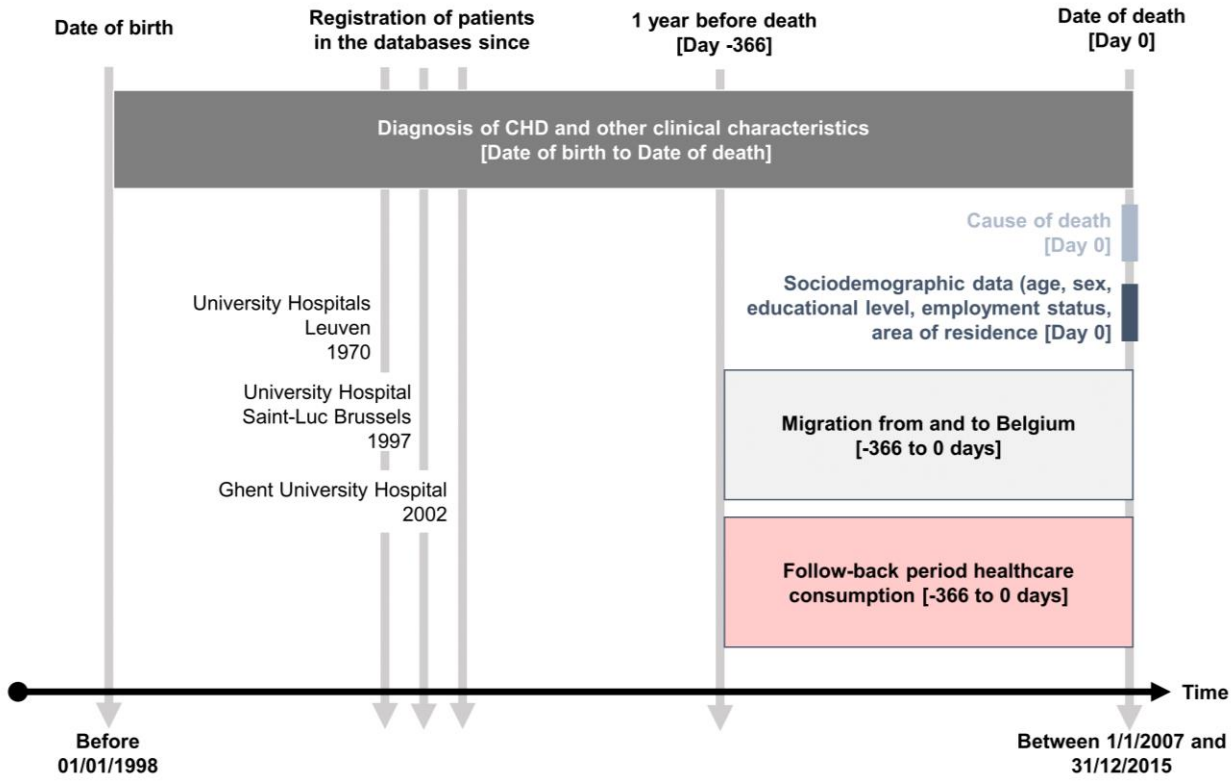
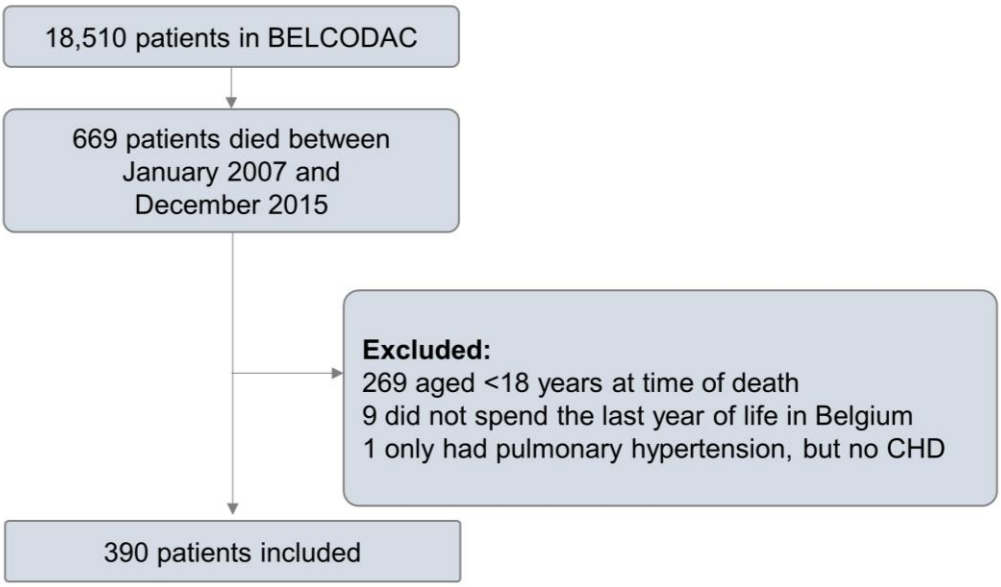
eFigure 1 – Graphical representation of the timeline and design of the substudy



eFigure 2 – Flowchart



Legend. BELCODAC = BELgian COngenital heart disease Database combining Administrative and Clinical data; CHD=congenital heart disease

eTable 1 – Variables and codes used to identify clinical characteristics in the clinical and administrative databases

Clinical characteristics	Definition	Source	Variables and codes used to identify the clinical characteristics
Heart failure	Prescription of loop diuretics in last year of life	InterMutualistic Agency	Variables used: SS00135 & SS00015 CNK codes of loop diuretics: 710392, 710392, 198036, 710392, 710376, 710376, 117572, 710376, 763227, 763227, 1530369, 763227, 729301, 729301, 17301, 729301, 710384, 710384, 763227, 763227, 2379709, 763227, 729301, 729301, 2566735, 729301, 710350, 3070414, 710350, 710368, 710368, 7716434, 7716434, 716442, 7716442, 1414309, 736157, 675850, 736157, 736165, 736165, 675835, 736165, 702217, 702217, 702217, 743583, 743583, 1182963, 743583, 739292, 739292, 305938, 739292, 777805, 777805, 2159986, 777805, 777797, 777797, 2159952, 777797, 777789, 777789, 2159929, 777789
Diabetes	Prescription of anti-diabetes medication in last year of life	InterMutualistic Agency	Variables used: SS00135 & SS00015 CNK codes of anti-diabetes medication: 33316, 33324, 38174, 44057, 44248, 44255, 44842, 49114, 50153, 50468, 56440, 57760, 57778, 73742, 108894, 108936, 109017, 110395, 114066, 115998, 127373, 133728, 245399, 245407, 245415, 245423, 245431, 245449, 245472, 245480, 245498, 262063, 262071, 263269, 263277, 263285, 263293, 263301, 263319, 263327, 274548, 291195, 291203, 321612, 444182, 458018, 458026, 458042, 458067, 461830, 461855, 461863, 461871, 461889, 483875, 483883, 483891, 483909, 532796, 603258, 633388, 685024, 704106, 704809, 704817, 706713, 708057, 708081, 708099, 709295, 709303, 709311, 709337, 709352, 711812, 716217, 716225, 726752, 726760, 728907, 730069, 730309, 732172, 732180, 733808, 733816, 734384, 734954, 734962, 734970, 734988, 736710, 736728, 736736, 736744, 736892, 736900, 736918, 736926, 736934, 736942, 736959, 736967, 736975, 736983, 736991, 737007, 737015, 737023, 737031, 737064, 737080, 737098, 737106, 740464, 740472, 740480, 740498, 740506, 740514, 741207, 741314, 745505, 748756, 748764, 748772, 748780, 748798, 748806, 749259, 749267, 749275, 749283, 749291, 749309, 749317, 749325, 749333, 749341, 749358, 749366, 749374,

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PM/ICD implant	Presence of a pacemaker or ICD implant	Hospital databases	Not applicable

eTable 2 – List of categories and ICD-10 codes

Categorization	ICD-10 codes
Cardiovascular	I0710, I0790, I0800, I2190, I2480, I2510, I2590, I2690, I2700, I2780, I2790, I2880, I3300, I3500, I3510, I3590, I3800, I4200, I4240, I4290, I4580, I4690, I4720, I4800, I4890, I4900, I4990, I5000, I5090, I5100, I5160, I5190, I6080, I6090, I6140, I6190, I6290, I6320, I6330, I6390, I6400, I7100, I7120, I7150, I8220, Q2000, Q2030, Q2040, Q2100, Q2130, Q2180, Q2480, Q2490, Q2510, Q2880, Q7960, Q8740, R0920
Cancer	C0290, C1400, C1550, C1590, C1690, C1890, C2000, C2200, C2210, C2290, C2500, C2590,C2600, C3290, C3490, C4190, C4390, C4430, C4590, C4990, C5090, C5600, C6100, C6400, C6790, C7190, C7200, C8000, C8350, C8510, C9200, D3770, D3810, D4740
Respiratory	J0290, J1300, J1540, J1890, J4000, J4410,J4490,J6900, J8410, J8490, J8530, J9000, J9600, J9840
Non-cardiovascular congenital malformations, deformations and chromosomal abnormalities	Q3390, Q6050, Q6130, Q7980, Q8700, Q8710, Q8970, Q8990, Q9090
Digestive	K2230, K5090, K5590, K7110, K7160, K7210, K7290, K7460, K7670, K8590, K9220
Endocrine, nutritional and metabolic diseases	E1090, E1450, E1490, E2300, E7620, E8300, E8480, E8600, E8750
Infectious and parasitic	A0900, A4090, A4190, A4980, B1820, B4490, B9900
Nervous system	G3100, G3190, G4090, G7100, G7110, G7120, G9310
Other	D7610, D8680, F0110, F0300, F1020, F1920, F7990, M0699, M4190, M7090, M7260, M8690, N1850, N1890, N1900, R6400, Y4799, Y5799, Y8833
Accidental or violent	V8929, W100, W1999,W7519, X0000, X5999, X6100, X7000, X7009, X7029, X7088, X7149, X7600, X8249, X9100, Y0900, Y3400, Y3409, Y3499
Missing/unclear	R9800, R9900

eTable 3 – Variables and codes used to identify healthcare utilization in the administrative database

Healthcare utilization	Description	Source	Variables and codes used to identify healthcare utilization (started from the nomenclature codes available for the included patients)
Contacts with the general practitioner (GP)	Encounters with GPs at the patient's house or at the doctor's office were included	InterMutualistic Agency	Variables used: SS00020 Nomenclature codes: 101010, 101032, 101076, 103110, 103132, 103235, 103412, 103434, 103515, 103530, 103552, 103913, 103935, 103950, 104215, 104230, 104252, 104274, 104370, 104392, 104414, 104436, 104532, 109082
Days hospitalised	Days hospitalised are days within a hospital admission. A hospital admission was defined as an inpatient stay of at least one night. Hospitalisations with an emergency department visit on the first day of the hospitalisation or the day before were seen as potentially unplanned hospitalisations.	InterMutualistic Agency	Variables used: SS00075_C, STAY_CAT, PROCEDURE_AH_CAT, SS00110
Emergency department (ED) visits	ED visits include all care provided by a healthcare worker specialised in emergency care, both at the ED and during an extramural intervention.	InterMutualistic Agency	Variables used: SS00020 Nomenclature codes: 590310, 590435, 590446, 590472, 590516, 590531, 590553, 590575, 590634, 590656, 590671, 590693, 590752, 590774, 590796, 590811, 590870, 590892, 590914, 590951, 590973, 590995

Contacts with a CHD physician	Contacts with a CHD physicians include encounters with both pediatric and adult CHD physicians.	InterMutualistic Agency	Variables used: VERSTR_CARDIO_KIND and VERSTR_CARDIO_VOLW, variables especially designed to identify CHD physicians, working in paediatric and/or adult care, in Flanders and Brussels
Cardiovascular procedures	Cardiovascular procedures include cardiovascular surgeries and catheter-based cardiovascular interventions..	InterMutualistic Agency	Variables used: SS00020 Nomenclature codes: 212214, 212225, 229025, 229121, 229143, 229180, 229224, 229526, 229541, 229600, 229622, 318065, 475963, 475985, 464170, 464181, 464203, 476022, 476044, 476066, 476070, 476081, 476206, 476652, 476663
Admissions to the intensive care unit (ICU)	Admissions to the ICU refer to care provided at the intensive care or critical care unit.	InterMutualistic Agency	Variables used: SS00020 Nomenclature codes: 211223, 211245, 478181, 478203
Specialist palliative care	Specialist palliative care is care provided by a healthcare worker specialised in palliative care and could be provided in a palliative care unit of a hospital (inpatient) or by a multidisciplinary palliative care team at home (outpatient).	InterMutualistic Agency	Variables used: SS00020 Nomenclature codes: 597763, 599782, 599804, 768143, 774056, 774071

eTable 4 – Causes of death per CHD diagnosis (n=390)

Characteristics	Total	Cardiovascular	Cancer	Other diseases	Missing
N	**n=390**	**n=174**	**n=64**	**n=144**	**n=8**
CHD diagnosis					
Univentricular physiology	12 (3%)	10 (83%)		2 (17%)	
Tricuspid atresia	2 (1%)	1 (50%)	1 (50%)		
Tetralogy of Fallot	30 (8%)	22 (73%)	1 (3%)	7 (24%)	
Pulmonary atresia with ventricular septal defect	1 (0%)	1 (100%)			
Double outlet right ventricle	8 (2%)	5 (62%)		3 (38%)	
Double inlet left ventricle	2 (1%)	1 (50%)		1 (50%)	
Truncus arteriosus	2 (1%)	1 (50%)		1 (50%)	
Transposition of the great arteries	10 (3%)	7 (70%)	1 (10%)	1 (10%)	1 (10%)
Congenitally corrected transposition of the great arteries	6 (2%)	6 (100%)			
Coarctation of the aorta	28 (7%)	16 (57%)	2 (7%)	9 (32%)	1 (4%)
Atrioventricular septal defect	20 (5%)	9 (45%)	2 (10%)	9 (45%)	
Atrial septal defect type 1	12 (3%)	7 (58%)		4 (34%)	1 (8%)
Ebstein malformation	4 (1%)		1 (25%)	3 (75%)	
Pulmonary valve abnormality	25 (6%)	8 (32%)	9 (36%)	8 (32%)	
Aortic valve abnormality	30 (8%)	13 (43%)	1 (3%)	14 (47%)	2 (7%)
Aortic abnormality	6 (2%)	1 (17%)	1 (17%)	4 (66%)	
Left ventricular outflow tract obstruction	1 (0%)			1 (100%)	
Atrial septal defect type 2	88 (22%)	34 (39%)	17 (19%)	35 (40%)	2 (2%)
Ventricular septal defect	31 (8%)	10 (32%)	9 (29%)	12 (39%)	
Mitral valve abnormality	15 (4%)	4 (27%)	1 (7%)	10 (66%)	
Pulmonary vein abnormality	10 (3%)	5 (50%)	3 (30%)	2 (20%)	
Other	47 (12%)	13 (28%)	15 (32%)	18 (38%)	1 (2%)

Chapter 9

Overall discussion

Guided by the Andersen Behavioral Model of Health Services Use, this PhD project has examined (predictors of) healthcare use and PROs. More specifically, this thesis scrutinised the predictive value of illness identity for healthcare use and patient-reported outcomes (PROs) (Obj 1), the association between healthcare system characteristics and PROs (Obj 2), and palliative and end-of-life care provision (Obj 3). Adults with congenital heart diseases (CHD) were chosen as a sample case population, representing a population of young people afflicted by a chronic condition.

In this final chapter, a reflection on the findings, methodological considerations, implications for daily practice and recommendations for future research are presented.

Reflection on findings

Is there sufficient evidence to confirm that illness identity is a predictor of healthcare use and PROs?

The concept of 'illness identity', which is the degree to which the illness is integrated into the identity,[1] was found to be clinically relevant for patients with chronic conditions. However, the predictive value of illness identity for healthcare use and PROs was not yet well investigated. In the studies included in this PhD thesis, the concept of illness identity was found to be associated with healthcare use and PROs in adults with congenital heart disease. The question arises whether this body of evidence is strong enough to confirm that illness identity is a predictor of healthcare use and PROs.

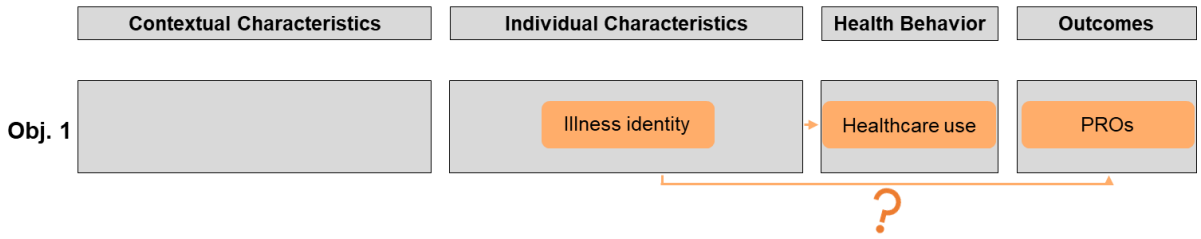

Figure 1. Visual representation of the question on whether illness identity is a predictor of healthcare use and PROs.

Illness identity is a unique concept, but there is some overlap with concepts such as personal identity and illness perceptions. They are all part of the broader self-concept. Personal identity can be seen as the degree to which an individual

integrates different self-assets into a coherent sense of self.[2] A chronic illness is one self-assets that needs to be integrated, aside from other self-assets.[3] Hence, the extent to which individuals with a chronic illness have attained a coherent identity may be related to illness identity integration as well.[4] Health beliefs, or illness perceptions are also related to illness identity. However, they are only partly overlapping. Illness perceptions do not explicitly describe the degree to which people succeed to integrate their illness into their identity, as is done by illness identity.[5] Kihlstrom and Kihlstrom stated that, in order to know how people understand illness (and adherence), we do not only need to understand how people view the illness and the treatment, but also how they view themselves as a person.[6]

Arguments in favour

First, illness identity has been shown to have a unique contribution in predicting the healthcare use of adults with CHD. As discussed in Chapters 2 and 3 of this PhD thesis, we have found associations between the illness identity dimensions and healthcare use in adults with CHD. More specifically, we found that, when adjusting for confounders, the level of engulfment was related to the number of hospitalisations, visits to the medical specialist, as well as to the general practitioner, for medical reasons related to the CHD. When looking at the disease trajectories over time, we found that fewer hospitalisations and visits to the general practitioner and medical specialist were reported by participants who had low levels of engulfment or who had high levels of acceptance over time. Patients with low rejection scores and high enrichment scores over time reported more visits to the family doctor.

To the best of our knowledge, we were the first to investigate the association between the different dimensions of illness identity and healthcare use in chronically ill patients. However, previous studies have provided evidence about associations between related concepts. First, a study has investigated how patients with psychiatric disease(s) become engulfed.[7] The study reported that hospitalisation is a threat to the patients viewing themselves as competent and can lead to an identity crisis.[7] This implies that healthcare use influences engulfment.[7] Second, studies have investigated the associations between illness identity and treatment adherence, a concept closely related to healthcare use.[1,8] In adolescents and emerging adults with type 1 diabetes, rejection was found to be related to poor treatment adherence and acceptance was related to

good treatment adherence.[1] When looking at these concepts over time, rejection was found to negatively predict and enrichment was found to positively predict treatment adherence one year later. This, in turn, negatively predicted engulfment and positively predicted enrichment over time.[8] Third, a study has investigated the association between healthcare use and illness perceptions, which is a concept related to illness identity, in adults with CHD.[9] Illness perceptions are the beliefs surrounding the symptoms, consequences, time course, controllability, and causes of an illness.[10] The study found that adults with CHD who felt that their disease had a severe impact on their life, and patients who believed that their disease could be managed by themselves or by treatment, reported more healthcare use.[9]

Second, the association between illness identity and patient-reported outcomes has been confirmed in our study (in Chapter 3), as well as in several other chronically ill patient populations. We found that patients who did not reject their illness, were not engulfed, or accepted their disease over time reported better health and quality of life and less psychological distress. The directions of associations remain unknown, because healthcare use was only measured at one point in time. These findings are in line with prior research. In adults with CHD, associations between the illness identity dimensions and depression, anxiety, self-reported health, and illness symptoms were found.[11,12] In young adults with refractory epilepsy, adolescents with celiac disease, and adults with inflammatory bowel disease, engulfment was found to be a predictor of health-related quality of life.[13-15] In adults with inflammatory bowel disease, higher scores on engulfment were also associated with more depressive symptoms, a poorer health status and lower life satisfaction.[15] In adolescents and emerging adults with type 1 diabetes and in patients with systemic diseases, engulfment and rejection were related to maladaptive psychological and physical functioning, with worse treatment adherence and more diabetes-related problems.[1,12] Contrariwise, acceptance and enrichment were associated with better treatment adherence, more adaptive psychological and physical functioning and fewer diabetes-related problems.[1,12] Enrichment was associated with more adaptive psychological functioning.[1,12] In participants with autism spectrum disorder, enrichment was related to quality of life.[16] In adolescents and emerging adults with neuromuscular disease, patients who used a wheelchair reported marginally significant higher scores on engulfment.[17] In the latter

population, no significant associations were found between the illness identity dimensions and age, time since diagnosis and severity of physical disability.[17]

Counterarguments

First, it can be argued that the association between illness identity and healthcare use still needs a more in-depth and thorough investigation. The association has only been studied in adults with CHD. Indeed, the generalisability of these findings remains limited. Moreover, because of shortcomings in the designs of the studies, the directionality of the associations still needs to be discovered. Hence, it remains to be examined whether illness identity influences healthcare use or whether it is the other way around. Therefore, it is especially difficult to confirm that illness identity is a predictor of healthcare use and PROs.

Second, one can wonder whether the predictive value of illness identity for healthcare use can be confirmed or whether only the predictive value of the dimension of engulfment for healthcare use can be confirmed. Throughout the studies performed in adults with CHD, as well as other chronically ill patient populations, strong associations were primarily found between the illness identity dimension ‘engulfment’ and healthcare use and outcomes.

Third, because illness identity was found to be rather stable over time in our study, the question rises whether illness identity is a modifiable concept for adults with CHD. When the aim is to intervene upon high and possibly avoidable healthcare use, it is evident that the identified predictors should be modifiable. If an predictor is not modifiable, it is still interesting to be aware of the impact of certain variables, but, it will not be possible to build interventions around this concept to improve patient-reported outcomes or healthcare use. Concerns about the modifiable character of illness identity might have raised because the concept was found to be relatively stable over time in our study on the longitudinal trajectories of illness identity.[18] Except for the longitudinal trajectory of acceptance, for which one group had increased scores over time, the dimensions of engulfment, rejection and enrichment remained stable over time. However, the stability of the concept in our study can be explained by the fact that patients with CHD received their diagnosis at birth or at least ten years before inclusion in the study. Another explanation is that only three measurement waves with one-year intervals were used. Previous research has

shown that restructuring one's identity is a dynamic and ongoing process.[19] A study in adolescents with diabetes type 1 showed that many patients changed cluster membership over time and that illness identity dimensions were likely to change over the different stages of the illness trajectory.[3,8] Hence, although the concept was found to be rather stable in our study, illness identity has shown to be a modifiable concept on which can be intervened in other studies. Different ways to intervene upon maladaptive illness identity integration have been identified. Cognitive-behavioural therapy and emotion-focused group interventions can help individuals reframe their beliefs and attitudes towards their condition and become more aware of their emotions and needs.[3,20,21] Moreover, healthcare providers could administer the Illness Identity Questionnaire (IIQ), but more creative tools can be used as well.[15] For instance, inspired by the PRISM-D, the drawing version of the Pictorial Representation of Illness and Self-Measure, healthcare providers could ask patients to draw two circles, one circle representing the illness and one circle representing their identity.[15,22]

Final answer

Relevant associations between illness identity and healthcare use and PROs were found. However, before the predictive value of illness identity for healthcare use and PROs can be confirmed entirely, the associations will have to be confirmed in other chronic populations and the direction of the associations should be investigated.

Answer in broader context

Confirming that illness identity can be seen as a predictor of healthcare use and PROs again emphasizes the clinical relevance of this concept and puts increased attention on the importance of tracking and intervening upon mental health issues. Over the past decades, mental health has moved up on policy agendas.[23] Although there is still a long way to go, mental health is put more centrally in the healthcare system, leading to increased attention to psychological concepts, such as identity.[3] Also in research, increasing attention has been given to examining psychosocial factors, illness perceptions and the psychosocial window of opportunity.[24,25] The psychosocial window of opportunity is a concept mainly used in rheumatoid arthritis that refers to the

opportunity to intervene upon psychosocial issues in the early phase of the disease.[26]

Can the association between healthcare system characteristics and patient-reported outcomes be confirmed in adults with congenital heart diseases?

The Andersen Behavioral Model presumes a relationship between healthcare system characteristics and PROs, but this relationship was not well investigated yet. Therefore, in this PhD thesis (Chapters 4 and 5), healthcare system performance and resources were associated with PROs. The question is now to what extent these associations can be confirmed in adults with CHD or what kind of research is still needed.

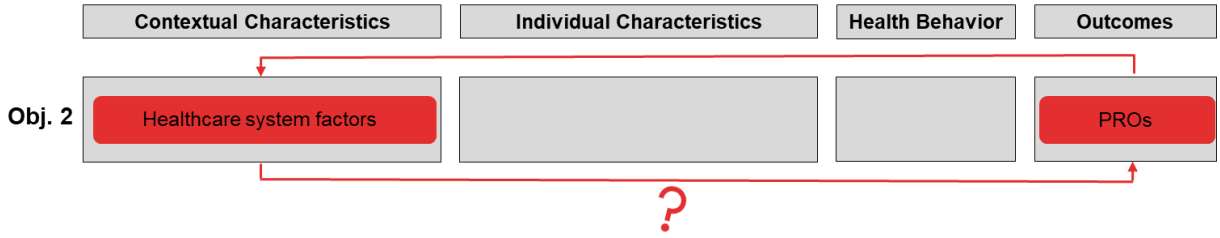

Figure 2. Visual representation of whether the association between healthcare system factors and PROs can be confirmed.

Arguments in favour

As described in Chapters 4 and 5, we found that features of healthcare system performance were associated with PROs. In more detail, we found that risky health behaviours were associated with the subdomains of the Euro Health Consumer Index about health outcomes and financing, patient rights and information, and access to pharmaceuticals. Self-reported physical health was associated with prevention of chronic diseases, a Euro Health Consumer Index subdomain. In addition, we found that a greater number of physicians was associated with better perceived physical and mental health, less psychological distress, and better quality of life. A greater density of nurses was associated with better perceived physical health, less psychological distress, and less unhealthy health behaviour. No associations were found between a higher density of hospital beds and PROs.

We were not the first study to investigate the association between healthcare system performance and PROs in adults with CHD. Another study in adults with

CHD, which has also used the data of APPROACH-IS, examined the association between the overall healthcare system performance, as measured by the WHO, and PROs.[27] The study found that overall healthcare system performance was related to the physical health status, above and beyond patient characteristics and unmeasured country differences.[27] Also other country-level factors were brought in association with PROs in an attempt to explain geographic variability in PROs.[27,28] National level of happiness, cultural dimensions and standard of living also partly explained the variance in PROs, when adjusted for patient characteristics.[27,28]

Also in other chronic patient populations, a couple of studies have found associations between healthcare system characteristics and PROs. A study showed that the variation of physician density within Canada determined the self-reported general health status.[29] Adding one additional family physician per 10,000 population yielded a 2-4% increase in self-reported general health.[29] An American investigation showed that a higher supply of primary care physicians was related to a higher probability of reporting good self-rated health.[30] Also with regard to nurse density, an American study showed that more hours of direct nursing care provision on a shift was related to lower levels of pains- and better self-reported health of patients.[31] Most research about the associations between healthcare system characteristics and PROs was performed on a national level, not allowing for comparisons between different countries and healthcare systems. We have studied the association between healthcare system characteristics (on country level) and PROs (on individual level) internationally.

Counterarguments

First, both existing literature and our studies have used study designs with considerable shortcomings. We have used observational cross-sectional exploratory study designs to investigate the associations between healthcare system characteristics and PROs. As a result, no conclusions in terms of the direction of effects or causality can be drawn. In addition, it cannot be determined whether an association was direct or indirect, as it is very likely that there are underlying patterns and confounders that we did not measure. Other healthcare system characteristics (e.g., accessibility of care, financing, insurance) or country-specific characteristics (e.g., education level, overall wealth of the population) might be confounding the association. The Andersen Behavioral Model assumes that the association is bidirectional and can be both

direct and indirect, but this can, based on the used study design, not be determined. Moreover, we must be careful with the generalisation of the results. We have used a non-random selection of centres within countries and have assumed that national averages applied to these centres. On top of this, there is a risk of selection bias. As we have only tested the associations across countries, no statements can be made with regard to the within-country associations. The regional differences could be interesting to investigate in future studies. Also, in Chapter 4, we have only included high-income European countries. It would have been interesting to include middle-income European countries, such as Croatia, Macedonia, Albania and Kosovo. Future studies should investigate the effect of the general healthcare system performance on PROs beyond Europe. In Chapter 5, all but two (i.e., India and Argentina) of the included countries were high-income countries. Moreover, there was an unequal division of participants across the countries. This might have impacted the results, as some countries have been overrepresented with regard to other countries. As mentioned in the discussion of Chapter 4, the performance measurement instruments used (i.e., EHCI and EHI) were not well validated yet and were criticised by some on their transparency, methodology and validity.[32,33] However, we were unaware of any better measures of components of healthcare system performance. In both Chapters 4 and 5, there is a risk of data inequivalence, meaning that slightly different performance measures or inputs were measured in the different countries. Of course, the Health Consumer Powerhouse and World Health Organization have put these numbers together and have provided clear instructions on how the numbers should be gained in the different countries. However, it can be that the concepts are not exactly the same in the different countries, which can have consequences for the results of the study.

Second, the studies performed as part of this PhD thesis have found an association, but the explained variation might be very small. The study by Moons and colleagues showed that the overall health system performance, as measured by the WHO, could explain only 0.25% of the variation in physical health of adults with CHD.[27]

Third, our studies have focused on the healthcare system performance and the density of physicians, nurses, and hospital beds as healthcare system characteristics. These are important indicators of the healthcare system.

However, other aspects of the comprehensive organization of the healthcare system (e.g., accessibility to care and quality of care metrics) were not studied yet. Also, it could be interesting in the future to investigate the association between healthcare inputs that are especially interesting

Final answer

The studies performed have provided indications that an association between healthcare system characteristics and PROs of adults with CHD may be present. However, because of the shortcomings in the study designs and performed analyses, no strong statements can be made. The studies should be seen as a preliminary step encouraging researchers to further investigate the influence of healthcare system inputs and performance on PROs of adults with CHD.

To what extent is the Andersen model useful or applicable in the end-of-life and palliative care context?

Palliative care and advance care planning are associated with healthcare use at the end of life and it is widely known that healthcare use is significantly more pronounced in the terminal phase of life. The question is to what extent the Andersen Behavioral Model can be validated within the specific context of the end of life.

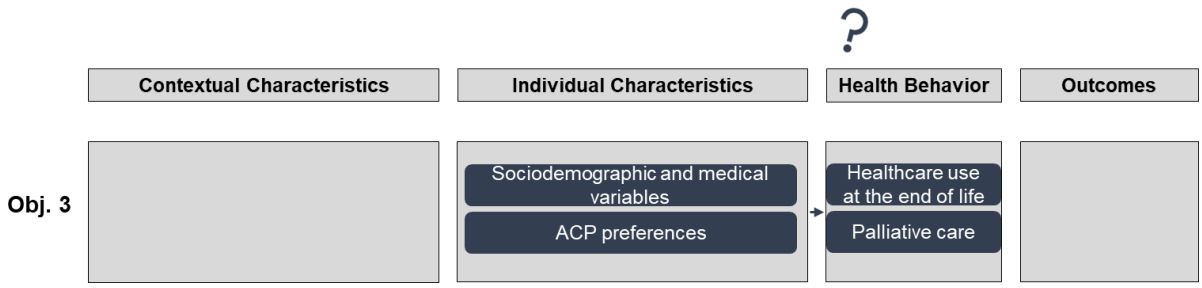

Figure 3. Visual representation of the Andersen Behavioral Model and the validation of the model in the end-of-life phase

There are significant differences between the concepts of palliative care, end-of-life care and advance care planning, although still commonly used interchangeably by patients and healthcare workers in clinical practice. Whereas end-of-life and hospice care take place at the terminal phase of life, palliative care is a much broader term and can also be provided early in the disease trajectory to patients with a life-limiting disease. Palliative care can be

defined as an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering.[34] Often, palliative care is still only linked to the terminal phase of life. This idea is based on the traditional and outdated model of care that palliative care is associated with the cessation of curative therapy and a focus on terminal care.[35] However, in the more recent integrated model, an early integration of palliative care, that is provided simultaneously with curative therapies, is advocated.[36] There are different levels of palliative care provision, from a non-specialised palliative care approach or primary palliative care, to the provision of specialist palliative care and the development of centres of excellence.[37] The palliative care approach is characterized by the integration of palliative care methods, principles and procedures into settings that are not specialised in palliative care.[37] This is also often called primary palliative care.[38] In specialist palliative care or secondary palliative care, the main activity is the provision of palliative care and these healthcare workers take care of patients with complex and difficult needs.[37] Advance care planning can be seen as a type of palliative care provision. It can be defined as a process that supports and empowers individuals at any stage of their lives or disease process to consider, communicate, and document preferences for future health care.[39] Advance care planning aims to identify personal values and goals to align future medical treatment and care with these personal beliefs and convictions.[39,40]

Recognizing the importance of palliative care for all patients with a life-limiting illness is relatively new.[41] Since 2002, a law on palliative care in Belgium is implemented, which states that every citizen has the right to receive palliative care.[42] Back in 2002, palliative care was defined as care provided to patients with a life-threatening disease that does not respond to curative treatment anymore.[42] In 2016, the definition of palliative care in the law was broadened.[43] Palliative care is now defined as any care provided to patients who, regardless of their life expectancy, are in an advanced or terminal stage of a seriously evolving and life-threatening disease. Palliative care is currently mostly provided to patients with cancer, but there is increasing recognition of the importance of palliative care in other conditions as well.[44,45]

Arguments in favour

First, advance care planning and palliative care consultations were found to be associated with healthcare use in the final phase of life in previous studies in chronic patient populations.[46-48] Indeed, less aggressive medical care and lower costs at the end of life were reported for patients who had end-of-life conversations or palliative care consultations.[46-48]

Second, palliative care and advance care planning could also be considered as particular types of healthcare use that are influenced by predisposing, enabling and need factors. In our studies reported in Chapters 7 and 8, associations were found between patient-related factors and country-specific factors on one hand and palliative care provision and advance care planning practices on the other hand. We showed that palliative care provision varied depending on the cause of death (Chapter 8) and that advance care planning practices, needs and preferences depended on age, sex, disease complexity, NYHA class and geographic variability (Chapter 8). Hence, palliative care and advance care planning, as types of healthcare use, were found to be related to contextual and individual predisposing and need factors.

Furthermore, some other studies have used the Andersen Behavioral Model while investigating palliative or end-of-life care. Two studies have investigated racial and ethnic differences in ACP discussions and completion of ADs, while accounting for predisposing, enabling, and need factors of the Andersen Behavioral Model.[49,50] Moreover, Di Nitto and colleagues have described factors that are associated with receiving specialist palliative care, while categorizing the variables as predisposing, enabling and need factors according to the Andersen Behavioral Model.[51] They found that the use of specialist palliative care services was not only influenced by need factors, but also by social and contextual factors.[51] Furthermore, Lindley and colleagues have studied the effect of palliative care policy on hospice use in children and their families and have analysed the child and family factors associated with hospice versus home healthcare use in the last year of life.[52,53] She used the Andersen Behavioral Model to create groups of children and family covariates, based on their predisposing, enabling and need characteristics.[52] She also studied the determinants of access to paediatric hospice care, while using the Andersen Behavioral Model as the theoretical framework.[54]

Counterarguments

Palliative care and advance care planning can both be seen as types of healthcare use and as predicting factors for healthcare use. Indeed, palliative care provision is a type of healthcare use provided to patients with a life-limiting condition. However, palliative care provision can also be seen as a predictor for healthcare use at the end of life. Patients that had palliative care consultations have been shown to have less aggressive medical care and lower costs at the end of life.[46-48]

Final answer

The available literature has shown the value of palliative care and advance care planning for the Andersen Behavioral Model, both as predictors and types of healthcare use. Therefore, we can conclude that the Andersen Model can also be valuable within the context of the end of life.

Should the palliative and end-of-life care provision to adults with congenital heart disease be redesigned?

Palliative and end-of-life care currently provided to adults with congenital heart diseases have been examined in Chapters 7 and 8. The question arises whether, based on these results, we can advocate for a redesign of the current end-of-life and palliative care provision.

Arguments in favour

First, there are mismatches between the preferences of patients and the actual care they receive with regard to advance care planning. According to our patients, the best time to initiate advance care planning is early in the disease trajectory (Chapter 7). However, an earlier study reported that 63% of healthcare providers thought that patients were not ready for end-of-life discussions if the estimated life expectancy is over five years, and 79% thought that patients were not ready if the estimated life expectancy is over ten years.[55] Another study reported that only 38% of providers think early end-of-life discussions are appropriate.[56] Indeed, CHD providers seem to be concerned about whether their patients are ready for these discussions, particularly for patients who are in good health.[55,57] Moreover, although previous studies showed that both providers and patients indicated that they thought that advance directives were important [57,58],

we found that only 9% of our patients have such documents in which they have written down the care they want to receive in the future.

Second, as reported in Chapter 8, we observed high resource use in terms of (unplanned) hospital admissions, emergency department visits, cardiovascular procedures, and intensive care unit admissions at the end of life, mainly in the last three months of life in adults with CHD. Meanwhile, specialist palliative care was only provided to a tiny proportion of patients, and this proportion was even much smaller when only looking at the patients with cardiovascular causes of death. One other study has investigated the end-of-life healthcare use of adults with CHD using administrative or clinical data.[59] In that study, Steiner and colleagues described that 39% of patients were hospitalised, 39% had an intensive care unit admission and 3% had an emergency department visit in the last month of life.[59] Moreover, a couple of qualitative and questionnaire studies also provided some relevant findings in this regard.[57,60,61] A total of 91% of adults with CHD indicated that they were at least moderately willing to speak to a clinician specialised in palliative care, but only 3% had actually met one.[60] Furthermore, adults with CHD often related the concept of palliative care to the terminal phase and described it as “giving up”.[61] Besides, CHD healthcare providers seemed to have only little palliative care knowledge.[57] Moreover, only a small proportion (14%-32%) of the CHD providers indicated that they would initiate a palliative care referral.[57] Hence, also in these studies, high resource use in terms of hospital and intensive care unit admissions and low provision and attention for proper palliative care was reported. As palliative care is typically seen as desirable at the end of life and hospitalisations, emergency department visits and intensive care unit admissions are not necessarily seen as appropriate at the end of life, these studies indicate that the healthcare provision at the end of life can be improved.

Third, to take into account the cardiovascular risks and symptoms at the end of life, it is recommended to keep the CHD physician involved, also at the final stage of life. However, in our study, we noticed that only 25% of patients saw a CHD physician in the last year of life and 11% in the last month of life (Chapter 8). Hence, these findings raise the question of whether CHD physicians are sufficiently involved in the last phase of life and whether the cardiac needs and symptoms are adequately taken into account at the end of life.

Fourth, we have indications that the profiles of adults with CHD are changing over time, which might also cause changing end-of-life and palliative care needs. Due to improved treatment of long-term sequelae and better follow-up of patients with mild-to-moderate CHD during childhood and adolescence, the cause of death is changing, and the median age of decedents is increasing.[62] Especially for patients with mild and moderate CHD lesions, increasingly more patients die of other causes than their heart disease. The median age in our study was 55 years (Chapter 8), which is higher than the median ages at death reported in older studies.[63-65] Therefore, palliative and end-of-life care needs could be different than they were in the past.

Counterarguments

First, based on the results that we have right now, it is too early to make a decision about whether the palliative and end-of-life care should be redesigned and how the redesign should look like. Indeed, more research is needed before recommendations about a reform of the palliative and end-of-life care provision can be formulated. Aside from our study, only one other study has investigated end-of-life healthcare use of adults with CHD using administrative or clinical data.[59] Also, the actual end-of-life and palliative care needs and patient preferences of adults with CHD remain understudied. Also, research on specific quality indicators of potentially inappropriate and appropriate end-of-life care for this patient population is still lacking. Hence, there is no consensus yet on what appropriate and inappropriate end-of-life care is and no monitoring on the extent to which patients receive inappropriate (aggressive life-prolonging) care. Indeed, the development and application of such indicators are needed to guide further discussions on whether and how end-of-life care for adults with CHD should be reformed. The quality indicators can be used to evaluate healthcare system performance in terms of end of life and will allow to identify variation in countries, regions and settings.[66] Hence, it is probably only by doing so that a good evaluation of the current care provision and recommendations with regard to reforms will be possible.

Second, our studies had several shortcomings. We could not distinguish whether healthcare use was for a reason related to the heart disease or not, because this information was not available. Moreover, only information with regard to specialist palliative care was available in the administrative data. A

higher proportion of patients likely received care with a palliative approach or received general palliative care.

Final answer

There are reasonable indications that the palliative care provided to adults with CHD can be optimised and the balance between under- and overtreatment at the end of life has not yet been found. There seem to be mismatches between the preferences of patients and the actual care provided. In addition, there is a tendency towards aggressive healthcare use at the end of life, with only limited attention to palliative care and advance care planning. Before clear recommendations can be formulated on how the redesign should look, more research is needed about the actual needs and preferences of patients and indicators should be developed.

Methodological considerations

The methodological limitations of each study were described in the discussion section of the respective chapters. However, a couple of general methodological considerations require further discussion.

Appropriate versus inappropriate healthcare use

As the healthcare system struggles with scarce healthcare resources and rapidly rising healthcare expenditures, decreasing inappropriate healthcare use is a priority.[67,68] Inappropriate healthcare use is not only harmful for the patient, but also raises economic and ethical concerns, since the resources are spent on actions that provide only limited benefit and even possible harm.[41,68,69]

Unfortunately, in the studies of this PhD thesis, no distinction could be made between appropriate and inappropriate healthcare use. A treatment is found to be appropriate when the expected health benefits outweigh the possible disadvantages.[70] Inappropriate health care occurs when bad clinical practices are overused, good clinical practices are underused or other practices are misused.[67,71] Hence, to make a distinction between inappropriate and appropriate healthcare use, the benefits and possible risks of the treatment and clinical practices should be taken into account. Of course, also the decisions made by the patients, in the light of shared-decision making and patient autonomy, are important to consider. All this information was not available in the studies included in this dissertation. Because of this shortcoming, we are unable to make strong statements about the possibility that certain variables, such as illness identity, can play a role in (the diminishment of) inappropriate healthcare use.

Defining whether healthcare use is inappropriate or appropriate is slightly more straightforward at the end-of-life care.[41] Palliative care is typically seen as desirable at the end of life. Oppositely, hospitalisations, emergency department visits and intensive care unit admissions are not necessarily seen as appropriate, but rather as inappropriate, at the end of life. Recent studies have developed quality indicators to evaluate the appropriateness of care provision at the end of life for patients with chronic conditions.[66,72,73] Also for children with genetic or congenital conditions, quality indicators have been developed and validated.[73] Indicators of appropriate healthcare use were, for example,

physiotherapy, comfort medication and pain control.[73] Quality indicators for inappropriate care were, for example, excessive magnetic resonance imaging monitoring, surgeries or starting dialysis.[73] As previously mentioned, no such quality indicators have yet been developed and validated for adults with congenital heart diseases.

Study designs and bias

All research projects included in this PhD thesis rely on a quantitative observational study design.

In Chapters 3 and 6, an observational retrospective cohort design was used. This type of study design looks back in time to gather information on past events or exposures and their associations with an outcome of interest. Using this type of design is interesting, because it allows the collection of a large amount of data in a relatively short period of time. The study from Chapter 2 uses an observational ambispective design. Ambispective indicates the fact that the observations have both retrospective and prospective components.[74] In our study, patients were prospectively asked to report about their healthcare use in the past six months. Chapters 4, 5, 7 and 8 used a cross-sectional study design. Cross-sectional studies are performed to examine the presence or absence of an outcome at a single point in time. The concepts and associations have only been investigated quantitatively. Using a qualitative research design, a deeper understanding of the concepts and underlying motivations, opinions, wishes or needs could have been identified.

The study designs used might have induced several types of bias, such as confounding, recall bias, nonresponse bias and selection bias.

Confounding

Because confounding variables and reverse causality may be present, it is challenging to achieve causality.[75] In other words, using observational studies, associations between exposure and outcome can be investigated, but making cause-and-effect relationships is often more challenging to establish and requires careful consideration of deconfounding strategies and temporality. Careful consideration of existing evidence and plausible causal assumptions that guide the deconfounding strategies, can be used to get closer to causality.[75,76] Causal directed acyclic graphs and target trails can be used to help understand the potential interplay between exposure variables,

confounders and outcomes.[77,78] In our studies, we have tried to take confounders as much as possible into account by correcting for them in our models. Moreover, we refer to the investigated associations not as causal relationships, because it is very likely that we were not able to include all confounders in our models. Future studies that investigate the associations described in this PhD project should consider using more deconfounding strategies and advanced statistical techniques to take confounders into account and, thereby, to gain a better understanding of the cause-and-effect relationships of these variables.

Recall bias

In Chapters 2 and 3, information on healthcare use over the past six months was gathered through self-report of the patients. This includes a risk for recall or telescoping bias. Recall bias is a systematic error that occurs when participants do not accurately remember a past event or experience when reporting about them. Telescoping bias describes the temporal displacement of an event whereby people perceive recent events as being more remote and distant events as being more recent than they are. With regard to hospitalisations, patients often have a good recall, but their memory of outpatient healthcare use might be more unreliable.[79] The longer the recall timeframe, the less accurate the reporting is.[80] Indeed, underreporting increases sharply for longer recall periods.[80] Therefore, in the studies in Chapters 2 and 3, a recall period of 6 months was used.

Nonresponse bias

Low response rates can induce nonresponse bias when it creates differences between responders and non-responders on the variables of interest and when these differences cannot be eliminated or controlled for. Consequently, the generalisability of the findings can be affected. To increase the response rates in our studies, a modified Dillman approach was used. Non-responders received a first personalized reminder approximately after four weeks, a second reminder (formal letter) after eight weeks and a third reminder (formal letter) after twelve weeks. To optimize retention rate across time, some incentives (e.g., gift vouchers) were also raffled upon completion of the questionnaires at each measurement wave.

We have indications that the nonresponse bias is limited for our studies. The study reported in Chapter 8 used a population-based dataset. Moreover, for the Belgian branch of the APPROACH-IS study, the response rates were found to be high (T_{2013}: 69%, T_{2014}: 74% and T_{2015}: 80%). Furthermore, Berghammer and colleagues have investigated differences between participants and non-participants of APPROACH-IS in terms of demographic, clinical and health status characteristics.[81] These differences appeared to be very small.[81]

Selection bias

To minimize the risk of selection bias, which is bias that has occurred because of a substantial difference in the characteristics between those who were selected for the study and those who were not selected, we have applied a random sample technique in two of our studies (Chapters 2 and 3). The patients were selected at random from the clinical hospital database. Non-response is a threat to selection bias, but the response rates were rather high as discussed above.

Missing data

Except for the study that used administrative data in Chapter 8, all studies had to deal with missing data. This was handled a bit differently in the different chapters. In Chapters 2, 4, 5 and 7, we included only the patients with full data on the variables of interest in the analyses. In Chapter 2, 5-8% of patients had missing data on some variables of healthcare use. Hence, in these analyses, 198 to 205 patients were included. In Chapters 4 and 5, only a small proportion of patients had missing data for PROs (0.0–2.1%) and patient-related predictors (0.0–2.5%). In Chapter 7, no multiple imputations were performed, because the missing data were limited and some medical data will still be added in the next months, as a couple of centres are still entering their medical data. In Chapter 3, there was a total of 13.0%-13.3% missing data on the four illness identity dimensions at T2013-T2015. In this study, we used the full information maximum likelihood (FIML) procedure to handle the missing data. Since the missing data were rather limited in most of our chapters and FIML was used in Chapter 3, we think that the bias created by missing data in our studies was rather limited.

Selection of decedents

In Chapter 8, a retrospective design was used to study the healthcare use of decedents. The use of such a "study of decedents" for this purpose has been criticised by Bach and colleagues.[82] They state that studies of decedents, which typically analyse the care provided to patients over a defined interval prior to death, can create invalid conclusions about the quality or type of care provided to dying patients.[82] However, other colleagues have replied that retrospective assessment of decedents remains an important methodology, given the substantial uncertainty in prognostication for many patients.[83]

Data and measurement inequivalence

We could have paid more attention in the studies included in this PhD project to the data and measurement equivalence across countries, as this inequivalence could have influenced the extent to which the results are reliable and generalizable. However, in the APPROACH-IS and APPROACH-IS II studies, a uniform methodology was used in all participating centres. Standard operating procedures were set up to guide the data collection in all centres. However, some centres had to slightly adjust the methodology because of practical reasons. The patient population in Pakistan, for example, had an overall low literacy rate making it very hard to find sufficient patients that could complete the surveys. Hence, therefore, they have also interviewed patients over the phone. This could have influenced the results of the study. Also, measurement equivalence could have been taken into account better. This refers to the extent to which the instruments and methods used are culturally and linguistically appropriate and produce comparable results. Although the guidelines for translations of the World Health Organization were followed, it would have good to have tested the surveys extensively in different cultures and contexts. Especially the survey on ACP preferences, practices and needs could be heavily influenced by measurement inequivalence.

Administrative data

In Chapter 8, routinely collected administrative healthcare data were used to find an answer to the formulated research questions. We choose this type of data, because it offered many advantages. Using administrative data, we had access to a large number of collected data, which were relatively inexpensive to

use, free from non-response and dropout and especially interesting for sizable groups, such as decedents with CHD in Flanders.[84]

However, using these data to answer our research questions also had methodological limitations. In the BELCODAC database, a lot of information was missing. Not only was the information often not very detailed, information on non-reimbursed healthcare use, over-the-counter medication and variables with regard to the health status, quality of life and preferences of the patients were lacking. Because non-reimbursed healthcare use and over-the-counter medication were lacking, it was not possible to get a complete overview of the healthcare use and the healthcare costs of this population. Also, we could only have a limited understanding of the investigated associations, as the above-mentioned variables could have confounded the associations and hence, were also needed to have a complete understanding of these associations. Moreover, the BELCODAC database, like many other administrative databases, suffered from coding faults, inconsistencies across care settings, changes in coding policies over time and weak accuracy of the data.[85] However, this issue was probably smaller in the BELCODAC database, compared to other administrative sources, because BELCODAC combined both clinical and administrative data of adults with CHD.[88] By combining the two sources, we hoped to have improved the quality of the data. The data from the hospitals provided more accurate information about medical variables (e.g., diagnosis, intervention type and complications). In addition, several variables were included in both clinical and administrative care; hence, data could be cross-validated, resulting in more reliable data.[88] Furthermore, the use of administrative data for this study also impacted the external validity of the results and hence, the extent to which the results were generalised to other populations, settings and contexts. BELCODAC only included patients from Flanders and Brussels. Hence, the findings of our study may not be generalisable to different regions or systems. The extent to which the findings of our study are applicable to other patients populations and settings is not clear yet. Moreover, the accuracy of the underlying causes of death, expressed in ICD codes, in BELCODAC might be limited.[86,87] In BELCODAC, thanks to a collaboration with Statistics Belgium, data on mortality were added to the database, making it possible to investigate decedent patients. However, we know that very often the death certificate is not filled out by a congenital cardiologist, but by a regular physician. Hence, it is

likely, especially for adults with CHD who have a very complex cardiovascular profile, that there might have been diagnostic issues or an ambiguous cause of death, which could have induced errors in the causes of death.[88] Moreover, there might have been input errors. Altogether, these issues could have generated mistakes in the causes of death reported for our patients.[86,89] Moreover, unfortunately, only the primary cause of death was available in BELCODAC and we did not have information on whether the death was sudden or not. A big strength of BELCODAC was, however, that patients were not identified using ICD coding, but they were identified in the clinical files of the hospitals. In other studies, patients are often identified using the International Classification of Diseases and Related Health Problems (ICD) ninth or tenth revision codes, which often lead to misidentifications.[86]

Heterogeneity within the study population

It is difficult to make general statements about the entire population of adults with CHD, because it is a very heterogenous population. There are many different diagnoses, all varying in terms of anatomical complexity. These anatomic defects are treated by a great variability of interventions. Some patients step into CHD care without prior interventions, while others have a history of one or more surgical interventions, potentially in combination with one or more catheter-based procedures. Other patients have residual defects, sequelae, and complications, accompanied by hospitalisations or medical emergencies.[90] On top of this, there is an important layer with regard to the mental health status of the patients. Patients with CHD have a higher risk for displaying emotional distress, such as depression and anxiety, but the psychological state of the patient can significantly vary as well.[27,91] Indeed, some patients suffer greatly from their illness both physically and mentally, while others are only impacted to a very limited extent. Therefore, we must be careful not to lump all these patients together.

However, the heterogeneity of this population can also be seen as an advantage. Patients with CHD represent the whole spectrum of patients, from those whose daily lives are heavily impacted by their disease to those who are only affected limitedly. This makes our results potentially generalizable to a large group of other chronic conditions, from mild to severe.

Lack of involvement of patients

The research presented in this dissertation has only involved patients and their families to a limited extent. We did not systematically include patients in the development, data analyses or interpretation phase of a study. It could have been very valuable to involve patients in the design of a new research project, to hear how they interpreted the results and what they felt the implications were for clinical practice.

When one of our articles on illness identity was published [92], we were contacted by a patient with a congenital heart disease who recognised herself strongly in the different illness identity dimensions. As a supplement to our quantitative article, she has written a patient perspective on how she has experienced the different illness identity dimensions as a patient.[93] Thereby, she was able to bring the dimensions to life for patients and healthcare workers. Such collaborations should be encouraged in the future and we must ensure that patients have a voice as well.

Strengths

There are also some overarching strengths that are worth mentioning. In more than half of the studies we have conducted, we were able to provide an international and often global perspective (Chapters 4, 5, 6 and 7). In these studies, at least eight countries were included and large sample sizes from 1,591 to 8,231 patients were used. Moreover, whereas many previous studies have only studied inpatient healthcare use or hospital admissions, we have investigated the use of a broad range of services. Indeed, we have also included outpatient consultations, visits at the general practitioner or medical specialist. In the studies on PROs, we used validated surveys that were well-known and of which the translations to different languages were well validated. Although it is impossible to pass judgment on the cause-effect relationships, as discussed earlier, we have tried to correct for relevant confounders and for hierarchical models as much as possible, by applying multivariable and multi-level analyses. Furthermore, in Chapters 2, 3 and 8, we used a study design that measured the variables of interest on more than one time point. Additionally, in Chapter 8, palliative and end-of-life care provision to adults with CHD was examined. This study used the BELCODAC database, in which clinical data from hospitals were combined with qualitative data from Statistics Belgium and the InterMutualistic

Agency. Also, patients were reliably identified as patients with a congenital heart disease based on the hospital data.

As part of this PhD thesis, the APPROACH-IS II project was set up (Chapter 6). This project has collected PROs in over 8,000 adults with CHD from 53 centres in 32 countries. The project has also measured cognitive functioning and frailty in a subgroup of older adults. Although only the results with regard to advance care planning have been reported in this PhD thesis, this project will be able to generate much more interesting findings that will lead to an optimization of the quality of life and quality of care for adults with CHD.

Implications for practice

The findings conceived from this PhD have several implications for clinical practice and healthcare policy.

Measurement and acknowledgment of illness identity issues

As discussed in Chapters 2 and 3, a group of patients has less favourable scores (over time) for all identity dimensions. This shows that, although patients have lived with their CHD for a long time already, some patients still have trouble integrating their illness into their identity. These patients with maladaptive illness identity dimensions need additional support from their healthcare practitioners, starting with the measurement and acknowledgment of the identity issues.[12] Indeed, if healthcare workers can measure and acknowledge patients' identity issues, they can help patients to become more aware of how their chronic illness influences their daily lives.[3] This can be done by using the Illness Identity Questionnaire (IIQ) to measure illness identity, by opening the dialogue and actively challenging the negative thoughts, and by referring to psychological counselling.[3] To achieve this, the usefulness of the concept of illness identity and how to intervene upon the concept should be promoted among healthcare providers. For example, the concept could be integrated into the general caregiver education or specific trainings on psychological health and wellbeing.

As discussed in Chapter 3, older patients are more prone to be overwhelmed by their illness or to reject their illness over time and patients with more complex heart disease have higher chances of being overwhelmed and enriched. Hence, older patients and patients with a complex heart disease could be the first to target when trying to identify patients with a maladaptive illness identity integration.

Development of tailored interventions to tackle maladaptive illness identity integration

As illness identity is found to be associated with healthcare use and PROs in adults with CHD, illness identity could be taken into account when trying to understand why certain people consume more healthcare services as compared to others and when trying to understand variation in PROs. When the underlying pathways become more transparent, tailored interventions can be established

that aim to tackle maladaptive illness identity integration and thereby aim to optimise healthcare use and PROs of adults with CHD.

Policy recommendations with regard to the importance of healthcare system characteristics

Policymakers should safeguard healthcare system factors that are protective of patient outcomes. Chapters 4 and 5 of this PhD project have contributed to this knowledge base. Although no strong statements could be formulated, the studies provided good indications about the importance of certain elements of the healthcare system for PROs. When future research confirms the findings from our studies, countries that score low on the domains of the healthcare system performance, 'outcomes', 'prevention', 'patient rights and information', and 'pharmaceuticals' could consider investing in these features in order to improve PROs of specific patient populations. Also, as we found positive associations between the density of healthcare workers and PROs. Thus, policymakers should consider the impact on PROs before deciding on downsizing the healthcare workforce.

Need for integrated care for adults with CHD at the end of life

As we found that less than half of the sample of adults with CHD within our study died because of their heart disease and many patients have comorbidities, it is clear that care at the end of life should go beyond cardiovascular care. Indeed, there is a need for integrated care provided by healthcare providers from different disciplines working altogether. As a first step, research and clinical practice should explore the development of best practice models with an interdisciplinary approach regarding palliative care, CHD and comorbid conditions, such as cancer and respiratory diseases and evaluate whether this could improve outcomes for this patient population.

Improve quality of palliative and end-of-life care for adults with CHD

Our findings from Chapters 6 and 8 showed that improving the quality of palliative and end-of-life care provision for adults with CHD will be an important challenge for our healthcare systems in the upcoming years. The discipline of cardiology is still very much oriented towards treating and healing. To make structural improvements, a paradigm shift in cardiology is warranted.[94] A first recommendation in this regard is to seek ways to improve the identification of patients with palliative care needs, by developing and validating palliative care

needs assessment tools in this population. In addition, cardiology providers should receive training enabling them to implement a palliative approach in their care delivery. Moreover, a campaign regarding misconceptions about palliative care for providers and patients could be useful. Interventions should also be established to improve recognition of cardiovascular patients with palliative care needs.

Avenues for future research

In my opinion, this PhD thesis delivered a substantial contribution to the current body of knowledge regarding healthcare use and patient-reported outcomes in adults with CHD. However, gaps in the body of knowledge still remain. Some suggestions for future research have been discussed in the respective chapters. In this section, we suggest some additional overarching avenues for future research.

More research on the Andersen Behavioral Model

On top of the gaps that we have identified in the literature based on the Andersen Behavioral Model, many more gaps can be identified. Lederle and colleagues have performed a scoping review about applying the Andersen Behavioral Model to health services research.[95] They have listed the elements that were found to be missing in the model by researchers, such as, health literacy, individualised care, trust, previous experiences, informal care system, characteristics of informal caregivers and spirituality.[95] Hence, in further research, attention should be paid not only to the variables discussed in our studies, but to these variables as well. The review also found that the publications adopting this model are mostly (70%) stemming from North America and have used the framework in the general population.[95] Not often has the framework been used to study healthcare of specific patient populations yet.[95] Hence, future studies examining healthcare in specific patient populations and elsewhere in the world, can be encouraged to use the Andersen Behavioral Model as a guiding framework. Thereby, these studies will also contribute to the validation of the model in these settings. Moreover, another review found that most studies have used very simple statistical models, such as univariable testing.[96] To better investigate how the different elements contribute to healthcare use, proper statistical analysis and good deconfounding strategies that can deal with the model's complexity should be used.[96] Such examinations can better understand the associations between the main factors (predisposing, enabling, need) and investigate feedback loops.[96]

The role of illness identity as mediator or moderator

In the present thesis, the predictive value of illness identity for healthcare use has been examined. Future studies should consider investigating illness identity

as a mediator or moderator within associations between other individual characteristics and outcomes or healthcare use.

Qualitative studies

All studies from this PhD thesis rely on a quantitative research design. Future studies should investigate concepts such as illness identity, healthcare use, and advance care planning using a qualitative paradigm. Qualitative studies can provide a deeper understanding of these concepts and the underlying pathways. The concepts can be investigated using interviews or focus groups and can, thereby, provide a more holistic and deeper understanding of the retrieved associations. The qualitative research could build further on our quantitative studies by, for example, interviewing the group of patients that were identified as patients with very high engulfment scores in Chapters 2 and 3. This research could try to understand how the engulfment manifests itself in daily life and how this influences their healthcare use and PROs. Alternatively, it could also be interesting and relevant to focus on the subgroup of adults with CHD whom indicated they did not want to talk about what care they want to receive in the future (Chapter 7) and try to understand their underlying reasons. Future qualitative studies should be encouraged to use the Andersen Behavioral Model as a framework. A review has shown that the model is mainly used in quantitative studies but is also suitable for qualitative research.[95]

Different patient populations

Only adults with CHD have been included in the studies of this PhD thesis. However, it would be interesting for future studies to include children and adolescents with CHD. Studying the development of illness identity in these populations can be very interesting, as these patients could have gone through different stages of the illness trajectory. Moreover, children with CHD are expected to be treated differently (probably more aggressively) at the end of life as compared to adults, because of their younger age. It would be interesting to investigate the provision of end-of-life care to children with CHD in the future. Furthermore, future studies should investigate the studied associations and findings in other chronically ill patient populations and thereby investigate to what extent the findings of our studies can be generalised to other patient populations.

Longitudinal research

Longitudinal studies are needed to investigate the concepts and associations further. These studies can shed light on the directionality of effects. In Chapter 3 on illness identity, only 3 measurement waves with a one-year time interval were included, which represents a rather short period. This could be one of the potential reasons why only little change in the development of illness identity was found. Another reason could be that the patients had been diagnosed with the disease for a very long time already. Longitudinal research with continuous follow-up could provide more information on the development of illness identity over time. Cross-lagged path analysis could be applied to examine the predictors of illness identity or predictive value of illness identity over time. In Chapters 4 and 5, the association between the healthcare system performance and density of human resources and infrastructure, and outcomes was studied cross-sectionally. To be able to set up statements for health policy and planning[29], longitudinal studies on these associations should be performed to better understand the directionality of the findings and underlying pathways. It is only with the availability of such scientific data that we will be able to advise policymakers about aspects of the healthcare system impacting PROs.

Palliative and end-of-life care in cardiology

More research is needed in the field of palliative and end-of-life care in patients with cardiovascular conditions. Future studies should focus on the palliative and end-of-life care needs of adults with CHD and identify how the healthcare system can effectively respond to these needs. Additionally, there is a need to focus on economic evaluations of the end of life to determine the costs and benefits of certain types of healthcare use at the end of life. Moreover, it would be helpful to perform scientific projects entailing patients whom are alive still as well, but that have similar clinical profiles. Such studies, comprising a control population, can provide great insides into the real underlying dimensions of healthcare use at the end of life. Furthermore, more research is needed on how conversations, with regard to advance care planning, should take place. It remains unknown how and when such conversations should be initiated and how family members can be involved in these discussions.[41] Also, future studies should focus on the identification of appropriate outcome measures of advance care planning and to make sure such outcome measures are truly patient-

specific. Meanwhile, good measurement tools to investigate the effects of advance care planning interventions should be developed. [41]

Overall conclusion

Guided by the Andersen Behavioral Model of Health Services Use, this PhD project has provided evidence with regard to (predictors of) healthcare use and PROs of adults with CHD.

Illness identity has been identified to be related to healthcare use and PROs. Moreover, associations were found between healthcare system characteristics and PROs of adults with CHD. However, additional research with regard to these associations is needed. Furthermore, there are reasonable indications that the end-of-life and palliative care provided to adults with CHD can be optimised and the balance between under- and overtreatment at the end of life has not yet been found.

More research is needed, mainly focusing on improving the generalisability of findings and determining the directionality of the effects. The use of longitudinal studies, qualitative research and intervention studies is recommended.

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Chapter 2. Illness Identity: A Novel Predictor for Healthcare Use in Adults with Congenital Heart Disease

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Chapter 3. Illness identity in adults with congenital heart disease: Longitudinal trajectories and associations with patient-reported outcomes and healthcare use

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Chapter 4. Patient-reported outcomes of adults with congenital heart disease from 8 European countries: scrutinizing the association with healthcare system performance

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Chapter 5. Healthcare system inputs and patient-reported outcomes: a study in adults with congenital heart defect from 15 countries

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Chapter 6. Rationale, design and methodology of APPROACH-IS II: International study of patient-reported outcomes and frailty phenotyping in adults with congenital heart disease

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Chapter 7. Advance Care Planning in Adults with Congenital Heart Diseases: current practices, preferences and needs of 8,285 adults from 32 countries

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Chapter 8. Last year of life of adults with congenital heart diseases: causes of death and patterns of care

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Other contributions: Statistics Belgium and the InterMutualistic Agency contributed to the data collection and merging of the data. Steffen Fieuws helped with the analyses of the data in SAS.

Personal contribution

The studies described in Chapters 2, 3, 4 and 5 use data of APPROACH-IS. The PhD candidate Liesbet Van Bulck was not involved in the set-up or data collection of this project. Though, she has performed the statistical analyses, interpreted the results, and wrote and revised the manuscripts.

The studies described in Chapters 6 and 7 are based on data of APPROACH-IS II. Liesbet is the international project coordinator of this project. She has played an essential role in the set-up, execution, data collection and management of the study around the world. She has also executed the statistical analyses, interpreted the results, and drafted the manuscripts presented in Chapters 6 and 7.

The study described in Chapter 8 relies on data of BELCODAC. The BELCODAC database has mainly been set up by Dr. Fouke Ombelet, Prof. Eva Goossens and Prof. Philip Moons. Liesbet Van Bulck was responsible for the approval from the Belgian Privacy Commission and helped with the data collection and data management. Liesbet has performed the statistical analyses, interpreted the results, and wrote and revised the manuscript presented in Chapter 8.

Conflict of interest

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Ambassa, Jean-Claude	No conflict of interest
Amedro, Pascal	No conflict of interest
Andresen, Brith	No conflict of interest
Annemans, Lieven	No conflict of interest
Apers, Silke	No conflict of interest
Araujo, John Jairo	No conflict of interest
Areias, Maria Emília	No conflict of interest
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Professional career and publications

Professional career

Liesbet obtained her Bachelor in Nursing at the Hogeschool Universiteit Brussel in 2014. In 2016, she obtained the degree of Master in Nursing and Midwifery at KU Leuven (with greatest distinction). She started her PhD at the Academic Center of Nursing and Midwifery in October 2016. In 2019, she received a PhD fellowship by the Research Foundation Flanders to continue her PhD research for 4 years.

During her PhD, Liesbet completed a research stay of one year at the University of Franche-Comté and the University Hospital of Besançon in France. She also performed two shorter research stays at Johns Hopkins Hospital in the United States and the University of Gothenburg in Sweden.

Liesbet is embedded in several scientific and professional organizations. She is a committee member of the Young Committee of the European Association of Cardiovascular Nurses and Allied Professionals, vice-chair of the Belgian Working Group on Cardiovascular Nursing, member of the Task Force on Big Data for End-Of-Life Research and Editorial Board member of the European Journal of Cardiovascular Nursing.

For the research executed during her PhD, Liesbet received several prices and awards. She received the Nursing and Allied Professions Training Grant 2021 by European Society of Cardiology, the grant ‘Cardiale Transmurale Zorg’ 2021 by Viviane Conraads Stichting, the first price Magda Dierendonck 2021 by University Hospital Ghent, the best abstract award on the European Society of Cardiology 2022 in category “Adult Congenital Heart Disease”, and the Interuniversity Twitter thread competition 2021 organized by Vlaamse Interuniversitaire Raad. Her article “Impact of the COVID-19 pandemic on ongoing cardiovascular research projects” was awarded as one of top downloaded papers of European Journal of Cardiovascular Nursing in 2020, and her article “Patient-reported outcomes of adults with congenital heart disease from eight European countries: scrutinizing the association with healthcare system performance”, was elected as one of five best papers of European Journal of Cardiovascular Nursing in 2019.

Publications

Publications in international peer reviewed journals

27. **Van Bulck L**, Moons P. What if your patient switches from Dr. Google to Dr. ChatGPT? A vignette-based survey of the trustworthiness, value and danger of ChatGPT-generated responses to health questions. European Journal of Cardiovascular Nursing. 2023. Peer reviewed; IF=3.593

26. Giffard M*, **Van Bulck L***, Seydou Sall F, Becoulet N, Quenot JP, Seronde MF, Ecarnot F. Profiles of patients referred to palliative care from the cardiology department: An 11-year longitudinal retrospective study. Panminerva Med. 2023. Peer reviewed; IF=5.268
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25. Moons P, **Van Bulck L**, Daelman B & Luyckx K. Mental health in Adult Congenital Heart Disease. International Journal of Cardiology Congenital Heart Disease. 2023. Peer reviewed.

24. Moons P, **Van Bulck L**. ChatGPT: Can artifical intelligence language models be of value for cardiovascular nurses and allied health professionals. European Journal of Cardiovascular Nursing. 2023. https://doi.org/10.1093 /eurjcn/zvad022. Peer reviewed; IF=3.593

23. **Van Bulck L**, Couturier R, Moons P. Applications of artificial intelligence for nursing: has a new era arrived? European Journal of Cardiovascular Nursing. 2022; zvac097, https://doi.org/10.1093/eurjcn/zvac097. Epub ahead of print. Peer reviewed; IF=3.593

22. Acuña Mora M, Raymaekers K, **Van Bulck L**, Goossens E, Luyckx K, Kovacs AH, Andresen B, Moon JR, Van De Bruaene A, Rassart J, Moons P, APPROACH-IS II consortium and ISACHD. Gothenburg Empowerment Scale (GES): Psychometric properties and measurement invariance in adults with congenital heart disease from Belgium, Norway and South Korea. Health and Quality of Life Outcomes. 2022; 20(1):145. Peer reviewed; IF=3.077

21. **Van Bulck L**, Goossens E, Morin L, Luyckx K, Ombelet F, Willems R, Budts W, De Groote K, De Backer J, Annemans L, Moniotte S, de Hosson M, Marelli A, Moons P, BELCODAC consortium. Last year of life of adults with congenital heart diseases: causes of death and patterns of care. European Heart Journal. 2022; 43(42):4483–4492. Peer reviewed; IF=35.855

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19. **Van Bulck L**, Kovacs AH, Goossens E, Luyckx K, Zaidi A, Wang JK, Yadeta D, Windram J, Van De Bruaene A, Thomet C, Thambo JB, Taunton M, Sasikumar N, Sandberg C, Saidi A, Rutz T, Ortiz L, Mwita JC, Moon JR, Menahem S, Mattsson E, Mandalenakis Z, Mahadevan VS, Lykkeberg B, Leye M, Leong MC, Ladouceur M, Ladak LA, Kim Y, Khairy P, Kaneva A, Johansson B, Jackson JL, Giannakoulas G, Gabriel H, Fernandes SM, Enomoto J, Demir F, de Hosson M, Constantine A, Coats L, Christersson C, Cedars A, Caruana M, Callus E, Brainard S, Bouchardy J, Boer A, Reyes FB, Areias ME, Araujo JJ, Andresen B, Amedro P, Ambassa JC, Amaral F, Alday L, Moons P; APPROACH-IS II consortium, on behalf of the International Society for Adults Congenital Heart Disease (ISACHD). Rationale, design and methodology of APPROACH-IS II: International study of patient-reported outcomes and frailty phenotyping in adults with congenital heart disease. International Journal of Cardiology. 2022; 363:30-39. Peer reviewed; IF=4.039

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16. Moons P, Goossens E, Luyckx K, Kovacs AH, Andresen B, Moon JR, Van De Bruaene A, Rassart J, **Van Bulck L**, APPROACH-IS II consortium and ISACHD. The COVID-19 pandemic as experienced by adults with congenital

heart disease from Belgium, Norway, and South Korea: impact on life domains, patient-reported outcomes, and experiences with care. European Journal of Cardiovascular Nursing. 2022; 21(6):620-629. Peer reviewed; IF=3.593

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“Now this is not the end.

It is not even the beginning of the end.

But it is, perhaps, the end of the beginning.”

Winston Churchill