Summary

In ***Chapter 1*** the aim of this thesis is introduced, which is the investigation of Health related Quality of Life in children aged 0-12 years. As medical successes have increased, a systematic outcome measure was needed that could account for the different ways children can react to a certain physical problem. Although the individual paediatrician already recognised these individual differences, a systematic and quantifiable outcome measure was missing. This gap was filled by the introduction of the construct *Health related Quality of Life (HRQoL)* also referred to as Quality of Life (QoL). As a generally accepted definition or theoretical framework is missing, we define HRQoL as: the individual's perception of problems in health status, combined with the affective responses to such problems. *Health Status (HS)* is the assessment by a person of his or her own health. The 'health' component involves physical, psychological as well as social functioning. Furthermore, we subscribe to the notion that HRQoL is multi-factorial (physical, psychological and social well-being), patient self-administered, subjective and variable over time. In this thesis, the usefulness of this definition was explored.

Chapters 2 to 6 describe how to define and obtain HRQoL in children. In ***Chapter 2*** the development of the 56-item TNO-AZL-Child-Quality-Of-Life (TACQOL) questionnaire is presented. The instrument is developed to meet the need for a reliable and valid instrument for measuring HRQoL in children. HRQoL was defined as HS in seven scales plus the emotional responses to problems in HS. The TACQOL explicitly offers respondents the possibility of differentiating between their functioning and the way they feel about it. A random sample of 1789 parents of 6-11 year olds completed the TACQOL, as well as 1159 8-11 year olds themselves. Multiple correspondence analyses showed that item response categories were ordinal, and that the TACQOL scales may be regarded as metric. Cronbach's alpha ranged from 0.65-0.84. Only 57% of reported HS problems were associated with negative emotions, which supports our definition of HRQoL. Intraclass correlation coefficients between Parent Forms and Child Forms ranged from 0.44-0.61. Pearson's correlation coefficients between TACQOL and the Dutch version of a German HRQoL instrument (KINDL) ranged from 0.24-0.60. Univariate analyses of variance showed that children with chronic diseases and

children receiving medical treatment had lower TACQOL scores than healthy children. The study showed that with the TACQOL, children's HRQoL can be measured in a reliable and valid way. In addition, the study provided a large norm group for children age 6 to 11 years.

In Chapters 3 and 4 the relation between child and parent report on children's HRQoL is studied. ***Chapter 3*** evaluates the agreement between child and parent reports on HRQoL in a representative sample of 1105 Dutch children (age 8 to 11 years old). Both children and their parents completed the TACQOL. The Pearson correlations between child and parent reports were between 0.44 to 0.61 ($p<0.001$). Intraclass correlations were between 0.39 to 0.62. Children on average reported significantly lower HRQoL than parents on the physical complaints, motor functioning, autonomy, cognitive functioning, and positive emotions scales (paired t-test: $p<0.05$). Agreement on all scales was related to the height of the HRQoL scores and on some scales to some background variables (gender, age, temporary illness, visiting a physician). According to multitrait-multimethod analyses, both child and parent reports on HRQoL proved to be valid. We recommended using both children's and parent's evaluations whenever possible.

In ***Chapter 4***, the agreement is evaluated between child and parent reports on children's HRQoL in a sample of 416 Dutch children with a chronic disease (8 to 15 years). Both children and their parents completed the TACQOL. The correlations between child and parent reports varied from -0.10 to 0.99 amongst the various chronic conditions. Children reported lower HRQoL on the physical complaints, motor functioning and positive emotions scales. Parents reported lower HRQoL on the social, and negative emotions scales. Agreement on all scales was related to the type of chronic illness. The child and the parent each provide different information on HRQoL. Knowledge of both judgements will enhance the care of children with a chronic illness and their parents.

Chapter 5 describes the development of the 46-item TNO-AZL Pre-school Quality Of Life (TAPQOL) questionnaire. HRQoL was defined as HS in 13 scales plus the emotional responses to problems in HS. The TAPQOL has to be completed by the parents. A sample of 121 parents of preterm children completed the TAPQOL questionnaire as well as 362 parents of children from the open

population. On the base of Cronbach's alpha, item-rest correlation, and factor-analysis, the TAPQOL scales were constructed on the data of the preterm children sample. The psychometric performance of these scales was evaluated for both the preterm children sample and the open population sample. Cronbach's alpha ranged from 0.66-0.88 for the preterm children sample and from 0.26-0.85 for the open population sample. The uni-dimensionality of the separate scales was confirmed by principal component analysis for both samples. Pearson's correlations between scales were low. T-test analyses showed that very preterm children and children with chronic diseases had lower scores (indicating a poorer HRQoL) on the TAPQOL scales than healthy children. This study shows that the TAPQOL is a good instrument to measure HRQoL in pre-school children, but more research is needed to evaluate the psychometric performance of the TAPQOL in different clinical populations.

In ***Chapter 6***, the relationship of preterm birth with HRQoL is examined for children aged 1-4. From the study groups in Chapter 5, three gestational age groups were selected, < 32 weeks (n=65) , 32-37 weeks (n=41), $\geq$37 weeks (n=54), and a reference group from the open population (n=50). The main instrument was the TAPQOL, which was completed by the parents, and provided HRQoL as well as HS scores. Other outcome measures obtained from parents or neonatologists were investigated in addition. It was shown that children born <32 weeks had significantly lower HRQoL than the reference group on the scales for lungs, stomach, eating disorders, motor functioning, communication and anxiety. We found differences between the neonatologist and the parent in perception of the child's situation, which can have clinical consequences. Parents of children born very preterm noticed many motor problems(=HS), but considered less emotional impact (=HRQoL) than would be expected from this number of problems. The judgement of the neonatologist related to the HS but not to the HRQoL as obtained by the parents. As a result, parents evaluated motor problems as being less of an emotional burden than the neonatologist does. In reverse, parents evaluated problems relating to lungs, stomach and sleeping as being more of an emotional burden than the neonatologist did. It can be stated that neonatal intensive care after birth has HRQoL implications for all children, particularly in children born after <32 weeks of gestation.

Summary

Chapters 7 to 10 deal with HRQoL in a longitudinal perspective. ***Chapter 7*** explores the time variability of QoL in children between 0 to 12 years of age. This was done by means of a systematic review of original studies, with at least two QoL assessments, and published between 1966 and 1998. The publications were identified from medical and psychological sources by computerised searches followed by manual selection. Thirty-two publications were selected and discussed according to their general characteristics, QoL assessment, longitudinal QoL research design and approaches to what changes QoL. It appeared that only two publications met all QoL assessment requirements (multi-factorial, self-administered, subjective) as well as longitudinal requirements (clear description of assessment period, recall period, sample size at end of study, within-subject statistics). The approach to change that underlay the 32 publications can be described as: stable physical health gives stable QoL and changes in physical health changes QoL. It is rarely acknowledged that psychological, social and situational variables can change QoL as well. It can be concluded that there is a need for more studies that meet QoL assessment as well as longitudinal requirements. In the future, discussion is necessary about what exactly changes QoL, as this influences the planning of the assessments and guides the interpretation of changes.

Chapters 8 and 9 both study the same sample consisting of 688 children, born preterm in 1983 with a gestational age of less than 32 weeks and/or a birthweight of less than 1500 grams. Whereas Chapter 8 places the accent on the methodology, Chapter 9 focuses on the paediatric details. ***Chapter 8*** presents a strategy for analysing longitudinal QoL data that suffer from differences in measurement instruments over time. The strategy was applied to a set of longitudinal data from the cohort of preterm born children. HS data, differently defined at 5, 9 and 10 years of age, were prepared for longitudinal analyses with qualitative and quantitative item selection. Expert ratings fitted the data into physical, psychological and social HS domains. Principal component analysis (PCA) was used to match the data between measurements. Longitudinal PCAs were performed using the matched HS data. The impact of background variables such as gender and birthweight on HS changes was studied. It was concluded that this strategy to reconstruct and combine an imperfect data set, provided valuable information about the development of HS in preterm born children.

Chapter 9 describes the long-term effects of the complications that accompany a preterm birth. The HS at the age of 5 and 10 years in the cohort of children born preterm was studied to determine the impact of preterm birth on HS development. Prospectively collected HS variables, obtained from the parents, were analysed in a longitudinal perspective, using principal component analyses. One third of the sample had minor to severe HS problems at both ages of measurement. One third had problems on one assessment only. The remainder of the sample had no HS problems at either age. The analyses grouped the HS variables into three combinations: Problems in basic functioning, such as mobility or speech, decreased with age. Negative moods substantially increased, and concentration problems increased slightly. Specifically at risk (for HS problems) were preterm born children with handicaps, boys, and children born small for gestational age. In conclusion, according to the parents, one third of the cohort had no HS problems at either age. The pattern of HS problems of the preterm born children changed between 5 and 10 years of age.

In ***Chapter 10***, changes in HRQoL and self-esteem Are studied in children with Idiopathic Short Stature (ISS) participating in a prospective randomised controlled study on the effect of Growth Hormone (GH) treatment. The sample consisted of forty prepubertal children (age 4 to 10 years old at start) with ISS (height <-2 SDS). The children were randomly assigned to a treatment or control group. HRQoL and self-esteem were assessed three times: shortly after randomisation (T1), and one (T2) and two years (T3). Children with ISS, their parents and the paediatrician completed questionnaires. At T1, children with ISS did not have a lower HRQoL and self-esteem than the norm population, except for the domain of social functioning as reported by children and parents. Children, parents and physician assessed HRQoL differently: At T3, children of the treatment group reported in some scales lower HRQoL and self-esteem than the control group did. The parent reports did not differ between groups, but the physician reported improved HRQoL in the treatment group. Changes in HRQoL and self esteem between T2 and T3 hardly related to growth (objectively measured or as perceived by the child). Instead, changes in several HRQoL and self-esteem scales related to the height appreciation by the child her/him self. The assumption that GH treatment improved HRQoL in children with ISS could not be supported in this study.

Summary

Chapter 11 contains the general discussion of the thesis, in which four themes are discussed that are relevant in the study of HRQoL in children. Firstly, it was shown that children as well as parents distinguish between the HS problems they observe, and the emotional appreciation of these problems incorporated in HRQoL. This justifies the distinction we made between the definitions of HRQoL and HS. Secondly, it was concluded that scientific tools are available to measure HRQoL in children. Two instruments were exhaustively described in this thesis (TACQOL and TAPQOL) and appeared reliable and valid. Thirdly, it appeared that children, parents and physicians assessed HRQoL differently. As all three reports had their value, it was recommended using all informants whenever possible. Finally, it was stressed that when the term *health related* QoL is used, it should be recognised that health contains physical, psychological as well as social health. This implies that when changes in physical health cannot be realised in children with a chronic illness, changes in psychological and social health may be able to improve the HRQoL of these children.