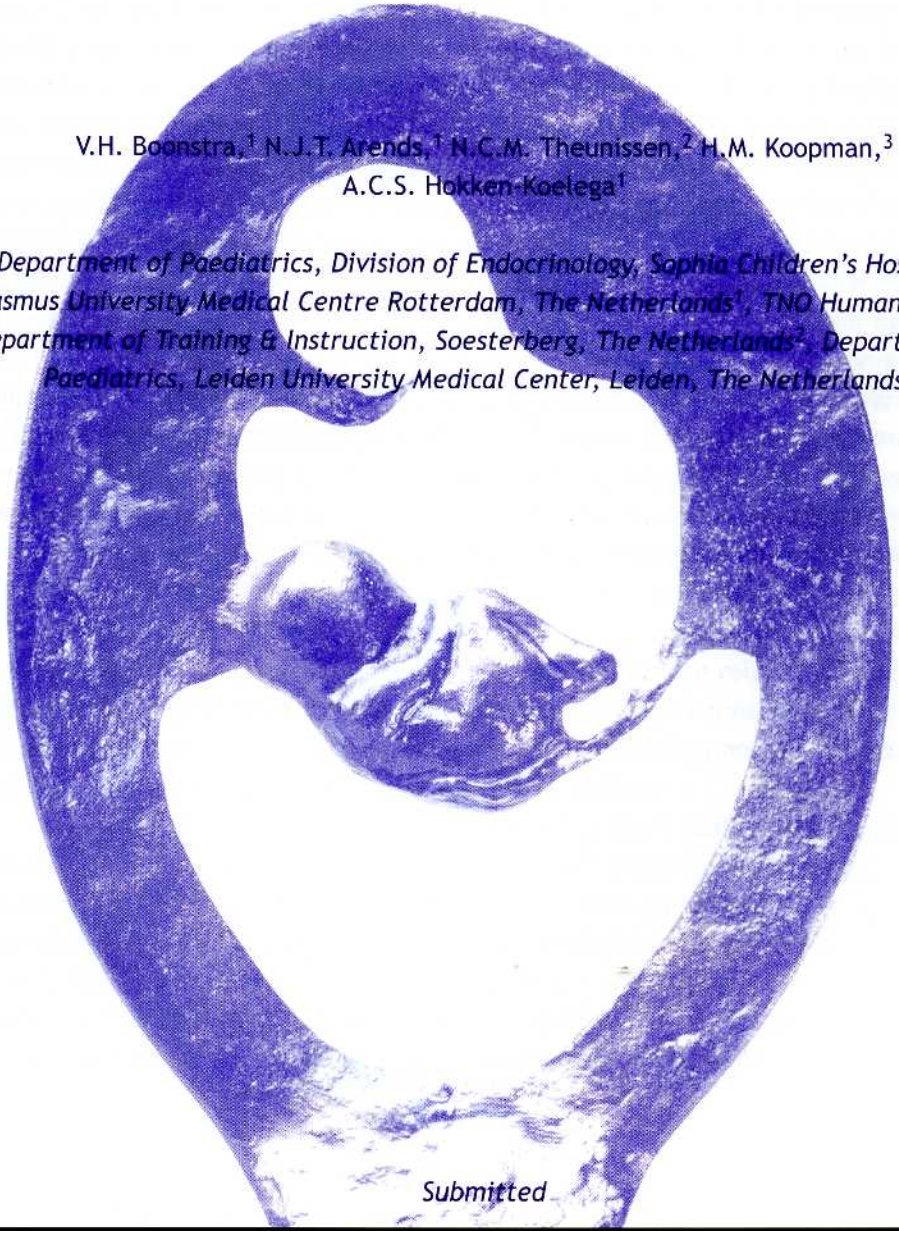
Chapter 7

Improved health related quality of life in growth hormone-treated children born Small for Gestational Age (SGA)



V.H. Boonstra,[1] N.J.T. Arends,[1] N.C.M. Theunissen,[2] H.M. Koopman,[3] A.C.S. Hokken-Koelega[1]

Department of Paediatrics, Division of Endocrinology, Sophia Children's Hospital, Erasmus University Medical Centre Rotterdam, The Netherlands[1], TNO Human Factors, Department of Training & Instruction, Soesterberg, The Netherlands[2], Department of Paediatrics, Leiden University Medical Center, Leiden, The Netherlands.[3]

Submitted

This is the first study evaluating HRQOL with a specific short stature questionnaire in short children born SGA. We hypothesized that the specific questionnaire will measure larger differences between control and treatment groups than the generic questionnaire. In addition we hypothesized that children with more catch-up growth will have a better HRQOL.

Methods

Subjects

Eighty-five Dutch children (37 boys and 48 girls) with short stature born SGA were included in a randomised GH-trial.[17] These children were referred to the hospital because of short stature. At the time of HRQOL and HS measurements the children were between 5 and 7 years of age. The inclusion criteria of the GH-trial were: 1) birth length or birth weight standard deviation score (SDS) below -2.00 SDS for gestational age;[18] 2) an uncomplicated neonatal period, without signs of severe asphyxia (defined as Apgar score below 3 after 5 minutes), sepsis or long-term complications of respiratory ventilation such as bronchopulmonary dysplasia; 3) chronological age (CA) between 3.00 and 7.99 years at start of the study; 4) height SDS for age below -2.00 according to Dutch standards;[19] 5) height velocity SDS for age below zero to exclude children with spontaneous catch-up growth;[19] 6) prepubertal, defined as Tanner stage 1 or a testicular volume < 4 ml;[20] 7) normal liver, kidney and thyroid functions. Exclusion criteria were: endocrine or metabolic disorders, chromosomal disorders, growth failure caused by other disorders (emotional deprivation, severe chronic illness, chondrodysplasia) or syndromes except Silver Russell syndrome, and previous or present use of medication that could interfere with GH treatment. All children used Dutch as their primary language.

Nine centres in the Netherlands participated in the study. The study was approved by the Ethics Committees of each participating centre. Written informed consent was obtained from the parents or custodians of each child.

Study design

The study design was an open-labelled, multicenter study with a randomised control group. The patients were randomly assigned to either the GH-group (2/3 of children) or the control group (1/3 of children). The GH-group started with GH treatment at a dose of 1 mg/m^2/day (≈ 33 µg/kg/day). The control group remained untreated for 3 years and subsequently received the same GH treatment as the GH-group.

Biosynthetic GH (r-hGH Norditropin^{R}, Novo Nordisk A/S, Denmark) was given subcutaneously once daily at bedtime. Three-monthly, the GH dose was adjusted to the calculated body surface area.

Quality of life measurements

The quality of life was measured by two different questionnaires: The generic TNO-AZL Questionnaires for Children's Quality of life (TACQOL)[16,21] and the TACQOL-Short Stature.

Both questionnaires are based on the same principle. They explicitly offer respondents the possibility of differentiating between their health status (HS) and the way they feel about it (HRQOL). The reference period is formulated as 'the last few weeks my child....'. Each item starts with a specifically formulated HS problem. Response categories are 'never', 'sometimes' or 'often'. If the answer is 'sometimes' or 'often' the item leads to a second part about emotional response: 'During this time my child felt.....' : '(very) good', 'not so well', 'rather bad', or 'bad'. Figure 1 shows an example of such a question. The answers of the HS questions were scored on a 0–2 scale (0 = often, 1 = sometimes, 2 = never), the question scores were counted up excluding the evaluation of the emotional response. HRQOL was scored on a 0–4 scale (added in Figure 1, between brackets), the question scores were counted up including the evaluation of the emotional response. As a result two series of scales were obtained: a HS-score and HRQOL-score. A higher score indicated a better HS or HRQOL. The questionnaires consist of different scales with questions, each with its own specific topic. Two parallel questionnaires were available: a parent form (PF) and a child form (CF), both with good measurement properties.[13] The PF is designed for parents of children aged 6–15 years and the CF is designed for children aged 8–15 years. In this study we used the PF since the children were younger than 8 years at the start of the study.

Did people think that your child was younger than he or she actually was?

❑ never [4] ❑ sometimes ❑ often

During this time my child felt:

❑ (very)good [3] ❑ not so well [2] ❑ rather bad [1] ❑ bad [0]

Figure 1. An example of a question from the TACQOL-Short stature (scale: body image).

The generic TACQOL is a 63-item questionnaire for assessing HS and HRQOL, applicable to children with different diseases and handicaps.[16,21] This questionnaire contains seven

scales: physical functioning, motor functioning, autonomy, cognitive functioning, social functioning, positive emotions and lack of negative emotions. The last two scales did not have a HRQOL part because the questions already include an emotional dimension. In these two scales HS equalled HRQOL. All scales had a Cronbach alpha above 0.70. The parents were asked to fill in the generic TACQOL before randomisation and after 3 years of GH treatment or control period.

The TACQOL-Short Stature is a 47-item questionnaire for assessing HS and HRQOL of children with short stature. This questionnaire contains six scales: physical abilities, vitality, contact with peers, contact with adults, body image and future prospects. Table 1 shows a examples of a question of each scale. In case of a normal stature it is possible to give the response: not applicable or never. All scales had a Cronbach alpha above 0.70 except for the future prospects scale that had an alpha of 0.62. Since the TACQOL-Short Stature was not yet available at start of the study, the parents filled in this questionnaire after 3 years of GH treatment or control period.

Table 1. Example of HS scale and the number of items per scale.

Scales	NI	Example of an item
Physical abilities	7	Were the chairs and tables at school too high?
Vitality	8	Did your child get tired quickly
Contact with peers	8	Did other children lift up your child?
Contact with adults	9	Did someone mistreat your child because of his/her short stature?
Body image	8	Was your child sometimes concerned about his/her short stature
Future prospects	6	Did your child ever think about the fact that he/she will have a shorter stature compared to others in the future?

Each item was followed by an additional question "During this my child felt....." (HRQOL), NI=Number of Items.

Anthropometric measurements

Standing height (H) was measured 3-monthly by two trained investigators (NA and later on VB) using a Harpenden stadiometer. The mean of 4 measurements was used for analysis. Height was expressed as standard deviation score (SDS) for sex and chronological age (HSDSCA) using Dutch references.[19] Target height was calculated using Dutch reference data according to the formula: $1/2 * (H_{father} + H_{mother} + 13) + 4.5$ for boys and $1/2 * (H_{father} + H_{mother} - 13) + 4.5$ for girls, where the addition of 4.5 cm represents the secular trend. TH was expressed as SDS using Dutch references.[19] Pubertal stages were assessed according to Tanner,[20] using an orchidometer in boys.

Statistical analyses

Scale scores were obtained by summing the item scores within scales, and transforming crude scale scores to percentages on a linear 0 to 100 scale, with higher scores indicating better HS and HRQOL. Data were expressed as the mean (SD) at all points of measurements. The differences in clinical characteristics between groups were tested with the independent t-test. The scale score differences between groups at each time were tested by Mann-Whitney test. Differences between HS and HRQOL were tested with the Wilcoxon test. The reliability of the internal consistency of each scale in both questionnaires was evaluated by calculating Cronbach's alpha's.[22] In general a Cronbach alpha range from 0.65 and 0.84 is regarded as satisfactory for comparing different groups.[23,24] The Spearman rank correlation test was used to test the correlations between height SDS and the different scales of the generic TACQOL and TACQOL-Short Stature. A p-value < 0.05 was considered significant. All analyses were performed using SPSS version 10.0.

Results

GH trial

Table 2 shows the clinical characteristics at start and after 3 years for the GH group and control group. Both groups had similar initial characteristics. At start of the study the mean (SD) height SDS of the GH group and control group was −3.0 (0.7) and −3.0 (0.5), respectively, being not significantly different between groups. After 3 years, however, the mean (SD) height SDS was −1.3 (0.7) and −2.7 (0.8) respectively, being significant higher in the GH-treated children ($p < 0.001$).

After 3 years, parents of 8 children did not fill in the questionnaires for the following reasons: 1 child was satisfied with her height and was not motivated to continue GH treatment and the parents of 7 children forgot to fill in the questionnaire. Five children were excluded from the analysis because they were less than 3 years in the study at the moment of evaluation.

Table 2. Clinical characteristics.

	GH group (n = 58)	Control group (n = 27)
Male/Female	25/33	12/15
Gestational age (wks)	36.8 (3.6)	36.7 (3.3)
Birth length SDS	-3.0 (1.3)	-3.3 (1.3)
Birth weight SDS	-2.2 (1.2)	-2.7 (1.0)
Age at start (yr)	6.6 (0.9)	6.6 (0.9)
Height SDS - At start	-3.0 (0.7)	-3.0 (0.5)
- After 3 years	-1.3 (0.7)	-2.7 (0.8)*
Target Height	-0.5 (0.9)	-0.5 (0.8)

Expressed as mean (SD), * $p < 0.001$

Generic HS and HRQOL

Table 3 shows the HS and HRQOL scores obtained by the generic TACQOL for the GH group and control group at start and after 3 years of the study. There were no significant differences between the GH group and the control group at start of the study. After 3 years only the HS and HRQOL score of physical functioning was significantly higher in the GH group compared to the control group. The GH group and control group had significantly higher HRQOL scores than HS scores at start and after 3 years.

Short stature specific HS and HRQOL

Table 4 shows the HS and HRQOL scores of the TACQOL-Short Stature after 3 years for the GH and control group. For all scales the HS scores of the GH group were significantly higher than the HS scores of the control group. Furthermore, in all scales the GH group had a significantly higher HRQOL score compared to the control group. In both groups the HRQOL scores were significantly higher than the HS scores.

Table 3. Generic HS and HRQOL in SGA children at start and after 3 years.

	At start				After 3 years			
	GH group (n = 58)		Control group (n = 26)		GH group (n = 49)		Control group (n =23)	
	HS	HRQOL	HS	HRQOL	HS	HRQOL	HS	HRQOL
Physical functioning	81.3 (14.5)	85.8 (12.2)	77.6 (15.3)	81.6 (14.2)	88.0 (10.9)	89.6 (10.8)	77.9 (19.0)*	80.7 (16.3)*
Motor functioning	90.1 (15.8)	93.7 (10.6)	91.4 (12.7)	94.4 (8.4)	91.6 (14.2)	93.6 (12.8)	94.2 (6.3)	95.9 (5.1)
Autonomy	88.2 (15.7)	92.8 (12.3)	90.3 (12.8)	93.6 (10.4)	94.0 (13.5)	95.7 (11.2)	96.9 (6.3)	98.0 (3.5)
Cognitive functioning	79.1 (21.2)	88.1 (13.7)	81.4 (28.7)	89.9 (14.8)	74.2 (23.0)	82.6 (16.2)	73.3 (26.6)	82.5 (17.0)
Social functioning	89.2 (9.8)	93.0 (6.7)	86.2 (15.8)	91.1 (9.5)	87.6 (12.3)	91 (10.8)	83.2 (12.9)	87.1 (11.3)
Positive emotions		92.7 (10.4)		84.2 (18.5)		89.8 (14.3)		80.0 (21.8)
Negative emotions		67.2 (13.9)		63.0 (18.3)		67.7 (17.0)		68.3 (18.9)

Data expressed as mean (SD) percentage of maximum scores (100%); Higher scores represent better HS and HRQOL, * p = 0.03 GH group *vs* control group.

Table 4. Short stature specific HS and HRQOL in SGA children after 3 years.

	After 3 years			
	GH group (n = 49)		Control group (n = 23)	
	HS	HRQOL	HS	HRQOL
Physical abilities	90.0 (11.6)	92.4 (9.6)	76.2 (18.3)***	85.3(12.8)**
Vitality	87.3 (13.3)	91.4 (10.7)	79.4 (14.6)*	87.1 (9.7)*
Contact peers	82.5 (14.4)	84.2 (14.0)	64.7 (20.3)***	70.3 (17.3)***
Contact adults	82.8 (14.4)	88.9 (10.6)	65.5 (17.7)**	80.4 (13.5)*
Body image	75.7 (23.1)	88.1 (12.8)	52.7 (27.9)**	79.5 (11.3)**
Future prospects	69.6 (20.1)	90.0 (6.8)	56.5 (19.8)**	85.2 (8.0)**

Data expressed as mean (SD) percentage of maximum scores (100%); higher scores represent better HS and HRQOL, * p < 0.05 GH group *vs* control group, ** p < 0.01 GH group *vs* control group, *** p < 0.001 GH group *vs* control group.

Relationship between height SDS and HS or HRQOL

No correlations were found between height SDS and generic HRQOL scores at start and after 3 years. Table 5 shows the correlations between height SDS after 3 years and physical abilities, vitality, contact with peers, contact with adults, body image and future prospects of the TACQOL Short Stature. A highly significant correlation was found between height SDS and physical abilities, contact with adults, body image and future prospects. Figure 2 shows an example of correlation between height SDS and body image. In addition, it can be seen that there are individual differences. A small but significant correlation was found between height SDS and contact with peers. No correlation was found between height SDS and vitality.

None of the HRQOL scores of the TACQOL-Short were correlated with target height SDS, age of the child, and paternal and maternal height SDS (data not shown).

Table 5. Spearman correlation coefficient between height SDS after 3 years and the HRQOL scales of the TACQOL-short stature.

	r	P-value
Physical abilities	0.5	< 0.001
Vitality	0.2	ns
Contact peers	0.3	0.03
Contact adults	0.5	< 0.001
Body image	0.5	< 0.001
Future prospects	0.4	0.003

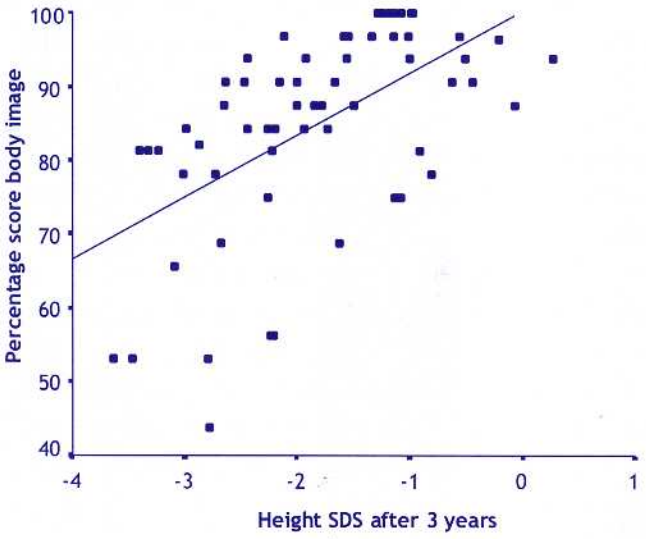


Figure 2. Correlation between height SDS after 3 years and body image.

Discussion

Three years of GH treatment resulted in a significantly taller height compared to the untreated children. At start the generic TACQOL showed no significant difference in HS and HRQOL between the GH group and control group. After three years the generic TACQOL showed that only the physical functioning was significantly improved in the GH group. In contrast, the TACQOL-Short Stature showed that SGA children treated with GH had a significantly better HS and HRQOL with respect to their physical abilities, vitality, contact with peers, contact with adults, body image and future prospects compared to untreated SGA children. Height SDS was positively correlated with HRQOL with regard to physical abilities, contact with peers, contact with adults, body image and future prospects.

The finding that three years of GH treatment results in a significantly taller height in children born SGA is comparable with previous studies in which short children born SGA were treated with GH.[3-5,25] Several studies have also shown that GH has a number of other benefits in short children born SGA. These include an increase in appetite and body mass index (BMI), as well as a reduction in blood pressure and a significant improvement in the serum lipid profile.[26-28] However, the effect of GH treatment of children born SGA on HS and HRQOL has not been studied before. Our study demonstrates that at baseline the generic TACQOL showed no significant difference in HS and HRQOL between the GH group and control group. Three years of GH treatment resulted only into a better HS and HRQOL score for physical functioning. This means for example, that, according to the parents, after 3 years the GH-treated children compared to the untreated children felt less fatigued but were both equally able to run, to climb the stairs, to dress themselves, to wash themselves, to talk, to write, to play, to talk with their parents and were equally angry or scared. In contrast, the specific questionnaire, the TACQOL-Short Stature showed that 3 years of GH treatment induced a significantly better HS and HRQOL regarding physical abilities, vitality, contact with peers, contact with adults, body image and future prospects, indicating that the GH-treated children had a better quality of life than untreated short SGA children. This means that, according to the parents, GH-treated children compared to untreated children did not experience that chairs and tables at school were too high. They had more energy and liked to play and eat better. They had less problems in social contacts with peers such as less teasing, less loneliness and less problems in contact with adults as they were more treated according to their age than short untreated SGA children. They were more satisfied with their height and more confident about their bodily appearance. According to the parents, GH-treated children had more positive thoughts about the future such as that they would attain the same height as their peers.

In this study the parents were asked about their children's health status and their children's emotional reactions to health status. Preferably, HRQOL and HS are self-administered, however, some of the younger children cannot be used as informants because children may lack the necessary language skills, as well as the cognitive abilities to interpret the questions, and the long term view on events. In addition, HRQOL and HS are usually assessed through paper and pencil questionnaires. Alternatively, a proxy respondent can be used and the parent is the most preferable proxy informant about the child's HRQOL.[16,29] As the choice of informant influences the QOL judgements[29-31] we used the same informant, the parent, for all children. Parents are the main decision-makers in respect of the rearing and medical treatment of their children. This makes their perception of HRQOL at least clinically relevant.

The discrepancy between the outcome of the two QOL questionnaires shows that SGA children do not have problems mentioned in a generic questionnaire but have more specific problems related to short stature. This is supported by a study of Haverkamp *et al* which demonstrated that for attaining growth disorder-specific information a special questionnaire is needed.[26] The questions in the TACQOL-Short Stature are more applicable for effects of short stature in contrast to the questions in the generic TACQOL. The last one has more reference to children with a chronic illness or handicap and in case of short stature they ask the "wrong" questions. For this reason significant changes of several aspects of quality of life during GH treatment of short SGA children will not be noticed by the generic questionnaire. Interestingly, the physical functioning scale of the generic TACQOL and the vitality scale of the TACQOL-Short Stature contain both questions that are focused on energy. In the generic TACQOL this scale was the only one which was significantly higher in the GH group compared to the control group. At start of the study no data was available of the TACQOL Short Stature. Theoretical, it might be that the HS and HRQOL scores were already different between the control and GH-treated group at start. However, this seems unlikely since the children were randomly divided to the groups.

In both the GH and control group, the HRQOL scores were higher than the HS scores in all scales. This indicates that health related problems do not necessarily result in a similar reduction of the HRQOL. In the paediatric field, most studies investigating the quality of life have been focused on the HS but not on the HRQOL of the patient. It is important to make a distinction between functioning of children and how they feel about their functioning. This is supported by a study of Verrips *et al* which showed that only half of the reported health status problems were associated with negative emotional reactions in children.[23] The severity of the emotional and social consequences of short stature may vary from one child to another.[32,33] The fact that some short children will not be referred to a hospital does not diminish the seriousness of the problems in those who are referred.[32,34] For this reason, in our study, we evaluated the effect of GH on the HRQOL in referred SGA children by comparing GH-treated to untreated children.

To our knowledge there are no published data on the effect of GH treatment on HRQOL in short SGA children. Two studies have shown that children born SGA with persistent short stature have a higher risk for subnormal intellectual and psychological performance.[6,7] HRQOL was, however, not evaluated in these studies. Theunissen *et al* have investigated the effect of GH on HRQOL in children with idiopathic short stature (ISS) and showed that GH had no effect on the psychosocial well being.[13] They investigated the effect of GH treatment on vitality with a specific questionnaire but vitality did not improve in the ISS treatment group whereas in our study vitality was better for the SGA treatment group. An explanation for this might be that the background of children with ISS is different from that of children born SGA.

The positive correlations between height SDS and HRQOL regarding physical abilities, contact with adults, body image and future prospects, obtained using the TACQOL Short Stature, show that height SDS is important for many aspects of the quality of life of SGA children. GH-treated children had a significantly higher HRQOL score for vitality compared to untreated short SGA children, whereas no correlation was found between height SDS and HRQOL for vitality. An explanation might be that GH treatment increases vitality due to an increase of muscle mass[27] rather than an increment of height SDS.

In conclusion, our study shows that short children born SGA have short stature specific problems. For this reason a specific questionnaire is more applicable for measuring quality of life in short children than a generic questionnaire which has more reference to children with a chronic illness. We demonstrated that GH treatment in children born SGA improves several aspects of quality of life in SGA children with short stature.

References

1. **Albertsson-Wikland K, Karlberg J** 1994 Natural growth in children born small for gestational age with and without catch-up growth. *Acta Paediatr Suppl* 399:64-70
2. **Hokken-Koelega ACS, De Ridder MA, Lemmen RJ, Den Hartog H, De Muinck Keizer-Schrama SM, Drop SL** 1995 Children born small for gestational age: Do they catch up? *Pediatr Res* 38:267-71.
3. **Van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A** 2003 Adult height after long-term, continuous growth hormone (GH) treatment in short children born small for gestational age: results of a randomized, double-blind, dose-response GH trial. *J Clin Endocrinol Metab* 88:3584-90.
4. **Sas T, de Waal W, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A** 1999 Growth hormone treatment in children with short stature born small for gestational age: 5-year results of a randomized, double-blind, dose-response trial. *J Clin Endocrinol Metab* 84:3064-70.
5. **de Zegher F, Albertsson-Wikland K, Wollmann HA, Chatelain P, Chaussain JL, Lofstrom A, Jonsson B, Rosenfeld RG** 2000 Growth hormone treatment of short children born small for gestational age: growth responses with continuous and discontinuous regimens over 6 years. *J Clin Endocrinol Metab* 85:2816-21.
6. **Lundgren EM, Cnattingius S, Jonsson B, Tuvemo T** 2003 Intellectual and psychological performance in males born small for gestational age. *Horm Res* 59:139-41.
7. **Pryor J, Silva PA, Brooke M** 1995 Growth, development and behaviour in adolescents born small-for-gestational-age. *J Paediatr Child Health* 31:403-7.
8. **Stabler B, Siegel PT, Clopper RR, Stoppani CE, Compton PG, Underwood LE** 1998 Behavior change after growth hormone treatment of children with short stature. *Journal of Pediatrica* 133:366-373
9. **van der Reijden-Lakeman I, Slijper FM, van Dongen-Melman JE, de Waal WJ, Verhulst FC** 1996 Self-concept before and after two years of growth hormone treatment in intrauterine growth-retarded children. *Horm Res* 46:88-94.
10. **Sandberg DE** 2000 Should short children who are not deficient in growth hormone be treated? *West J Med* 172:186-9.
11. **Kranzler JH, Rosenbloom AL, Proctor B, Diamond FB, Jr., Watson M** 2000 Is short stature a handicap? A comparison of the psychosocial functioning of referred and nonreferred children with normal short stature and children with normal stature. *J Pediatr* 136:96-102.
12. **Haverkamp F, Noeker M** 1998 'Short stature in children--a questionnaire for parents': a new instrument for growth disorder-specific psychosocial adaptation in children. *Qual Life Res* 7:447-55.
13. **Theunissen NC, Kamp GA, Koopman HM, Zwinderman KA, Vogels T, Wit JM** 2002 Quality of life and self-esteem in children treated for idiopathic short stature. *J Pediatr* 140:507-15.
14. **Vogels T, Verrips GHW, Koopman HM, Theunissen NC, Fekkes M, kamphuis RP** TACQOL Manuel Parent Form and Child Form. Leiden Center for child health and pediatrics LUMC-TNO.
15. **Perrin EC, Stein RE, Drotar D** 1991 Cautions in using the Child Behavior Checklist: observations based on research about children with a chronic illness. *J Pediatr Psychol* 16:411-21.
16. **Vogels T, Verrips GH, Verloove-Vanhorick SP, Fekkes M, Kamphuis RP, Koopman HM, Theunissen NC, Wit JM** 1998 Measuring health-related quality of life in children: the development of the TACQOL parent form. *Qual Life Res* 7:457-65.

17. **Arends NJ, Boonstra VH, Mulder PG, Odink RJ, Stokvis-Brantsma WH, Rongen-Westerlaken C, Mulder JC, Delemarre-Van de Waal H, Reeser HM, Jansen M, Waelkens JJ, Hokken-Koelega AC** 2003 GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of a randomized, controlled GH trial. *Clin Endocrinol* (Oxf) 59:779-87.
18. **Usher R, McLean F** 1969 Intrauterine growth of live-born Caucasian infants at sea level: Standards obtained from measurements in 7 dimensions of infants born between 25 and 44 weeks of gestation. *J Pediatr* 74:901-10.
19. **Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, Roede MJ, Verloove-Vanhorick SP, Wit JM** 2000 Continuing positive secular growth change in The Netherlands 1955-1997. *Pediatr Res* 47:316-23.
20. **Tanner JM, Whitehouse RH** 1976 Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child* 51:170-9.
21. **Vogels T, Theunissen NCM, Verrips GHW, Koopman HM, Verloove-Vanhorick SP, Kamphuis RP** 1996 Het meten van kwaliteit van leven bij kinderen met chronische aandoeningen. *Tijdschrift voor adolescenten zorg* 2:104-111
22. **Cronbach L** 1951 Coefficient Alpha and the internal structure of tests. *Psychometrika* 16:297-334
23. **Verrips EGH, Vogels TGC, Koopman HM, Theunissen NC, Kamphuis RP, Fekkes M, Wit JM, Verloove-Vanhorick SP** 1999 Measuring health-related quality of life in a child population. *European Journal of Public Health* 9:188-193
24. **Bland JM, Altman DG** 1997 Cronbach's alpha. *Bmj* 314:572.
25. **Carel JC, Chatelain P, Rochiccioli P, Chaussain JL** 2003 Improvement in adult height after growth hormone treatment in adolescents with short stature born small for gestational age: results of a randomized controlled study. *J Clin Endocrinol Metab* 88:1587-93.
26. **Boonstra V, Arends N, Stijnen T, Blum W, Akkerman O, Hokken-Koelega A** 2005 Food intake of children with short stature born small for gestational age (SGA) before and during a randomised GH-trial. Accepted for publication in *Hormone Research*
27. **Leger J, Garel C, Fjellestad-Paulsen A, Hassan M, Czernichow P** 1998 Human growth hormone treatment of short-stature children born small for gestational age: effect on muscle and adipose tissue mass during a 3-year treatment period and after 1 year's withdrawal. *J Clin Endocrinol Metab* 83:3512-6.
28. **van Pareren Y, Mulder P, Houdijk M, Jansen M, Reeser M, Hokken-Koelega A** 2003 Effect of discontinuation of growth hormone treatment on risk factors for cardiovascular disease in adolescents born small for gestational age. *J Clin Endocrinol Metab* 88:347-53.
29. **Theunissen NC, Vogels TG, Koopman HM, Verrips GH, Zwinderman KA, Verloove-Vanhorick SP, Wit JM** 1998 The proxy problem: child report versus parent report in health-related quality of life research. *Qual Life Res* 7:387-97.
30. **Achenbach TM, McConaughy SH, Howell CT** 1987 Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull* 101:213-32.
31. **Koopman HM, Theunissen NC, Vogels T, Zwinderman KA, Verloove-Vanhoick SP, Wit JM** 1999 Health related quality of life of children with a chronic illness: Parent versus child report. *Gedrag & Gezondheid* 27:118-125

32. **Stabler B, Siegel PT, Clopper RR, Stoppani CE, Compton PG, Underwood LE** 1999 Reply. *J Pediatr* 135:134.
33. **Sandberg DE, Brook AE, Campos SP** 1994 Short stature: a psychosocial burden requiring growth hormone therapy? *Pediatrics* 94:832-40.
34. **Busschbach JJ, Rikken B, Grobbee DE, De Charro FT, Wit JM** 1998 Quality of life in short adults. *Horm Res* 49:32-8.