Chapter 3

Quality of life in 1 year old preterm infants born before 32 weeks of gestational age

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Abstract

Objective: To determine the effect of prematurity (gestational age (GA) < 32 wks) on Health Status (HS) and Health Related Quality of Life (HRQoL) at the corrected age of 12 months in a regionally defined, prospective cohort study. *Methods:* The Leiden Follow-Up Project on Prematurity (LFUPP) includes all liveborn infants of < 32 wks GA born in 1996 or 1997 (n=266). HS and HRQoL were prospectively measured using the TNO-AZL- Preschool- Quality of Life-questionnaire (TAPQOL) (completed by the parents) which has 10 scales for children aged 1-1.5 yrs. Maximal HS- and HRQoL-scores are 100. The TAPQOL-data of 51 term born children drawn from "Well-Baby-Clinics" were used as reference. *Results:* We analyzed 171 TAPQOL's of 206 survivors (83%). Median HS- and HRQoL-scores were maximal in the stomach-, lungs- , skin-, positive mood and liveliness-scales. Compared with the control group, HS and HRQoL-scores were significantly lower in the stomach-, eating disorders and lungs-scales. Comparison within the study group showed that lower GA (24-28 wks), bronchopulmonary dysplasia (BPD) and abnormal neurological outcome at term and at 12 months corrected age were associated with significantly lower HS- and HRQoL-scores in one or more of the eating-related scales: stomach, appetite and eating-disorders. *Conclusions:* The majority of the preterm infants had maximal HS- and HRQoL-scores in 5 out of 10 scales at 12 months corrected age. The eating related scales were most frequently reported as being unsatisfactory, both in comparison with a term reference group and in infants of lower GA, infants with BPD and infants with neurological abnormalities.

Abbreviations:

BPD	:	bronchopulmonary dysplasia
DA	:	definitely abnormal
GA	:	gestational age
HS	:	Health Status
HRQoL	:	Health Related Quality of Life
LFUPP	:	Leiden Follow-Up Project on Prematurity
MA	:	mildly abnormal
MND	:	minor neurological dysfunction
NICU	:	neonatal intensive care unit

SES : socioeconomic status
SGA : small for gestational age
TAPQOL : Tno-Azl-Preschool Quality Of Life-questionnaire

Introduction

Since the introduction of neonatal intensive care in the sixties, the mortality of preterm infants has steadily decreased (1). Survival, especially of the very preterm infants has significantly improved with advances in neonatology, particularly the introduction of surfactant. However, the influence on morbidity of this improved survival remains unclear (2). The prevalence of handicaps among the very preterm infants varies between 12% and 70% (3-7). This wide range is partly caused by the use of different inclusion criteria and outcome measures. Comparison of outcome studies therefore remains difficult, but morbidity, especially in very preterm infants, has remained high.

Although objective outcome measures like neurodevelopmental status and growth are important determinants of the quality of neonatal intensive care, quality of life parameters are being used increasingly to evaluate health care practice (8). Reports about quality of life in NICU-survivors are however scarce. This study inquires into the parental perception of Health Status (HS) and Health Related Quality of Life (HRQoL) of a regional, prospective cohort of very preterm infants at the age of 12 months (corrected for preterm birth). 'Health Status' refers to the assessment by a person of his or her own health functioning, whereas the term 'Health Related Quality of Life' examines the impact of disease on quality of life (8). HRQoL includes the patient's emotional responses to HS-problems and limitations (9).

We hypothesized that the quality of life of very preterm infants would be worse than that of term born infants. We expected that among very preterm infants quality of life would be worse at lower gestational age (GA), in infants with bronchopulmonary dysplasia (oxygen dependence at 36 weeks postmenstrual age (10)) and in infants with neurological abnormalities.

Patients and methods

The Leiden Follow-Up Project on Prematurity includes all liveborn infants less than 32 weeks GA from the health regions Leiden, The Hague and Delft, born in 1996 or

1997 (n=266).
All infants ≥ 24 weeks GA were actively resuscitated at birth. The total number of live births in 1996 and 1997 in this region was approximately 17.800. Follow-up of the infants included physical examinations and assessment of neuromotor development by a paediatrician at term and at the corrected ages of 12 and 24 months. Psychomotor development was assessed with the Bayley Scales of Infant Development I at 18 and 24 months of corrected age by a developmental psychologist (11).
The study was approved by the Ethics Committee of the Leiden University Medical Center. Parental informed consent was obtained.
Obstetric data, perinatal factors and follow-up data were collected on precoded forms. Neurological examination was performed according to Prechtl at term (12) and according to Touwen at 12 months corrected age (13). At term, neurological outcome was classified as normal, mildly abnormal or definitely abnormal. Definitely abnormal means the presence of a full-blown neurological syndrome, mildly abnormal the presence of part of such a syndrome. At 12 months, the outcome was defined as normal, minor neurological dysfunction I (MND I), MND II or definitely abnormal (DA). MND I means an abnormality in one of the four neurodevelopmental clusters: tone/reflexes, gross motor function, fine motor function or cranial nerve function; MND II means abnormalities in at least two of these clusters. DA means the presence of cerebral palsy (14).
Socioeconomic status (SES) was determined by the level of education of both parents, a score of 1 was given if the parent's educational level was low, a score of 2 for an average educational level and a score of 3 for higher levels of education (15). SES-scores of both parents were then combined (range 2-6).
Ethnicity was defined as Dutch or non-Dutch origin (mostly Turkish, Moroccan or Surinamese origin).
The analyses of this study did not include 29 infants from the health region Delft as they did not receive a TAPQOL because most of them were seen by paediatricians of other university hospitals outside our study region. One child was excluded from the analyses because of Down's syndrome. The study group, receiving a questionnaire, therefore consisted of 206 infants (of 236 survivors). Fifty-one term born infants from the Dutch general population, aged between 1 and 1.5 years and drawn from 6 Dutch 'Well Baby-Clinics', were used as controls.

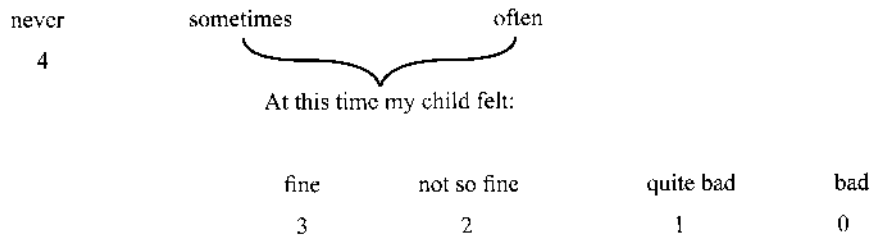
TAPQOL (TNO-AZL- Preschool- Quality Of Life-questionnaire)

The TAPQOL measures HS and HRQoL in children aged 1-5 years (9). This questionnaire was completed by (one of) the parents. The TAPQOL has 9 scales relevant for children aged 1-1.5 years: stomach, appetite, lungs, skin, sleeping, problem behaviour, anxiety, positive mood and liveliness. An additional scale concerning eating disorders was used as well.

The 10 scales include a total of 35 items (3 items in the stomach-, appetite-, eating disorders-, lungs-, skin-, anxiety-, positive mood- and liveliness-scales, 4 in the sleeping scale and 7 in the problem behaviour-scale). In the scales measuring stomach problems, appetite, eating disorders, lung problems and skin problems, items consist of two questions. In the first question the occurrence of a specific health problem in the last three months is recorded, resulting in a HS-score (0=often, 1=sometimes, 2=never). If a problem has occurred, the second question has to be answered, in which the emotional response of the child to the problem is evaluated, resulting in a HRQoL-score. HRQoL was scored on a 0-4 scale, with higher scores representing better HRQoL. An example of an item from the eating disorders-scale is presented in Figure 1.

Figure 1. Item-example of the eating disorders-scale

In the last 3 months, did your child have difficulties with swallowing food?

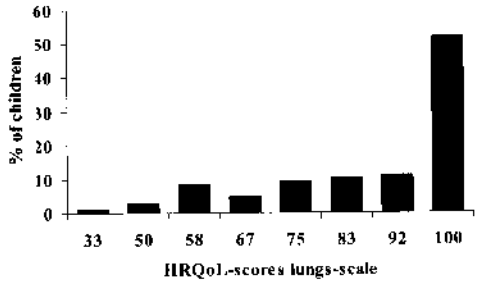


The items in the problem behaviour-, anxiety-, positive mood- and liveliness-scales do not include an emotional evaluation because they already imply a positive or negative emotional state. In these four scales HRQoL was scored on a 0-2 scale (0=often, 1=sometimes, 2=never). Crude scale scores were transformed linearly to a 0-100 scale, with higher scores indicating better HS and HRQoL in all 10 scales.

Statistical analysis

HS and HRQoL-scores were skewly distributed in all TAPQOL-scales, demonstrated for the lungs-scale in Figure 2.

Figure 2. Distribution of HRQoL-scores in the lungs-scale



HRQoL: Health Related Quality of Life

In view of this skewed distribution we report the data as median scores. Non-parametric tests were used for the statistical analysis. The Wilcoxon matched-pairs signed-ranks test was used for comparison of the HS and HRQoL-scores. The Kruskal-Wallis test was used for comparison of three or more patient groups and the Mann-Whitney test for comparison of two groups. The Spearman rank correlation was used to quantify the association between HS- and HRQoL-scores and quantitive factors. In addition, we dichotomized each scale using the threshold of 95, and compared groups with respect to the percentage of infants above and below this threshold using the chi-square test. In multiple regression analyses the following variables were used as confounding factors: GA, birthweight, gender, small for gestational age (SGA, birthweight < P10 (16)), multiple birth, SES of the parents and ethnicity. Rank transformed scores were used to correct for confounding factors (17). P-values below 0.05 were considered significant.

Results

The LFUPP included 266 children, constituting 92% of eligible infants born in 1996 and 1997 (97% of eligible infants born in 1996 and 88% of eligible infants born in 1997). Thirty (11%) of the 266 children died, 28 in the neonatal period and 2 more

before the age of one year. One hundred-sixtythree (61%) children were born in hospitals with a neonatal intensive care unit (NICU) (tertiary referral centers), 103 (39%) in hospitals without a NICU. Patient characteristics of the entire cohort are shown in Table 1.

Table 1. Characteristics of the LFUPP-cohort (n=266)

Antenatal steroids, % (n)	75 (182)
Male gender, % (n)	55 (147)
Gestational age:	
wks, mean (sd)	29.2 (2.1)
24-26 wks, % (n)	17 (46)
27-28 wks, % (n)	23 (61)
29-31 wks, % (n)	60 (159)
Birthweight, mean (sd)	1250 (383)
Small for GA (birthweight <P10), % (n)	13 (33)
Apgar 5 min, mean (sd)	7.7 (1.8)
Extra-uterine transport, % (n)	35 (93)
Hypotension*, % (n)	34 (98)
O2 at 28 days, % (n)	26 (67)
Bronchopulmonary dysplasia**, % (n)	19 (49)
Mechanical ventilation, days, mean (sd)	7.2 (9.3)
Dexamethasone postnatally, % (n)	17 (45)
Intraventricular haemorrhage, % (n)	
none	74 (190)
grade 1-2	18 (48)
grade 3-4	8 (20)
Periventricular leucomalacia (cystic), % (n)	3 (8)
In hospital mortality, % (n)	11 (29)
Dutch origin, % (n)	75 (167)
Level of education mother, % (n)	
high	29 (60)
average	50 (105)
low	21 (44)
Maternal age at birth, yrs, mean (sd)	30.5 (5.6)

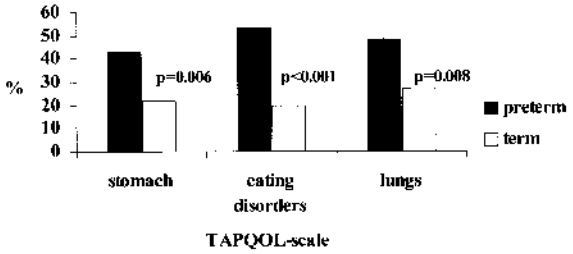
LFUPP: Leiden Follow-Up Project on Prematurity; sd: standard deviation; GA: gestational age;
* at least twice a mean bloodpressure < 30 mmHg; ** O2 at 36 weeks postmenstrual age

Of the 206 survivors who received a TAPQOL, 179 parents (87%) completed the questionnaire. Eleven patients (5%) were lost to follow-up because they moved to other cities or countries, 9 parents (4%) refused to cooperate and in 7 cases (3%) the parents did not complete the questionnaire due to a language barrier. Birthcharacteristics (GA, birthweight, gender) and incidences of respiratory distress syndrome, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (18), cystic periventricular leucomalacia (19) and abnormal neurological outcome at term of the lost-to-follow-up group did not significantly differ from those of the study group. Parents of the children from the lost-to-follow-up group were of lower SES and more frequently of non-Dutch origin.
Eight questionnaires were excluded because they had been completed after the corrected age of 18 months, so our final analysis included 171 TAPQOL's. The mean corrected age of the child at completion of the questionnaire was 1.1 years (range 0.9-1.48). The mean age of the control group was 1.2 years (range 0.8-1.5).

HS and HRQoL scores

The median values of the HS- and HRQoL-scores of the study and the control group are listed in Table 2 . Median HS- and HRQoL-scores of the study group were maximal (100) in the stomach-, lungs- , skin-, positive mood and liveliness-scales. Median HRQoL-scores were higher ($p<0.001$) than median HS-scores in 3 scales: appetite, eating disorders and sleeping.
Compared with the control group, HS- and HRQoL-scores of the study group were significantly lower in the stomach-, eating disorders- and lungs-scales, although the majority of preterm children had optimal HS- and HRQoL-scores in the stomach- and lungs-scales. However, the percentage of children with a HS/ HRQoL-score below 95 in these scales was significantly higher in the study group [Table 2, Figure 3 (only HRQoL shown , HS-scores comparable)].

Figure 3. Percentage of preterm (n=171) and term (n=51) children with HRQoL-scores < 95



HRQoL: Health Related Quality of Life,
TAPQOL: TNO-AZL-Preschool Quality of Life questionnaire

Table 2. Median (minimum-maximum value) HS- and HRQoL- scores of the study group compared to the control group

TAPQOL-scale	study group (n=172)	control group (n=51)	p**
Stomach:			
- HS-score	100 (16.7-100)	100 (33.3-100)	0.002
% score <95	44	22	0.005
- HRQoL-score	100 (33.3-100)	100 (33.3-100)	0.006
% score < 95	43	22	0.006
Appetite:			
- HS-score	83.3 (0-100)	83.3 (16.7-100)	0.5
- HRQoL-score	91.7 (25-100)	91.7 (41.7-100)	0.7
Eating disorders:			
- HS-score	83.3 (0-100)	100 (66.7-100)	<0.001
- HRQoL-score	91.7 (16.7-100)	100 (75-100)	<0.001
Lungs:			
- HS-score	100 (0-100)	100 (16.7-100)	0.01
% score < 95	48	28	0.008
- HRQoL-score	100 (33.3-100)	100 (0-100)	0.04
% score < 95	49	28	0.008
Skin:			
- HS-score	100 (0-100)	83.3 (0-100)	0.4
- HRQoL-score	100 (50-100)	91.7 (58-100)	0.5
Sleeping:			
- HS-score	75 (0-100)	75 (0-100)	0.8
- HRQoL-score	81.3 (0-100)	81.3 (31.3-100)	0.8
Problem behaviour*:			
- HRQoL-score	78.6 (14.3-100)	78.6 (42.9-100)	0.1
Anxiety*:			
- HRQoL-score	83.3 (0-100)	83.3 (50-100)	0.4
Positive mood*:			
- HRQoL-score	100 (50-100)	100 (50-100)	0.4
Liveliness*:			
- HRQoL-score	100 (16.7-100)	100 (50-100)	0.1

HS: Health Status, HRQoL: Health Related Quality of Life,
TAPQOL: TNO-AZL Preschool Quality of Life questionnaire

* In these scales HS HRQoL, ** Mann-Whitney U, chi-square

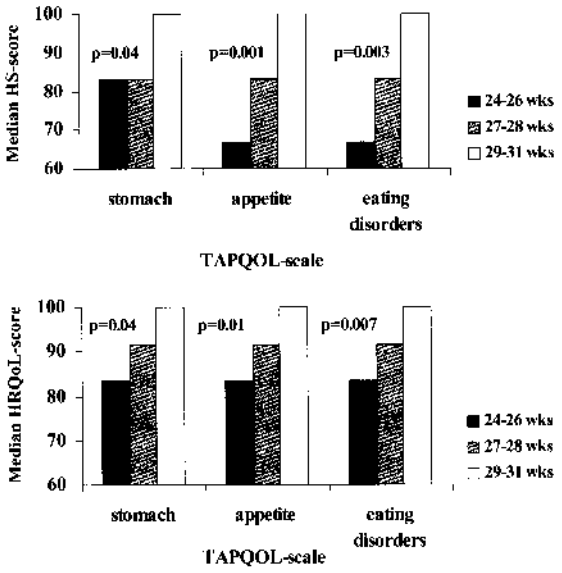
Influence of perinatal factors on HS and HRQoL

Gestational age:

Within the study group children with a GA of 24-26 weeks (n=22) were compared to children with a GA of 27-28 weeks (n=39) and 29-31 weeks (n=110). Significant differences were found in the stomach-, appetite- and eating disorders-scales for HS- and HRQoL-scores (Figure 4).

In these scales children of higher GA had better scores than those of lower GA. The differences remained significant after adjustment for the remaining confounding factors (p=0.02, p<0.001, p=0.002 for HS and p=0.03, and p=0.005, p=0.008 for HRQoL).

Figure 4. Median HS-and HRQoL-scores according to gestational age (24-26 wks: n=22, 27-28 wks: n=39, 29-31 wks: n=110)



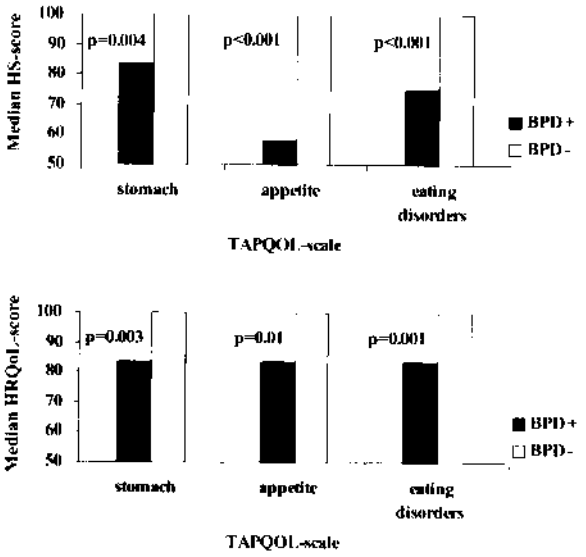
HS: Health Status, HRQoL: Health Related Quality of Life
TAPQOL: TNO-AZL-Preschool Quality of Life Questionnaire

BPD:

The 38 children (23%) with BPD had lower HS- and HRQoL-scores in the stomach-, appetite-, and eating disorders-scales compared to children without BPD (Figure

5). The differences in HS-scores remained significant after adjustment for the confounding factors (p=0.03, p=0.03 and p=0.008). For HRQoL-scores, only the differences in the stomach- and eating disorders-scales remained significant (p=0.03 for both scales).

Figure 5. Median HS-and HRQoL-scores in infants with (n=38) and without (n=133) BPD

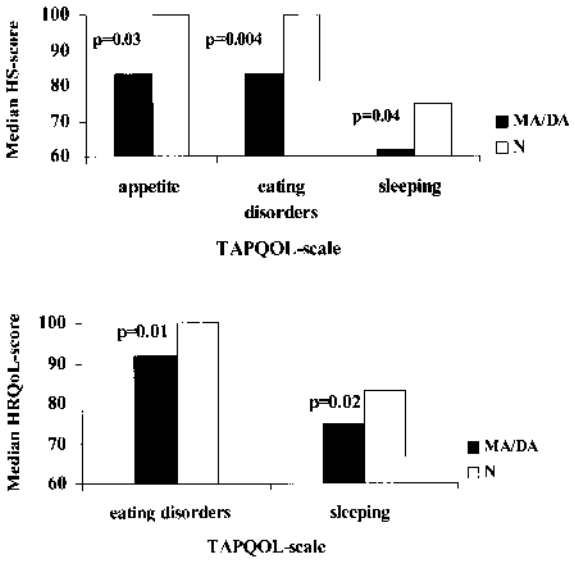


HS: Health Status, HRQOL: Health Related Quality of Life
TNO-AZL-Preschool Quality of Life Questionnaire

Neurological examination at term and at 12 months corrected age:

Since the number of infants with a definitely abnormal neurological examination at term was small (n=8), we compared infants with a mildly abnormal (MA) or definitely abnormal (DA) examination (n=82) to infants with a normal examination (n=88). The MA/DA infants had lower HS-scores on the appetite-, eating disorders- and sleeping-scales (Figure 6). After adjustment for the confounding factors only the difference in the eating disorders-scale remained significant (p=0.003). HRQoL-scores were lower in the eating disorders- and sleeping-scale (Figure 6). These differences remained significant (p=0.008, p=0.02) after correction for confounding factors.

Figure 6. Median HS-and HRQoL-scores in infants with normal (N, n=88) and mildly/definitely abnormal (MA/DA, n=82) neurological outcome at term



HS: Health Status, HRQoL: Health Related Quality of Life
TAPQOL: TNO-AZL-Preschool Quality of Life Questionnaire

At 12 months of age children with normal neurological outcome (n=118) or MND I (n=25) were compared to children with MND II (n=17) or definitely abnormal (DA) outcome (n=10). Median HS-scores of the MND II/ DA- group were lower in the stomach-, appetite- and eating disorders scales: respectively 83, 83 and 67 in this group and 100 in the normal/ MND I group ($p<0.001$, $p=0.02$ and $p<0.001$ respectively). The differences in the stomach- and eating disorders-scales remained significant after adjustment for the confounding variables ($p=0.001$ and $p<0.001$).
Median HRQoL-scores of the MND II/ DA- group were lower in the stomach- and eating disorders scales: 83 versus 100 for the normal/ MND I group in both scales ($p<0.001$ and $p=0.001$ respectively). Although the median score was 100 for both groups in the liveliness-scale, the percentage of children with HRQoL-scores < 95 in this scale was higher in the MND II/ DA group (28 vs 7%, $p=0.001$). The differences in all 3 scales remained significant after correction for the confounding variables ($p=0.001$, $p=0.004$ and $p=0.001$).

Discussion

The findings from this study show that, according to their parents, the majority of the preterm infants had no problems (median HS- and HRQoL-scores 100) at the corrected age of 12 months in 5 out of 10 TAPQOL-scales: the stomach-, lungs-, skin-, positive mood and liveliness-scales. When problems existed, the eating related scales were most frequently reported as being unsatisfactory, both in comparison with a term control group and in infants of younger GA, infants with BPD and infants with abnormal neurological outcome at term or at 12 months of age.

Median HRQoL-scores were higher than median HS-scores in 3 scales (appetite, eating disorders, sleeping), indicating that the impact of problems in these area's on the child's HRQoL (as perceived by the parents) is not always as great. Saigal et al. found that parents of extremely low birthweight children rated the HRQoL of their 12-16 year old children fairly high although they reported a higher frequency and more complex functional limitations than the parents of controls did. They ascribed this relatively high valuation of non optimal health states to parental resilience in coping with their children's disabilities (20).

When comparing the study to the control group, we expected HS- and HRQoL scores to be lower in more than just 3 scales in the very preterm infants, certainly in view of the high percentage of perinatal morbidity in this group. The scales in which significant differences did exist - stomach, eating disorders and lungs - represent the areas in which preterm infants often experience problems (21-23).

A possible explanation for a difference in only 3 scales may be that the questionnaire was completed around the child's first birthday, when problems could have ameliorated. On the other hand other problems, like neurological abnormalities, may not yet have developed. Nevertheless, at 12 months of age 31% of the children had neurological abnormalities. A more likely explanation is that parents learn to cope with the problems of their children and may judge the health state and quality of life of their child differently than an outsider would.

We expected infants of lower GA (< 29 wks) to have worse HS and HRQoL-scores than infants of 29-31 wks GA because of the inverse relation between gestational age and outcome. Our hypothesis was true for the eating-related scales.

Since the first year is centered around eating and growth, both in healthy term and in preterm infants, it is not unusual that parents report more problems in this area

with decreasing gestational age. Parents of children with BPD reported worse HS and HRQoL in the stomach- and eating disorders scales, but not, as expected, in the lungs-scale. Although HS and HRQoL-scores of children with BPD were lower in the lungs-scale than the scores of children without BPD, these differences were not significant. A possible explanation could be that by the age of 12 months the severity of the lung problems has decreased, either spontaneously or with treatment. Neurological abnormalities at term and at 12 months of age were strongly associated with the eating disorders-scale, in which problems with swallowing food and drinking are evaluated. Apart from this, neurological abnormalities at term were predictive of sleeping problems at 12 months of age. Neurological abnormalities at 12 months of age were associated with lower HRQoL-scores on the liveliness-scale. The problems in this scale could be a predictor of problems with psychomotor development later in life.

The lost-to-follow-up group differed from the study group in SES of the parents (lower) and ethnicity (more frequently of non-Dutch origin). Lower SES of the parents was associated with lower scores in the liveliness scale. Infants of non-Dutch origin had lower scores in the positive mood scale. Scores in these 2 scales would probably have been somewhat lower if data of all children had been available.

We conclude that, according to their parents, at 12 months corrected age eating-related problems have the greatest impact on quality of life of very preterm born infants. Possible problems in this area should be a main topic during the visits to the high risk follow-up clinic. We expect that, as the children get older, problems with motor-functioning and communication will have a considerable impact on their quality of life and that eating problems will become less important.

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