SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

MEASURING HEALTH-RELATED QUALITY OF LIFE IN HUNGARIAN CHILDREN WITH HEART DISEASE

Hungarian Validation of the A Pediatric Quality of Life Inventory ™ 3.0 Cardiac Module

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UNIVERSITY OF DEBRECEN

DOCTORAL SCHOOL OF HEALTH SCIENCES

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The Examination takes place at Department of Pediatrics, Medical and Health Science Center, University of Debrecen, 03.05, 2013.

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03.05, 2013.

1. Scientific background

1.1. Definitions of quality of life and health-related quality of life

In the late 1940s several articles were published signaled a shift in the way in which we would conceptualize health and evaluate medical interventions. In 1946, the World Health Organization gave a broaded definition of health as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity. According to this definition measurements generally used in clinical practice do not give an entire picture about patients' health. We offer a treatment to our patients if we believe that intervention increase the length of life, prevent future morbidity or make patients feel better. The first two are measurable with conventional medical methods. To get information about the third we need sophisticated measurements, which concentrate on aspects of personal experience that might be related to health and health care. Use of „quality of life (QOL) measures" has become widespread in recent years, but unfortunately there is no universially accepted definition of quality of life. Within the context of health care, it is important to distinguish „health-related quality of life" (HRQOL) from broader concepts of general well being. HRQOL refers to the subjective and objective impact of dysfunction associated with an illness or injury, medical treatment, and health care policy. According to the definition of Gill and Fenstein quality of life, rather than being a description of patients' health status is a reflection of the way that patients perceive and react to their health status and to other, nonmedical aspects their lives.

One point of agreement in the literature is that QOL is a **multidimensinal construct** comprising several domains. The multidimensional approach originated with the World Health Organization's definition of health as that identified three dimensions: physical, mental, and social. This defintion has become the cornerstone of the QOL construct, and these three dimensions have been expanded to four „core" domains: disease state and physical symptoms, functional status, psychological functioning and social functioning.

1.2. Areas of application of quality of life measures

Quality of life measures can be used in many areas of health care:

- Basic research of different populations, in sociological and anthropologycal studies, where the central interest is how different populations define and view qulaity of life.
- Observational epidemiological studies, which focus on the incidence and prevalence of HRQOL impairments in specific populations.
- Clinical trials, to demonstrate the effectiveness of prevention, treatment or rehabilitation programmes.

- Health economic research with utility-measurements, assessing costs and benefits of interventions.

Althoug the increasing application of quality of life measures and the results of several studies, which have shown that clinicians and parents find the information from these measures useful and informative, trials have found that the information does not greatly alter clinical decision. This can be arised from the inappropriate format and time of interpretation of data to clinicians.

According to Wirchow medicine is also a social science, just not all the doctors know it. The possible cause of forbearance from quality of life measures is the distance between health care professionals and social scientists. The other one is the missing knowledge about correct performance and interpretation of quality of life measures.

1.3. Requirements of quality of life measurements

By a critical appraisal of previous literature on quality of life, Gill and Fenstein set up the main requirements of quality of life measurements as follows:

- conceptualization of quality of life should be claryfied, which serves as a basis for selecting the isntrument to be used in the study
- according to the multidimensional construct of quality of life, investigators should state the domains they will measure as components of quality of life
- the investigators need to state their reasons for choosing the instrument
- aggregation results from multiple items, domains or instruments into a single score permits the the assessment of interrelationship between quality of life and other variables
- although the conceptualization as a multidimensional construct, asking the patients to give their global rating for quality of life is useful
- health related quality of life should be distinguished from overall quality of life
- adequate measurement should provide the possibility for respondents to indicate and supplement the domains that are important for their quality of life. Preferably these supplemental domains and the importance ratings are incorporated into the final rating.

1.4. Main methodologic properties of qualiy of life measurements

1.4.1. Who and how should measure quality of life?

Quality of life can be assessed ideally by the patient, or if it is not posssible (young children, physically handicapped), by someone close to the patient, such as a family number, and finally by a health care provider. Low level of agreement betwen patient and physician agreement is reported, nurses and other ancillary health care personnnel may provide more reliable ratings than do pysicians.

Interviews can be applied to the broadest spectrum of people, can minimize the problem of missing data, but standardized data collection is difficult. Self-administered quastionnaires are practical, efficient, inexpensive, can be administered frequently in clinical settings.

1.4.2. Types of health-related quality of life measures

Generic measures can be used with both sick and healthy populations, and therefore have special merit in situations where comparisons across disease groups or between sick and healthy groups are required. Since generic measures can be used with healthy samples, they have the advantage of being based on large samples, and population norms are often available. The disadvantages reflect the fact that generic measures lack sensitivity. They do not reflect specific impacts of treatments on quality of life.
Such instruments can be used at the population level and are potentially suitable for a number of applications:

- to evaluate multisectoral health policy interventions aimed at underpriviliged or disadvantaged people
- use in epidemiological research investigating factors that might impact upon the HRQOL of people
- use as screening tool for identifying patients in special need
- use in population surveys characterizing the health and health behaviours of children assesssing the health needs of local population
- to provide normative values with which to compare those frome patients.

In contrast, **disease specific** measures can be more sensitive to implications of different treatments and probably more appropriate for evaluations of interventions or for comparing the impact of alternative treatments. Including only relavant dimensions increases responsiveness, but lack of comparability is a disadvantage of this type of instruments.
The most extensive literature of disese specific measures in pediatrics is in the field of pediatric oncology, asthma, diabetes.
An alternative measurement model to the generic versus disease-specific dichotomy is an assessment strategy that combines both approches. In this **modular measurement** strategy, a generic core measure is paired with supplemental condition-specific modules. The supplemental modules assess specific disease or treatment effects and other relevant HRQOL issues not sufficiently covered in the core measure, whereas the core measure affords the opportunity to make comparisons across disease groups and with healthy population norms.

1.4.3. Statistical properties of HRQOL measures

The main required properties of HRQOL measures are the same as for other instruments assessing health status. Discriminative instruments which are designed to measure cross-sectional differences between people should be reproducible and valid. Evaluative instruments, designed to measure longitudinal differences within people over time should have sensitivity to change, so should be responsive also.

HRQOL measure instruments are designed for discriminative and evaluative studies, so all properties are required.

Validity

Face validity is concerned with whether an instrument measures what is intended. This can be evaluated quantitatively through factor analysis and comparisons with related variables. External construct validation includes comparisons with other quality of life instrument scores, with laboratory or clinical measures of severity of disease and with relating instrument scores to socio-demographic variables. Exact agreement with other instruments is not required since that would mean that quality of life scores were redundant.

Reliability

All instruments must produce the same results on repeated use under the same conditions. Reliability is concerned whether an instrument is internally consistent or reproducible. Internal consistency is tested with a single administration of an instrument and assesses how well items within a scale measure a single underlying dimension. Test-retest reliability is designed to take account of variation over time in stable patients. The results of tests of internal consistency and test-retest reliability are usually presented with Chronbach's alpha and test-retest correlation coefficients.

Responsiveness

Responsiveness or sensitivity of change focuses on the extent to which scores change when subjects improve or deteriorate. Responsiveness pertains to two measurement properties: "changeability", which refers to the extent to with subjects'scores increase or decrease with change in there state, and the degree of variability which can not be attributed to true change.

Practicality

At present quality of life measurements are mainly used in clinical trials and formal evaluation studies. Great effort is needed to provide clinically meaningful data on quality of life with brief and simple instruments.

1.4.4. Time-frame

It is essential to limit the time-frame to a relatively short period, which is generally ranges from „at this moment" to one month. If time frame is too long or undefined patients may be confused as to which period to report, and investigators should keep memory effects in mind as well.

1.4.5. Response scales

The most frequently used response scales are the Likert-type scale, linear analogue and hibrid scale. Likert-scale is categorical in nature and providing the patient with a set number of closed-ended response choices. A visual analogue scale is composed tipically a 10 cm line. The patient is asked to mark the point

that corresponds most closely to his experience, and the distance from the anchor points is measured. Hybrid form combines the categorical guides of the Likert-scale with the anchoring system employed in linear analogue scales.

1.5. Cross-cultural validation of HRQOL measures

The necessity of international collaboration in all fields of medical research, has gained the importance of developement of cross-culturally applicable QOL instruments.

Thinking about the main scopes of QOL instruments some special considerations are needed in an international aspect.

Cross-cultural differences are less relevant in basic research and epidemiologic studies, while cross-national distinctions are more relevant for clinical trials and health economic research.

There are cultural specific differences in the conceptualization of QOL and HRQOL, however there may be a universal meaning of having a good quality of life.

With the increasing importance of HRQOL measures a number of questionnaires have been developed in many countries in different languages.

In order to use these questionnaires in other countries/cultures, they have to be translated and culturally adapted in a standardized way. It is important that research in HRQOL is conducted according to accepted scientific principles and practices. Combining data in multinational clinical studies for objective outcomes pose important data for overall analysis. In these studies one can have the confidence that the same feature is being measured in each country. For questionnaires, the task of establishing the validity of combining data from different countries is more complex. Internationally applicable instruments should have:

- Functional equivalence, which pertains to whether or not the items in a translated version have a similar meaning to the source instrument
- Operational equivalence, which pertains to the comparability of procedures (e.g. self versus interviewer administered questionnaire)
- Scale equivalence, which pertains to the extent to which individuals in different cultural groups respond to the similar items in similar ways
- Metric equivalence, which pertains whether or not a measure orders individuals along a continuum in a comparable way across language and cultural groups.

Internationally acceptable instruments can be developed in three principle ways:

- Sequential approach includes forward and backward translations, followed by pilot testing.

- Parallel approach means that the international diversity of the group of creators assure that culturally relevant input was present throughout the questionnaire contruction process.
- Simultaneous approach means that an overall set of components for quality of life is developed internationally, from what working groups of different cultures formulate relevant questions.

The most frequenty used way is the sequential process. In the adaptation of HRQOL measures for other languages and cultures has become a complex and specialized procedure. The questionnaire must retain the measurement properties of the original, and it must also be adjusted to the cultural differences in patient-perceived impairments (content validity). Series of forward and backward translations and testing in patients ensure content validity. Ideally, each translation should undergo a full validation process however it is costly and time-consuming process, so not always feasible.

Providing evidence of the comparability of new translations to the original is to examine cross-sectional and longitudinal correlations between translations and other measures of HRQOL. If correlations across countries are consistent, this would suggest that the new translations are measuring the same construct as the original. If results from clinical studies are consistent with other clinical indices across countries, this constitutes further evidence of the validity of the new translations.

After forward and backward translations preferably cognitive interviews are performed for testing questionnaires in the target population. Cognitive testing is concerned how people interpret and comprehend questions, recall information and events, make judgments about how to respond, and provide response. The intent of cognitive testing is to examine the question-answering process to identify and address errors being introduced into process. This knowledge can be used to improve the accuracy and reliability of survey responses. The approach to conduct cognitive interviews can be concurrent, when the respondent is asked to think aloud during answering a survey question, or retrospective (debriefing) when the interviewer ask about the respondent’s experience and opinion after finishing the survey. Paraphrasing also enables researchers to see whether respondents understand the questions and interpret as it is intended. This method can also elicit possible alternative wordings and help to develop better survey questions.

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1.6. Special concerns about quality of life measures in pediatric populations.

Proxy problem

Children's conception about health is notably differs from that of adults. Health care interventions play much smaller part in their welfare than they do in older populations. There is much less agreement on the normal roles and functions of children at each age than there is for adults. Illness may be manifested by decelerations in the normal features rather than by evidence of abnormal function. Children with chronic diseases may have unique developemental sequences, and their life expectations can be quite different to those of other children. The subjectivism of quality of life gains a pronounced emphasis.

The assessment of quality of life in chronically ill children and adolescents has become increasingly important as the mortality rates associated with various chronic diseases have decreased and survival rates increased. Although medical intervention often results in the improved health status of pediatric patients, there is evidence to suggest that frequent hospitalizations, intrusive medical procedures, and uncertanity of survival, negatively impact childhood developement and adjustment. Consistently with the United Nations Convention on the Rights of the Child, there is a growing recognition that the views of the children should be sought with respect to decisions regarding their health. Therefore the measures of HRQOL should also reflect their views.

As studies have shown disagreement between the opinions of respondents, such as parents, nurses, physicians and children, others' information about children's HRQOL can not be considered sufficient. Discrepancy between children's and their parents' judgments about quality of life is often cited in the literature. This lack of agreement among reporters of pediatric patients' functioning has been termed:"cross informant variance". Children differ from adults in their understanding of health, the causes of illness, and their beliefs about how medications work. For all these reasons, we can not expect entire correlations between child and parent ratings. Parents are normally able to make accurate judgments on the illness' impact on the family, sibling relationships, and to a lesser extent school progress. Parents are less able to make judgments regarding symptom experience, peer relationships, or future worries.

This clearly underscores the need for pediatric patient self-report instruments with definitive measurement precision across the developemental stages of childhood and adolesce. According to an analysis of PedsQL™ scores children as young as 5 year old can reliably and validly self-report their HRQOL with an age-appropriate instrument.

Quality of life instruments for children should have the following properties:

- Use an accepted, clear conceptualizaton of HRQOL
- Its dimensions are acceptable for all children
- Has parallel self- and parent proxy report forms
- Dimensions with greater importance for children are emphasised
- Has good psychometric properties
- Gives equally acceptable values for the general and specific children populations
- Developmental changes are taking into account – it has different forms for different age groups.

Parent proxy-report is also important beacause children are rarely in position to refer themselves for treatment, even when they are experiencing symptoms and health-related problems, parents' perceptions of a child's HRQOL influences the likehood that health care will’be sought for the child. Parent proxy-report is necessary when the patient is unable or unwilling to complete the HRQOL measure because of young age or illness variables. Therefore the only solution is to regard both assessments as valid and contributing to the total picture regarding the child's quality of life.

1.7. Health related quality of life measures in pediatric cardiology

1.7.1. Effect of heart disease on HRQOL of children

Congenital heart diseases (CHD) present a special chronic condition from a number of aspects. These are the most frequent congenital anomalies with a birth prevalence of 3.7-50 ‰. There is a wide range of severity, from those with moderate clinical consequences to critical conditions that need intervention at birth, often with the requirement for multiple procedures. Progress in pediatric cardiology and pediatric cardiac surgery during the past decades has brought dramatic changes in the life expectancy of children with CHD. There are rarely untreatable cases any longer, with new surgical techniques providing surgical corrections for previously palliative care cases and catheter interventions replacing some surgical procedures. Most of these characteristics are true not only for congenital heart defects but also for other types of heart diseases in children, such as acquired conditions (e. g. Kawasaki-syndrome) or those which have had no effective therapy (e. g. some cardiomyopathies). Certain new techniques in the therapy of arrhythmias (e.g. implantable cardioverter defibrillator) present solutions for previously untreatable situations.
These advances in survival rates have lead to concerns with the quality of long-term survivability. CHD patients are reaching adulthood in rapidly rising numbers, and face numerous problems in their daily lives.

According to the description made by Daliento et al the most critical phases in the life of a patient with congenital heart disease are the following:

- *Infancy*: Cardiac surgery/frequent hospitalizations can cause interruption and/or modification of the relationship between child and parents. This is the onset of preschool, physical activity limitations. Limiting the time the infant is separated from the parents to the surgical event and pain protection is essential. Psychosomatic support of the parents is often needed.
- *Childhood*: Onset of school-learning difficulties. Psychosomatic integration of the child is needed.
- *Adolescence*: Adolescence crisis, corporeal image and sexuality. The importance of medical counseling usually increases, while parental controlling decreases.
- *Adult age*: Questions about pregnancy, employment, insurability.

To gain information from a different point of view on the outcomes of this population quality of life measures has increasingly been addressed. This helps optimizing their clinical management, evaluating specific interventions and therapeutic modes.

Previous studies have investigated the of cardiac interventions from biological aspects (anatomic, hemodynamic, electrophysiologic sequelae, exercise capacity) or focused on specific HRQOL dimensions such as school function, neuropsychologic, cognitive status, participation in activities in children, marital status, employment, health insurance coverage in adults.

While standardized questionnaires that measure the patients' perspective have been used in research for decades, their length and complexity prevented their widespread use on the routine basis.

Although the extent of literature on quality of life measures in patients with heart disease is increasing continually, major conceptual and methodological drawbacks can be found.

Recent studies on QOL outcomes in children with CHD that were based on a multidimensional perspective were limited by small sample size and other methodologic issues, often relied on parental proxy-report of the child's QOL, and reported health status or observed functional abilities 12–14 years of age or focused on delineating developmental impairments 15–17 years of age that may affect school functioning, a single dimension of QOL in children.

The interpretation of results is complicated when the investigators do not use a consistent conceptual basis to define quality of life. The term of quality of life is often used inappropriately; authors drew conclusions about patients' quality of life, even though it was not specifically measured. According to a review, performed by Moons and his study group in 2004 the poor conceptual and methodological basis used in

quality of life studies in patients with congenital heart disease implies that many results are inconclusive. Need of a critical appraisal of the literature in this field remains essential.

1.7.2 Instruments developed for the measurement of HRQOL in pediatric cardiac populations

There are only a few studies which have been carried out in pediatric populations using a generic HRQOL instrument or a cardiac disease-specific instrument.

The first available disease specific instrument was the cardiac module of PedsQL™, which has the broadest age spectrum from 2-18 years of age for parent proxy-report, and from 5-18 years of age for child self-report form. The generic core scale and the numerous other diseases specific modules of PedsQL™ give the possibility to compare the HRQOL of children with heart disease with healthy peers and also with patients with other chronic conditions. Linguistic and cultural validation of PedsQL™ modules into many languages gives the opportunity of international, multicenter studies as well.

Results with PedsQL™ cardiac module demonstrate that approximately 20% of children with cardiovascular disease report significantly impaired psychosocial quality of life irrespective of the severity of the disease. As perceived by parents, worse physical and psychosocial QOL is related to more severe heart disease.

Another instrument developed for the measurement of quality a life in this field is ConQol was developed using a child-centered philosophy, its items were derived from topics that children with heart disease considered important in determining their quality of life, and did not rely on views of experts, such as clinicians, psychologists or parents. ConQol has to versions, one for children aged from 8-11 years, and for young people aged from 12-16 years. The correlations of ConQol scores with those of PedsQL™ cardiac module demonstrated good validity. ConQol index does not cover many cardiac-specific items of the PedsQ™L, such as experience with treatment or problems with medications, because children did not indicate these areas important in terms of their quality of life. The initial study with ConQol showed a trend towards young people reporting poorer quality of life. Complexity of heart disease was not a strong differentiator of quality of life, but there is not a universally agreed system for determining the severity of the disease.

The third remarkable instrument in this field is Pediatric Cardiac Quality of Life Inventory (PCQLI). The validity and reliability of Pediatric Cardiac Quality of Life Inventory was confirmed in a multicenter study, comparing the PCQLI scores with generic and disease-specific scores of PedsQL™, and with results of non-quality of life instruments. This instrument is developed to assess HRQOL in children with heart disease, aged 8-18 years.

The study result showed that lower HRQOL was associated with greater disease severity and medical care utilization, poorer patient self-perception and competency, and increased behavioral and emotional problems.

2. Aims

2.1. General aims of the study

Patient-reported outcome (PRO) studies, including HRQOL studies have not appeared in Hungary until the recent years, and were mainly carried out in adult populations. As the standards of care and results of medical care of children with heart disease in Hungary correspond to international recommendations, with very good biological prognosis, and because the incidence of psychosocial problems is even greater in the Hungarian general population than in other European countries we considered it important to assess the outcomes of Hungarian pediatric cardiology care from the patients' point of view.

Consequently, the objective of the present study was to develop the Hungarian version of PedsQL™ cardiac module and test the Hungarian version of the PedsQL™ Generic Core Scales and Cardiac Module in a Hungarian pediatric cardiac disease sample.

2.2 Specific aims of the study

- Provide data, suitable for international comparison, on health-related quality of life of Hungarian pediatric population.
- Develop Hungarian version of a well validated, internationally widely used disease-specific instrument, to assess health-related quality of life of Hungarian pediatric population with heart disease.
- Compare health-related quality of life of Hungarian children with heart disease with general pediatric population.
- Compare health-related quality of life of children with different severity of heart disease, with that, of general Hungarian pediatric population.
- Compare health-related quality of life of children with different severity of heart disease, with that of children with simple heart disease with generic and disease-specific instrument
- Assess the consequence of therapeutic modalities on health-related quality of life in children with heart disease.
- Compare data on health-related quality of life of Hungarian children with heart disease with results on U.S. patient sample.

3. Methods

3.1. Instrument

The PedsQL™ Measurement Model is a modular approach to measure HRQOL for a wide age range of children and adolescents from 2 to 18 years of age. The development, refinement and validation of the original instrument and linguistic validation to a number of European and other languages have been described in many papers. Results of research with disease-specific modules are available. Methodology of application and evaluation can be found in several previous presentations. The PedsQL™ conceptualizes pediatric HRQOL as the patient's perceptions of the impact of disease and treatment in a variety of health and well-being domains.

3.1.1. PedsQL™ 4.0 Generic Core Scales

The 23-item PedsQL™ 4.0 Generic Core Scales encompass:

1. Physical Functioning (8 items)
2. Emotional Functioning (5 items),
3. Social Functioning (5 items)
4. School Functioning (5 items).

It was developed through focus groups, cognitive interviews, pre-testing, and field testing measurement development protocols. Cognitive interviews were carried out with children attending the pediatric cardiology outpatient unit. Five children were chosen from each age group, with different severities of heart disease, from different places of residence. To get information on children without proven heart disease, interviews were performed with 4 children with innocent heart murmur.

The PedsQL™ 4.0 Generic Core Scales are comprised of parallel child self-report and parent proxy-report formats. Child self-report includes ages 5-7 (young child), 8-12 (child) and 13-18 (adolescent) years. Parent proxy-report includes 2-4 (toddler), 5-7, 8-12 and 13-18 years of ages, and assesses parent's perceptions of their child's HRQOL. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first or third person tense. The instructions ask how much of a problem each item has been during the past one month. A 5-point response scale is utilized across child self-report for ages 8-18 and parent proxy-report (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). To further increase the ease of use for the young child self-report (ages 5-7), the response scale is reworded and simplified to

a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem), with each response choice anchored to a happy to sad faces scale. Parent proxy-report also includes the toddler age range (ages 2-4), which does not include a self-report form given developmental limitations on self-report for children younger than 5 years of age, and includes only 3 items for the school functioning scale.

Items are reverse-scored and linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better HRQOL. If more than 50% of the items in the scale are missing, the Scale Score is not computed. In addition to the single scale scores there is the possibility to calculate summary scores: the Physical Health Summary Score is the same as the Physical Functioning Subscale, whereas to create the Psychosocial Health Summary Score, the mean is computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning Subscales.

3.1.2. PedsQL ™ 3.0 Cardiac module

The PedsQL ™ 3.0 Cardiac Module consists of five scales related to symptoms (7 items), perceived physical appearance (3 items), treatment anxiety (4 items), cognitive problems (5 items) and communication (3 items) for child self-report ages 8-18 years, and parent proxy-report in all age groups. The communication scale was not included for toddlers and young children who lack the cognitive or linguistic ability to verbalize questions and explanations about the heart. An additional treatment barriers scale (5 items) measures the adherence issues in children taking cardiac medication (5 items).

3.1.3. Psychometric properties of the instrument

The PedsQL™ has shown good internal consistency, construct validity and known group validity and reliability in large samples of healthy and patient populations internationally (20, 68-70). The PedsQL™ generic core scale s were designed to be used across various pediatric conditions. List of existing translations of the generic core scales and disease specific modules are avaible on the PedsQL™ web site.

The PedsQL™ generic core scales and condition-specific modules have demonstrated good internal consistency reliability. Construct validity has been demonstrated for both item-level and scale-level analyses, clinical validity has been established by demonstrating that PedsQL™ scores distinguish between patients with different pediatric morbidities, and PedsQL™ scores are associated in the expected directions with the disease- and treatment related symptoms. The PedsQL™ is continuously field tested nationally in pediatric offices, hospitals, community settings, schools, as well as international field trials.

The PedsQL™ generic module is a 23 item measure and takes less than 5 minutes to complete. Missing data rates are generally about 0,001% of item responses, which means good practicality of the instrument.

3.2. Validation procedure

Validation of PedsQL™ generic core scales and condition-specific modules are carried out according to the instruction of the MAPI Research Institute, in accordance with the guidelines of the QOL-SIG TCA (Quality of Life – Special Interest Group Translation and Cultural Adaptation) group. The sequential validation procedure of the original U.S. version of the PedsQL™ 3.0 Cardiac Module was carried out this way by our study group.

The PedsQL™ 3.0 Cardiac Module was translated independently into Hungarian by two professional translators, native target language speakers, bilingual in the source language. The two translated versions of the questionnaires were discussed with both translator, a pediatric cardiologist, a pediatrician, a nurse in pediatric cardiology, and a teacher, and the final combined version was back translated into English. After review and comments by the instrument author, the new version was tested on 20 parents of children with heart disease aged 2-18 years and 15 children aged 5-18 years by cognitive interviews. Our study group has used concurrent and retrospective approach, and paraphrasing during the interviews. These interviews were performed to determine whether any questions were difficult to understand and/or irrelevant. After some modification on wording and proofreading, the final version was forwarded to the MAPI Research Institute, which gave the approval for the psychometric probe of the Hungarian PedsQL™ 3.0 Cardiac Module. The format, instructions, Likert response scale, and scoring method for the PedsQL™ 3.0 Cardiac Module are identical to the PedsQL™ 4.0 Generic Core Scales, with higher scores indicating better HRQOL (fewer symptoms or problems).

Our study group took part in the adaptation process for the PedsQL™ 3.0 Cardiac Module only; the Hungarian Generic Core Scale was already available through the MAPI Research Institute.

3.3. Participants and settings

Potential study subjects were recruited from the Pediatric Cardiology Outpatient Unit of the University of Debrecen Medical and Health Science Centre, Department of Pediatrics. Subjects were given detailed written information about the methods, aims, and the voluntary nature of participation in the study. Subjects of the patient group filled in the questionnaires in a room inside the outpatient clinic, while data collection from the comparison group was carried out through mail correspondence. Subjects of the patient group were excluded from

participation if the child had associated non-cardiac chronic disease or major developmental disability, mental retardation that might affect health-related quality of life, and if the child was <2 months after surgical intervention. 38 children were excluded because the child had associated non-cardiac chronic disease or major developmental disability, severe mental retardation. The most frequent disorders were hematologic diseases, asthma bronchiale, diabetes mellitus, epilepsy, which were not results of any kind of heart diseases. Mild somatomental retardation, which was observable in some children with CHD of great complexity, could be a consequence of the heart disease, but these children were not excluded from the study. No children were excluded due to psychological problems. All the diagnoses of usual occurrence at a pediatric outpatient unit were represented in the patient sample. Patients with congenital heart disease were classified according to the guidelines set at the 32nd Bethesda Conference of the American College of Cardiology and they were categorized into three groups, namely simple congenital heart disease (such as isolated small or repaired atrial and septal defect without residua), congenital heart disease with moderate complexity (for example, coarctation of the aorta, moderate-to-severe pulmonary valvar disease or tetralogy of Fallot), and great complexity (such as double-outlet ventricle or conditions with conduits or after Fontan procedure). Beside congenital heart defects the study sample included patients with cardiomyopathies, arrhythmias and acquired (such as carditis, Kawasaki syndrome) heart diseases.

Subjects of the comparison group were chosen by random selection from the general Hungarian population through the Population Register Office of the Ministry of the Interior, with distributional matching to the population treated at the pediatric cardiology outpatient unit on age, gender, and residence.

Informed consent and child assent were obtained from the participating families.

The research protocol was approved by the Research Ethics Committee of The University of Debrecen.

3.4. Sample characteristics

The Hungarian translations of the PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 3.0 Cardiac Module were administered to 195 children attending the cardiology outpatient unit aged 5-18 years and 254 parents of children aged 2-18 years.

From the total investigated patient population (254) there were 59 (23,23 %)toddlers(2-4 years of age), 49 (19,29%) young children (5-7 years of age), 73 (28,74%) children (8-12 years of age) and 73 (28,74%) adolescents (13-18 years of age. Subjects included 148 boys (58,27 %) and 106 girls (41,73%).

It was the mother who answered the questionnaire in 92.52% of the patient sample, and it was the father in 7.48% of the sample. No parent in the patient group refused to participate in the study, 3 patients ages 5-7 years were unwilling to answer during the interview.
Of 1000 families approached by post, 525 families as subjects of the comparison group were recruited into the study (52.5%). In the comparison group there were 152 (28,95%) toddlers, 111 (21,14%) young children, 160 (30,48%) children and 102 (19,43%) adolescents. Subjects included 268 boys (51.05 %) and 215 girls (40.95%) and 42 (8%) of unknown gender.
It was the mother who answered the questionnaire in 89.5% of the sample, it was the father in 4.57% of the sample, and it was someone else in 6.28% of the sample.

3.5. Statistical analysis

Construct validity was determined using the known groups method. PedsQL™ Generic Core Scales scores were compared between groups differing in known health conditions. HRQoL scores of children from the general population and children with heart diseases were compared using t tests for independent samples. Effect sizes were evaluated using Cohen's d statistics. Construct validity of the Cardiac Module was further assessed by estimating the intercorrelations among the Cardiac Module scale scores and relevant Generic Core Scales scores.
Agreement between self-report and parent proxy-report was assessed using the Pearson correlation coefficient (with thresholds for medium and large correlation at 0.30 and 0.50, respectively), the intraclass correlation coefficient for absolute agreement (ICC, interpreted using thresholds for moderate and good agreement at 0.4 and 0.6, respectively), Bland-Altman 95% limits of agreement (LOA), and by evaluating parent vs. child mean score differences in paired *t* tests.
Feasibility of the Hungarian version of the Cardiac Module was determined from the average percentage of missing responses. The percentage of all possible item-responses left unanswered was calculated for each subject on each single and summary scale and averaged over subjects. The utility of the instruments in terms of distributional coverage overall and by subscale was evaluated by calculating the percentage of subscale-level average responses reaching the minimum (floor) or the maximum (ceiling) of the scoring scale.
Scale internal consistency reliability was determined by calculating Cronbach's coefficient α.

4. Results

4.1. Descriptive statistics

No floor effects were seen on the Generic Core Scales. We found ceiling effects both in child self- and parent proxy-reports ranging from a minimal 0.9 to a moderate 30.2% in the patient group and 2.1-31.7% in the comparison group, with highest values in the Social Functioning Scale for child self- and parent proxy-reports from the patient and comparison samples. We also observed greater ceiling (1.1-77. 9%) than floor effects (0.4-3.7%) in the Cardiac Module, with a notable ceiling effect in the Heart Symptoms scale and a moderate one in the Treatment II Scale, Perceived Physical Appearance, and Cognitive Problems Scales subscales for child self- and parent proxy-reports. The recommended standard of 0.70 of Cronbach's coefficient α for group comparison was exceeded in the majority of the scales, and all scales exceeded the satisfactory level of internal consistency reliability of at least 0.40.

Missing values were found for the patient group's Generic Core Scale (ranging 13.8-25.9%), with highest values in the school functioning domain both for both self- and parent proxy-reports, and in the Cardiac Module (ranging 0.5-66.2%) with highest values in the Treatment II Scale (problems with taking heart medicine) domain. The percentages of missing values (ranging 1.2 – 4.4%) in the comparison group were consistent with previous results.

4.2. Construct validity

Assessing the construct validity of the PedsQL™ 4.0 Generic Core Scale, statistically significant difference was found between the patient group and the comparison group in Physical Functioning Scale (p=0.003) scores of the child self-report for the Generic Core Scales. For parent proxy-reports, statistically significant difference was found in the Physical Functioning Scale (p=0.022), Emotional Functioning Scale (p=0.017), and Psychosocial summary score (p=0.019), and also in the Total Scale Score (p=0.034). Mean scores were consistently higher in the comparison group for all scales, with Cohen's d values indicating no other than small effects (range 0.02-0.31).

As the intercorrelations among the various Generic Core Scales and the Cardiac Module scales were estimated using Pearson correlation coefficients, a high correlation was found between the Physical Functioning Scale scores and Cardiac Symptoms Scale scores for children (r=0.63) and for parents (r=0.66). Cognitive Problems Scale scores of the Cardiac Module were highly correlated with the School Functioning Scale (self-reports r=0.57, proxy-reports r=0.60), the Psychosocial Summary scores (both reports r=0.58), and with the Total Scale Score (self-reports r=0.58, proxy-reports r=0.58) of the Generic Core Scale.

4.3. Parent-child agreement

Moderate to good agreement was found in the Generic Core Scales of both the patient and comparison groups. ICCs were generally higher in the comparison group. Lower values were

obtained in the Emotional and Social Functioning Scales across all age groups, and in the School Functioning Scale in 5-7 and 13-18 year-olds from the patient group. All ICCs showed good agreement in the comparison group, except for the Physical and Social Functioning Scale scores of children aged 5-7 years. ICCs for the Cardiac Module indicated similarly moderate to good agreement, with lower values for the Treatment II Scale, Perceived Physical Appearance Scale, and the Treatment Anxiety Scale in most age groups. Poor agreement was detected in the Perceived Physical Appearance Scale for the 5-7 year olds and in the Treatment II Scale for the 8-12 year olds. The ranges of LOA as calculated following the Bland-Altman procedure are consistent with the mainly moderate agreements between child self- and proxy-report scales. Neither the ICC nor the LOA values indicate any tendency of improvement in parent-child agreement as age advances.

4.4. Comparison of PedsQL™ Generic Core Scales scores of Hungarian children with heart disease with Hungarian general population data

For the PedsQL™ Generic Core Scales scores, a statistically significant difference ($p<0.05$) between the entire patient group (not subdivided by severity of heart disease) and the general population for the child self-report was only found on the physical functioning subscale ($p<0.005$). For the parent proxy-report, a statistically significant difference was found for the total PedsQL™ scale score ($p<0.05$), and on the physical ($p<0.05$), psychosocial functioning ($p<0.05$) and emotional functioning ($p<0.05$) subscales.

No statistically significant differences were found for the parent proxy-report of toddlers (2-4 years) and teenagers (13-18 years) and for the child self-report of children (8-12 years) and teenagers (13-18 years). Statistically significant differences were observed for child self-reports of young children (5-7 years) in the PedsQL™ total scale score, physical, psychosocial, social and school functioning scores, and for the parent proxy-reports for the PedsQL™ total scale score, psychosocial, emotional and school functioning scores. Statistically significant differences for children (8-12 years) were observed for the parent proxy-report in the PedsQL™ total scale score and on the physical functioning subscale. Comparing the PedsQL™ Generic Core Scales scores of the diagnostic groups with the general population, statistically significantly lower scores were observed for children with CHD of moderate and great complexity and for children with cardiomyopathy. For children with CHD of moderate complexity, a lower social functioning score was calculated from child self-reports, and lower total scale score, physical, psychosocial and social functioning subscale scores from parent proxy-reports. For children with CHD of great complexity, lower total scale score, physical and social functioning subscale scores were seen in child self-

reports and also lower psychosocial functioning scores in parent proxy-reports. For children with cardiomyopathy, the total scale score was significantly lower for child self-reports and the total scale score, psychosocial, emotional, social and school functioning subscale scores for parent proxy-reports.

4.5. Comparing PedsQL™ scores of the different diagnostic groups and of patients with simple congenital heart disease

Comparing the scores of the PedsQL™ Generic Core Scales of the different diagnostic groups versus the scores of patients with simple congenital heart disease, we found statistically significant difference in total scale scores of patients with congenital heart disease with moderate ($p<0.05$) and great complexity ($p<0.05$) and in patients with cardiomyopathy ($p<.05$) according to parent proxy-reports. The physical functioning subscale scores were significantly lower in patients with great complexity by the opinion of the patients themselves ($p< 0.05$) and also by the parents ($p<0.005$) and in patients with moderate complexity by the opinion of the parents ($p<0.05$). Significantly impaired psychosocial functioning was calculated for patients with CHD of great complexity ($p<0.05$) and for patients with cardiomyopathy ($p<0.005$) from the parent proxy-reports. Emotional functioning was observed to be negatively affected only in patients with cardiomyopathies ($p<0.05$) by the opinion of the parents, while social functioning was significantly lower in patients with CHD of moderate (self: $p<0.01$, proxy: $p<0.05$) and great complexity (self: $p<0.05$, proxy: $p<0.05$) and patients with cardiomyopathies (self: $p<0.05$ proxy: $p<0.05$) according to both self- and parent proxy-reports. School functioning was impaired by opinion of the parents among patients with CHD of great complexity ($p<0.05$) and in patients with cardiomyopathies ($p<0.05$).

Significantly lower scores were obtained on the heart symptoms subscale of the cardiac module for patients with CHD of moderate and great complexity by the self- ($p<0.05$, $p<0.05$) and proxy-reports ($p<0.05$, $p<0.05$) as well. Parents of children of the ”Others” diagnostic group (children checked because of e.g., chest pain or innocent heart murmur) also reported significantly lower scores on the heart symptoms subscale ($p<0.01$). The perceived physical appearance score was significantly lower only in patients with cardiomyopathies ($p<0.01$) by the opinion of parents. Correlating with the impaired school functioning we observed significantly lower cognitive functioning scores in patients with CHD of moderate ($p<0.05$) and great complexity ($p<0.05$) and in patients with cardiomyopathies ($p<0.05$).

4. 6. Differences in PedsQL™ scores by therapeutic modality

We analyzed the PedsQL™ Generic Core Scales and Cardiac Module scores across the patient groups with different therapeutic needs. Comparing the scores of children requiring no therapy with those who had cardiac intervention, the only significant difference is observed in the treatment anxiety subscale of the cardiac module where parents reported lower scores if their child had had an intervention. The need of taking heart medicine impacted the PedsQL™ total scale score ($p<0.01$), the psychosocial ($p<0.005$), social ($p<0.05$) and school ($p<0.005$) functioning scores of the Generic Core Scales according to the parents, and the perceived physical appearance ($p<0.005$) subscale score of the Cardiac Module by the opinion of the children. Having had a cardiac intervention in addition to the need for taking medication increased the number of domains impacted, as the physical functioning score ($p<0.005$) of the Generic Core Scales was also lower according to parents and lower scores were calculated for the treatment anxiety subscale ($p<0.05$) of the Cardiac Module completed by the children themselves. No influences on the PedsQL™ domains were observed comparing patients taking heart medicine versus patients with a cardiac intervention, but the perceived physical appearance subscale scores were significantly lower according to both children ($p<0.01$) and parents ($p<0.05$) if the former patient group was compared with those who have to take heart medication beside the intervention. Social functioning scores were significantly lower in children who had undergone intervention and were taking heart medicine by the opinion of the patients ($p<0.05$) and their parents ($p<0.05$) as well, and the parents reported also impaired social functioning ($p<0.05$) for this group versus children only with an intervention.

4.7. Specific Concerns

Mean scores for items of PedsQL™ Generic Core Scales and Cardiac Module were ranked to identify the problems perceived most freqently by children with heart disease and their parents. The most comon problems for the general dimensions of HRQoL were related to physical functioning according to the patients (hard to run, hard to do sports, hard to lift heavy things). On parent proxy-reports feeling angry was found to be the most frequent problem but parents reported common difficulty on physical functioning (hard to run) and on school functioning (paying attention in class) as well. For the disease-specific dimensions catching cold was the most frequent problem both for children and their parents. Children commonly felt difficulty to speak about their heart condition to others and they were frequently disturbed by their fast heartbeat. Parents reported on their child's anxiety about going to the hospital and that their child's communication with the medical staff was difficult for their children.

4.8. Comparing PedsQL™ data on Hungarian children with heart disease with results on a U.S. patient sample

For the Generic Core Scales significantly lower scores were observed for the Hungarian sample on the physical ($p<0.05$) and social ($p<0.05$) functioning subscales of self-reports and for the PedsQL™ total scale score ($p<0.05$), physical ($p<0.001$) and emotional ($p<0.0005$) functioning subscales of proxy-reports. The only significant difference among the disease-specific domains was in the heart symptoms subscale scores ($p<0.05$) only by the opinion of parents.

5. Discussion

Our findings generally support the feasibility, reliability of the Hungarian translations of the PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 3.0 Cardiac Modul to assess HRQOL of Hungarian children 2-18 years of age.

This first survey with PedsQL™ in Hungarian children with heart disease affirms the **construct validity** of the instrument in differentiating between healthy and chronically ill children and between patients with different levels of heart disease severity.

Perceived psychosocial functioning of Hungarian children 2-18 years of age with heart disease was found to be similar to that of their general population peers, but their physical functioning was significantly lower. In a previous study with PedsQL™ there were no significant differences in physical functioning between healthy children and a mixed sample of children with heart disease, but recent results with PedsQL™ showed impaired self-perceived physical functioning in children 5-18 years of age with increasing cardiac disease severity. The physical functioning of Hungarian children with heart disease was observed to be worse also than that of the U.S. pediatric sample with heart disease by the opinion of children and parents as well.

Our finding could be a sign of poor physical state of Hungarian children with various levels of heart disease severity and it may reflect a general restrictive attitude of parents and health practitioners towards physical activities regardless of the severity of cardiac conditions. The parental underestimation of children's physical capacity coupled with overprotection leads to unnecessary limitation of social activities of chronically ill children resulting in poorer HRQOL. These findings emphasize the need for general actions in pediatric cardiology care in the field of physical activities. Cardiologists and pediatricians should help the patients and the families choose the proper kind of activity.

Although heart diseases from a medical point of view have influence primarily on physical states, the majority of HRQOL studies found expressed deficits in psychosocial dimensions.

Lower psychosocial scores by the parents' opinion indicate the necessity of integration of psychosocial support in the care of chronically ill children and their families.

Analyzing our data across the 4 age groups it is conspicuous that HRQOL of young children (5-7 years) is negatively affected by the illness through almost all HRQOL dimensions as perceived both by the children and their parents. The total HRQOL and physical functioning scores are significantly lower also in children 8-12 years of age according to the proxy-reports, but no further differences are observed in other age groups.

The reason why impairment is concentrated in the age group of young children may be that this is the time of entry into the community of other children, starting to go to nursery or school. This is when children with a chronic condition are faced for the first time with the stigmatization of being different. Besides awakening to the consciousness of their disease, this is often the period of reoperations which naturally can have expressed negative effects on HRQOL. A trend towards younger children reporting poorer quality of life was also observed by Macran et al. with the ConQol. These findings call attention to the need of support before and during first encounters with the peer community. This support should include detailed information given to the parents and the child about the disease and its potential associated problems. Detailed advice about physical activity is also essential for the family and also for the teachers. Results of previous studies indicate that children and their parents have limited knowledge of their cardiac condition, what they can and can not do, which makes it difficult to explain their condition to others.

An explanation for the lack of differences in HRQOL dimensions in children of 2-4 years of age according to the parents can be the relatively closed environment of the child and the family in this period, without the possibility of comparison to other children. Due to social support this could be more expressed in Hungary. Owing to the dramatic development of pediatric cardiac surgery and cardiology, looking at the growing up of a ”healthy child” to all appearances after the shocking event of the birth of a critically ill baby can bring the family into an euphoric state, which can be another possible cause for the absence of perceived HRQOL impairment by the parents' during this period. Lower expectations of parents may lead to denial of physical or psychosocial problems. It is a limitation that parallel questioning was not performed in this age group. The need for parallel questioning of children and parents is obvious in HRQOL measures but in this age group it is not accomplishable. The poor agreement between child self-report and proxy-report on certain domains of HRQOL has already been demonstrated.

The only significantly lower scores for children of 8-12 years were the PedsQL™ total scale score and the physical functioning score by the proxy-reports.

The discontinuance of HRQOL impairment to the older age groups may be a sign of good integration of children with heart disease into their society. Their capability and the effectiveness of coping mechanisms are often underestimated by clinicians, parents and teachers (85). Peers and teachers can have an important role, but they could also be sources of stress (88). It is important that there are systems within schools for ensuring that accurate information about children's health needs and impact of these on school life is passed to all those who teach the child.

The sample consisted of children with different severity of heart disease. The ratio of children with severe to those with simple heart diseases corresponded to the distribution of patients attending a typical pediatric cardiology outpatient unit. According to our and to previous results, overall quality of life of children with different severity of heart diseases – as a whole group – does not differ significantly from that of the general population. It means that the justification for stigmatization of heart disease, with its negative consequences, is strongly refuted by the children themselves. Thanks to the enormous advance in pediatric cardiac surgery, most pediatric heart diseases can be resolved by interventions, ensuring good quality of life for children.

Corresponding to previous findings with PedsQL™ our data affirm the instrument's validity in differentiating between groups with different levels of chronic disease severity. Comparing the groups of different heart diseases with the general Hungarian population and with the group of children with simple CHD we could observe more impaired HRQOL functions in children with more severe heart disease. Lower physical and psychosocial scores, school and cognitive problems observed among children with the most severe diseases (CHD with moderate and great complexity and cardiomyopathies) show the necessity of identification of these problems in these patient groups to make early intervention programs possible. Similar to previous studies confirming an incremental decrease in psychosocial functioning with the severity of the disease, show the importance of psychosocial problems in children with chronic conditions, which has already been recognized as the "new hidden morbidity". The lower social (by self-reports) and emotional (by parent-reports) functioning scores of Hungarian than U.S. children with heart disease stress the need for comprehensive pediatric cardiology care, which includes the involvement of experts in the psychosocial support of chronically ill children in Hungary.

The fact that parents of children with moderate heart disease report lower physical functioning calls attention to the possibility that parents often underestimate their child's physical ability, imposing unnecessary restrictions on them and depriving them of the psychological benefits of exercise. This can be related to the impaired social functioning in children with CHD of moderate complexity.

Analyzing our results of the disease specific Cardiac Module- in line with expectations- significantly lower scores were found on the heart symptoms subscale in patients with more severe CHD. Parents of children of the "Other" diagnostic group also reported significantly lower indices for this scale. It can be a consequence of the exaggeration of symptoms and of unjustified fears about chest pain, which generally means heart disease in the adult population. The misinterpretation of this symptom and of heart murmurs can be countered by accurate information from the pediatric cardiologist. Perceived physical appearance score was significantly lower only in patients with cardiomyopathies by parent opinion. In these patients, fears about the chronic condition and the need for continuous therapy can lead to decreased self-esteem. Correlating with the impaired school functioning we have observed significantly lower cognitive functioning scores in patients with CHD of moderate and great complexity and in patients with cardiomyopathies. These results are consistent with previous data and call attention to the need for early detection of school functioning deficits including attention problems and interventions for better neuropsychological development of these children.

Analyzing our data with respect to various therapeutic needs, we could observe that parents reported negative affects in more HRQOL dimensions than children themselves, mainly if patient groups requiring heart medication were compared to those requiring no therapy at all or intervention only. Taking heart medication alone could negatively influence perceived physical appearance by the opinion of children. Treatment anxiety is more expressed according to the parents if their child had a cardiac intervention. Lower social functioning scores were obtained from self-reports, when the group requiring heart medication beside intervention was compared with the one requiring intervention only.

These findings indicate that the impact of health care interventions on children's life is overestimated by the parents, and taking heart medication has the most expressive negative effect on HRQOL. In the exploration of health-related experiences of children with congenital heart disease, Birks et al found that medication was a problem only if it had an impact on school life.

The physical functioning of Hungarian children with heart disease was observed to be worse than that of the U.S. sample by the opinion of children and parents as well, which emphasizes the need for general actions in pediatric cardiology care in the field of physical activities. The expressed occurrence of items of physical functioning among the most frequently reported problems supports the weakness of physical ability of Hungarian children with heart disease. Cardiologists and pediatricians should help the patients and the families choose the proper kind of activity. Detailed information given to parents and teachers about the disease can help in stopping the serious restrictions rooting from the stigmatization surrounding heart disease. The lower social (by the self-reports) and emotional (by the parent-reports) functioning scores stress the need for comprehensive pediatric cardiology care, which includes the involvement of experts in the psychosocial support of chronically ill children. The remarkably invariable scores of the disease specific dimensions indicate the children's similar attitudes to their illness and to its care. Comparison of a Hungarian nationwide population with a U.S. standard sample would improve the completeness of analysis of these differences.

The discordance between the children's and parents' answers – as parents reported impaired HRQOL functions in expressly more dimensions – has already been demonstrated. Since previous findings with the PedsQL™ has shown that children as young as 5 years old can reliably and validly self-report their HRQOL, results of self-reports and proxy-reports should be interpreted together according to the professional guidelines. Identification of differences between parents and older children may provide important insight into knowledge gaps or unrecognized psychosocial needs and supports the need to measure the perspectives of both child and parent.

Concordantly with these previous findings, our data on parent proxy-reports also showed significant differences in the Emotional Functioning Scale and the Psychosocial Summary Score, and in the Total Generic Core Scales Score. This observation may indicate the parental underestimation of certain dimensions of HRQoL and the advanced levels of children's coping strategies.

The marked difference in missing values between the patient and the comparison group highlight the importance of situational circumstances at the time of the survey. In a medical institution, potential subjects tend to agree to participate much more willingly when asked by medical staff. On the other hand, patient and parent stress and time limitations could be factors that explain incompleteness of filling-in the questionnaire. In the postal survey of the comparison group, respondents' willingness was not influenced by any extraneous factors such as illness, fatigue and time limitations. Further, the general population was requested to

only complete the Generic Core Scales, while the cardiac sample was additionally requested to complete the Cardiac Module, which may increase respondent burden.

For the Cardiac Module, extremely high frequencies of missing values were detected for the Treatment II Scale (taking heart medication) and in the Perceived Physical Appearance subscales. Although there is an instruction in the questionnaire to skip the Treatment II Scale if the child does not take heart medication, many respondents failed to take notice of it this instruction. A written or – when it is possible – verbal notice might induce more focused attention and decrease the bias due to missing values. By deleting the missing values from the Treatment II Scale from the calculations, missing value percentages for the total cardiac module decreased from 15.0% to 5.4% for child self-report, and from 14.6% to 4.8% for parent proxy-report. The high proportion of patients without surgical treatment could result in a similar augmentation for the Perceived Physical Appearance Scale. As Hungarian children under 7 do not attend school, and because the social support system allows schooling to be postponed for children with chronic conditions, an over-representation of pre-school respondents may have raised the missing value frequencies for the Cognitive Functioning Scale. Other European investigators also reported that the daycare or school functioning subscale is not applicable for children aged 2-7 years.

Intercorrelations estimated by this study between generic core scales and cardiac module scales are consistent with the previous literature.

No (for Generic Core Scales) or minimal (for the Cardiac Module) floor effects and more accentuated ceiling effects for both scales means that distinction by the Hungarian translation of the instrument between persons who do extremely well or just well is less than excellent. Child and parent scores from the comparison group showed stronger ceiling effects than those from the patient group, as would be expected. Highest values appearing on the Social Functioning Scale can also be a sign of the success of coping mechanisms or peer acceptance. The notable ceiling effect in the heart symptoms subscale of the Cardiac Module is understandable in a mixed population of children with different heart disease severity, where a considerable proportion of the sample do not have a severe condition which would be expected to influence markedly their daily lives. Moderate ceiling effects in the Treatment II, Perceived Physical Appearance, and Cognitive Problems Scales for child self- and parent proxy-report are also consistent with the diversity of disease severity of the studied population, with some patients not taking heart medicine and having had no cardiac intervention.

Consistently with previous findings, some lower internal consistency reliability values were calculated in younger age groups and for the Social and School Functioning Scales of the Generic Core Scales and for the Treatment II, Perceived Physical Appearance, and Cognitive Functioning Scales of the Cardiac Module, where small sample size could possibly compromise the precision of results.

6. Conclusions

The first survey with PedsQL™ in Hungarian children with heart disease support the feasibility, reliability and validity of the Hungarian translation of PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 3.0 Cardiac Module, but highlight the importance of situational settings during completion and the necessity of explicit instructions for several scales. Our results affirm the validity of the instrument in differentiating between healthy and chronically ill children and between patients with different levels of heart disease severity.

Hungarian patients of 2-18 years report significantly lower physical functioning than the general Hungarian child population and than U.S. children with heart disease. This observation emphasizes the need for proper informing of families and teachers regarding physical activity of children with any kind of heart disease. Corresponding to previous results, parents report lower HRQoL scores in more dimensions than their children do.

Lower psychosocial scores by the parents' opinion indicate the necessity of integration of psychosocial support in the care of chronically ill children and their families. In the analyses of HRQoL scores of children with varied severities of heart disease, lower physical and psychosocial scores were observed among children with the most severe diseases (CHD with moderate and great complexity and cardiomyopathies). Parents reported lower emotional functioning, while children reported lower social functioning more often. School and cognitive problems were detected only among patients with CHD of great complexity and with cardiomyopathies. Therefore, identification of these problems is warranted in these patient groups to make early intervention programs possible. The fact that deficits of the various HRQOL dimensions are focused in children 5-7 years of age shows the difficulties of chronically ill children during integration into society and the good coping mechanisms which resolve many of these problems by later ages.

Our data on groups with different therapeutic needs show that parents overestimate the effects of health care on their children's HRQOL. Heart medication alone can have a negative affect on perceived physical appearance, and intervention increases treatment anxiety by the opinion

of children. Disease specific HRQOL scores of Hungarian children being similar to those of U.S. children, refers to some characteristics independent from the health care system and socio-economic status.

The results of this study, suitable for international comparison of children with heart disease in Hungary, highlight many questions about the effects of socioeconomic status of the population, of differences in standards of pediatric cardiology care, and of the customs and recommendations on physical activity for this population different from those in the U.S.A. or other countries with more experience in patient-reported outcome measurement. These questions could be answered by investigations on wider general and patient populations, exploring also the effects of socioeconomic factors influencing HRQOL.

Although the data from our study presents reasonable evidence for the psychometric properties of the Hungarian translation of the PedsQL™ 4.0 Generic Core Scales and PedsQL™ 3.0 Cardiac module for HRQOL studies in Hungarian children, future investigation with the instrument on larger samples of healthy children and on children with various levels of heart disease severity are recommended. Research focus should extend to other clinical populations, also testing sensitivity and responsiveness in longitudinal studies. The Hungarian translation of the PedsQL™ may further facilitate international comparisons and analysis of pediatric health care outcomes across countries.

Hopefully our study might stimulate this kind of research in Hungary and start the transition of health care of chronically ill children into a more comprehensive system. The wide international application of these measurements helps in improvement of health care by providing a better understanding of the function and effects of a diverse set of co-existing systems.

Hungarian patients of 2-18 years report significantly lower physical functioning than the general Hungarian child population and than U.S. children with heart disease. This observation emphasizes the need for proper informing of families and teachers regarding physical activity of children with any kind of heart disease. Corresponding to previous results, parents report lower HRQOL scores in more dimensions than their children do. Lower psychosocial scores by the parents' opinion indicate the necessity of integration of psychosocial support in the care of chronically ill children and their families.

7. Major findings of the thesis

1. Our results support the feasibility, reliability and validity of the Hungarian translation of PedsQL™ 4.0 Generic Core Scales and the PedsQL™ 3.0 Cardiac Module.
2. Measures with the Hungarian version of PedsQL™ 3.0 Cardiac Module will be suitable to provide data on the incidence and prevalence of health-related quality of life impairments in Hungarian children with heart disease.
3. Physical functioning of Hungarian children with heart disease significantly worse than that of the U.S. sample indicates a general restrictive attitude towards physical activities regardless of the severity of cardiac conditions. Choosing a physical activity adjusted to the type of heart disease, and proper information of parents and teachers give children the possibility to achieve a better quality of life.
4. Parental underestimation of children's physical ability with unnecessary restrictions causes impaired social functioning in children with CHD of moderate complexity.
5. Lower psychosocial scores by the parents' opinion, and lower than U.S. children's with heart disease stress the need of the involvement of psychosocial support of chronically ill children in Hungary.
6. Lower physical and psychosocial scores, school and cognitive problems observed among children with the most severe heart diseases show the necessity of identification of these problems to make early intervention programs possible.
7. Analyzing our data with respect to various therapeutic needs, we could observe that impact of health care interventions on children's life is overestimated by the parents.
8. Disease severity is not generally mean lower HRQoL.
9. Data suitable for international comparison give the possibility to assess the effect of differences in prevention, treatment and rehabilitation of children with heart disease.
10. Our study provides data for further measures on healthy population and on children with other chronic conditions.
11. Adjustment of HRQoL measures to health-care of chronically ill children can facilitate early intervention programs to decrease the negative consequences of the disease.

8. Own publications thesis based on

1. Berkes A, Mogyorósy G.: Az életminőség mérés alapjai, annak gyermekkori alkalmazása. Orvosi Hetilap 2008,149:1215-24.

2. Berkes A, Mogyorósy G.: Életminőség mérések a gyermek-kardiológiában. Orvosi Hetilap 2008, 149:1761-8.
3. Berkes A, Mogyorósy G.: A PedsQL™ gyermekkori életminőség mérő kérdőív kardiológiai moduljának magyarországi validálása. Orvosi Hetilap 2008,149:2261-8.
4. A Berkes, I. Pataki, M. Kiss, Cs. Kemény, L. Kardos, J. W Varni, G. Mogyorósy: Measuring health-related quality of life in Hungarian children with heart disease:psychometric properties of the Hungarian version of the Pediatric Quality of Life Inventory™ 4.0 Generic Core Scales and the Cardiac Module. Health and Quality of Life Outcomes 2010, 8:14.
5. Berkes A,Varni JW, Pataki I, Kardos L, Kemény C, Mogyorósy G.: Measuring health-related quality of life in Hungarian children attending a cardiology clinic with the Pediatric Quality of Life Inventory. European Journal of Pediatrics 2010, 169(3):333-47

9. Own publications not used in the thesis

Berkes A., Szegedi, I., Szikszay, E. és mtsai: Botulizmus csecsemőkorban- irodalmi áttekintés egy eset kapcsán. Orvosi Hetilap. 2007, 24, 1117-1125.

10. International congress presentations

Berkes, A, Mogyorósy, G, Kemény, Cs: Validation of the cardiac module of the Pediatric Quality of Life Inventory™ (PedsQL™) into Hungarian. New prospects in the medical care of chronically ill children in Hungary. WHO Congress on Health Promotion in Hospitals. 2008, Berlin

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List of publications related to the dissertation

1. **Berkes, A.**, Pataki, I., Kiss, M., Kemény, C., Kardos, L., Varni, J.W., Mogyorósy, G.: Measuring health-related quality of life in Hungarian children with heart disease: Psychometric properties of the hungarian version of the Pediatric Quality of Life InventoryTM 4.0 Generic Core Scales and the Cardiac Module.
   Health Qual. Life Outcomes. 8 (1), 1-14, 2010.
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3. **Berkes A.**, Mogyorósy G.: Életminőség-mérések a gyermekkardiológiában.
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List of other publications

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