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Quality of Life in Adolescents Born Small for Gestational Age: Does Growth Hormone Make a Difference?

Ellen M.N. Bannink[a] Yvonne K. van Pareren[a] Nicolet C.M. Theunissen[b]
Hein Raat[c] Paul G.M. Mulder[d] Anita C.S. Hokken-Koelega[a]

[a]Department of Pediatrics, Division of Endocrinology, Erasmus Medical Center/Sophia Children's Hospital Rotterdam, Rotterdam; [b]TNO Human Factors, Soesterberg, and Departments of [c]Public Health, and [d]Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands

Key Words
Growth hormone therapy · Small for gestational age · Short stature · Quality of life · Adolescents

Abstract
Background/Aims: To evaluate quality of life (QoL) in adolescents born SGA without spontaneous catch-up growth, treated with and without long-term growth hormone (GH) therapy. Additionally, to assess whether GH treatment has a positive effect on QoL, besides improving adult height and height SDS during childhood. ***Methods:*** Two groups of adolescents born SGA without spontaneous catch-up growth participated in the QoL evaluation; a GH-treated group (n = 44, mean GH duration: 8.8 (1.7) years) and an untreated group (n = 28), both mean age 15.8 (2.1) years. QoL was measured by self-reports of the TACQOL-S, a disorder-specific questionnaire, and the CHQ, a generic questionnaire. ***Results:*** The GH group scored significantly better health status and health-related QoL on several scales of the TACQOL-S. On all TACQOL-S scales the GH group scored better QoL than the untreated group, with effect sizes of moderate to large, not all differences reaching statistical significance. The generic CHQ did not reveal significant differences in QoL between the GH group and the untreated group. ***Conclusions:*** Firstly, adolescents born SGA, with a GH-induced improved height, had in many aspects a better QoL than untreated adolescents born SGA, according to the disorder-specific questionnaire. Secondly, we advise to use, in addition to a generic questionnaire, a disorder-specific questionnaire for measuring QoL in children treated for short stature, as the generic CHQ did not reveal such differences.

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Introduction

Quality of life (QoL) is increasingly recognized as an important measure of the impact of a special disorder, disease or therapeutic outcome. Over the past decades health status (HS) and QoL have been studied in a variety of diseases and disorders, including short stature [1–3]. Short stature during childhood and adolescence, resulting in a short adult height occurs regularly after being born small for gestational age (SGA). It is widely held that short children can suffer from physical, social and psychologi-

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Ellen M.N. Bannink, MD
Department of Pediatrics, Division of Endocrinology
Erasmus MC – Sophia Children's Hospital, Postbus 2060
NL–3000 CB Rotterdam (The Netherlands)
Tel. +31 10 463 6111, Fax +31 10 463 6943, E-Mail e.bannink@tiscali.nl

cal problems [4]. The physical limitations of short stature and their often younger appearance may result in being treated differently by peers, and they may receive unintentional discrimination from adults. Social interaction, in particular during sports and games with peers, subjects them to taunts and bullying [5]. Adult short stature is often perceived to be a disadvantage. It can be a major physical disability in terms of not being able to drive a normal car, reach for objects and perform ordinary daily tasks that a person of average height takes for granted. It can also cause difficulties, or even discrimination, in getting the preferred job or career. There are, however, some inconsistencies in the literature. It is reported that the psychosocial difficulties, associated with being short, seems to be less severe than assumed [1, 6]. However, hard data on QoL in short stature SGA children or adults are lacking.

About 10% of the SGA children will not catch-up to a height above –2 SDS and which will reach into an adult height below –2 SDS [7]. GH-treatment has been proven to be effective for obtaining a normal height during childhood, adolescence and adult height, after being born SGA [8–10]. With GH treatment during childhood, short SGA children will reach a normal height within 2 years after start of GH [9], and will acquire an adult height which is in 98% positioned within the target height range, and in 85% within the normal range of the population when treated with long-term continuous GH [10].

Some QoL questionnaires, such as the 'Health Utility Index', focus on the quantity and severity of limitations in executing ordinary daily tasks and psychosocial functioning due to a health problem, handicap, or disorder, the so-called 'health status'. Persons with short stature might not just experience physical limitations, but the accompanying social problems of short stature can overrule the physical limitations. For example, the problem is not that the adolescent can't go to a pub or club, but the problem is that he/she will not be asked by friends or is not permitted to enter due to younger appearance. Therefore, it is important to include the emotional impact of the HS on a person's life. The HS in combination with the emotional impact is called the health-related QoL (HRQoL). Its rating how the adolescent or child feels about their functioning, rather than functioning alone. Recently, a Dutch questionnaire for short stature was constructed as a disorder specific module of the generic TNO-AZL Children's Quality of Life (TACQOL), called the TACQOL-S. This questionnaire explicitly offers respondents the possibility of differentiating between their ability to function and their associated feelings. The quantity of problems is known as the HS. The HRQoL, qualifies the emotional impact of the problem. The study aims were to compare QoL scores between 2 groups of adolescents born SGA, a GH-treated group and an untreated group, who all had attained adult or near adult height. This was measured with a disorder-specific health-related QoL, the TACQOL-S, specially developed for children with short stature. Additionally, a generic questionnaire, the Child Health Questionnaire (CHQ) was applied. The adolescents completed both, the TACQOL-S and the CHQ.

Patients and Methods

GH-Treated SGA Group (GH Group)

All children with a height < –2 SDS were referred to a pediatric endocrinologist, according to national guidelines for short stature. Seventy-nine short children born SGA were enrolled in a multicenter, double-blind, randomized dose-response GH trial, which started in 1991. The inclusion criteria for participation in the GH-treated SGA group of the QoL evaluation were: completion of the GH trial until final height or satisfied height, age ≤ 18 years, be able to fill in the questionnaire, no growth interfering treatment other than GH therapy. Seventeen adolescents did not meet the inclusion criteria due to: >18 years old (n = 11), treatment for precocious puberty (n = 1), dropped out of the GH-trial within 4 years after start of GH therapy due to GH insensitivity (n = 1), due to moving abroad (n = 2), due to lack of motivation (n = 2). This leaves 62 of the 79 adolescents eligible for participation in the QoL evaluation. Forty-four adolescents out of the 62 (71%) agreed to participate, mean (SD) age 15.7 (2.1) years. No differences in clinical characteristics were found between the adolescents who participated and the adolescents who did not participate.

The GH trial evaluated the effect of GH on long-term growth and ultimately on adult height, as well as psychosocial development, cognition and QoL. Inclusion criteria for the dose-response trial were: birth length SDS below –2, chronological age (CA) between 3 and 11 years in boys and 3 and 9 years in girls, height SD score for CA below –2, no spontaneous catch-up growth, prepubertal stage, uncomplicated neonatal period without severe asphyxia. Biosynthetic GH (r-hGH Norditropin®, Novo Nordisk A/S, Denmark) was given subcutaneous once daily. GH was given double blindly in a dosage of 1 (group A) or 2 (group B) mg GH/m^2 body surface/day (~33 or 67 μg/kg/day). In 2001, at time of QoL evaluation, none of the participants knew their GH dosage. GH treatment was discontinued after reaching adult height (height velocity <0.5 cm in 6 months) or on patient's decision after reaching satisfactory height (near adult height). Twenty-three of the 44 participants (52%) had reached adult height or near adult height and had discontinued GH treatment.

For analysis of the QoL questionnaires we combined the 2 randomized GH dosage groups (GH group), as they were samples from the same underlying population at baseline because of the randomization. As a result there were no significant differences in height SDS at time of QoL evaluation, nor was there a difference in height SDS gain between the two dosage groups.

Untreated SGA Group (Untreated Group)

In 1990, 107 children, born in three academic hospitals in the Netherlands during the same time period as the GH group (1980 until 1989) with a birth length below –2 SDS, were included in a cohort study to evaluate natural growth in SGA children with short stature in parallel to the GH trial [7]. The inclusion criteria for participation in the untreated SGA group of the QoL evaluation were: age ≤18 years, be able to fill in the questionnaire, no growth interfering treatment. Fifty adolescents did not meet the inclusion criteria due to: >18 years old (n = 28), GH therapy (n = 19), treatment for precocious puberty (n = 1), not being able to fill in the questionnaire due to moving abroad (n = 2). This leaves 57 of the 107 adolescents eligible for participation in the QoL evaluation. Twenty-eight of the 57 (49%) adolescents agreed to participate (mean age (SD) 15.8 (2.1)).

Design and Clinical Evaluation Dose-Response GH Trial

Children of the study group were assigned to either group A, with a GH dose of 1 mg/m^2/day (33 μg/m^2/day), or group B with a GH dose of 2 mg/m^2/day (67 μg/m^2/day) [9–11]. A daily subcutaneous injection of biosynthetic GH (r-hGH Norditropin, Novo Nordisk A/S, Copenhagen, Denmark) was given at bedtime. Three-monthly, the total GH dose was adjusted to the calculated body surface.

Every 3 months height was measured using a Harpenden stadiometer [12]. Four measurements per visit were taken and the mean was used for analysis. Target height (TH) was calculated with Dutch reference data with addition of 3 cm for secular trend: ½ × (height$_{father}$ + Height$_{mother}$ + 12) + 3 for boys and ½ × (height$_{father}$ + Height$_{mother}$ – 12) + 3 [13]. Height and TH were expressed as an SD score for chronological age (CA) and gender [13].

Measurements

All QoL data were collected in the year 2001. For measuring the QoL, the child form (CF87) of the Child Health Questionnaire (CHQ) was used for adolescents ≤18 years. Participants ≤15 years had in addition to the CHQ, the TNO-AZL Children's Quality of Life Short stature module (TACQOL-S), a questionnaire developed by The Netherlands Organisation for Applied Scientific Research (TNO) in conjunction with the Academic Hospital in Leiden (AZL).

TACQOL-S: The TACQOL-S is a disorder specific questionnaire and was specially designed in the Netherlands to measure the impact of short stature on QoL for children aged 5–15 years. The questionnaire was constructed as a disorder-specific module of the generic TNO-AZL Children's Quality of Life questionnaire (TACQOL) [14–16]. The items were based on years of clinical and research experience and interviews with children with short stature. As such, it explicitly offers respondents the possibility of differentiating between their functioning; the quantity of problems, called the HS and their associated feelings with it, the emotional impact, called the HRQoL. We used the TACQOL-S child form (CF), a self-report questionnaire consisting of 37 items (all referring to the last few weeks) divided in 5 scales: physical abilities (e.g. Did you experience the tables at school as being too high?), vitality (e.g. Have you been getting tired quickly?), contact with peers (e.g. Have other children been bullying you?), contact with adults (e.g. Were adults surprised when they heard your age?), body image (e.g. Would you like to look different?). A higher test score indicates a better QoL on that specific scale. The TACQOL-S was performed in a subgroup of the total group, in participants ≤15 years of age (n = 39). Internal consistency of the scales of the TACQOL-S, the Cronbach's alpha [17] was studied in a larger group of short children (n = 63). The Cronbach's alphas were all above 0.70, except for vitality HS (0.57). In general, a Cronbach's alpha ranging from 0.70 to 0.84 is regarded as satisfactory for comparing different groups [18]. If a scale has a Cronbach's alpha <0.70 and significance occurs, conclusions should be drawn carefully.

Child Health Questionnaire (CHQ): The CHQ is a generic questionnaire developed in the USA [19, 20] and is widely used in the US, Australia, Slavic countries, Germany, Denmark, France, Belgian, China and the Netherlands. The child form (CF87) of the CHQ is a self-report form and is designed to measure generic HS covering physical and psychosocial domains in children and adolescents ≤18 years of age. A Dutch version [21], consisting of 87 items divided into 12 scales, was used. A higher test score indicates a better quality for that specific scale, with a maximum score of 100. The reference population consisted of 444 children of four representative schools in Rotterdam, the Netherlands, as prescribed previously by Raat et al. [21].

Socioeconomic Status

Data on occupational level were provided by the parents. Parental occupational level (SES) ranged from 1 (lower occupation) to 3 (higher occupation). When both parents were employed the highest of the two SES levels was used. For unemployment the lowest SES was used [22].

Statistical Analysis

All data are expressed as mean (SD) unless otherwise specified. Independent t tests were used to test for differences between participants and non-participants to the QoL study, analyzed per GH dosage group. Only in participants to the QoL study were independent t tests used to test for differences in clinical data between the two dosage groups (A and B) and compared to untreated group, and independent t tests were used to test for differences between the group ≤18 years and ≤15 years. Mann-Whitney U tests were used to test for differences in TACQOL-S and CHQ outcome between GH group, untreated group and references.

The magnitude and meaning of the differences in QoL outcome between groups can be calculated as Cohen's effect size *(d)* [23, 24]. The effect size *d* is calculated as follows: [mean(a) – mean(b)/largest standard deviation score (SDS)]; this means that differences between groups are expressed in units of the largest within-group standard deviation. According to Cohen, effect sizes between 0.2 and 0.5 indicate a small effect, an effect size between 0.5 and 0.8 indicates a moderate effect, whereas effect sizes of 0.8 or larger indicate a large effect [23, 24].

Multiple linear regression analyses were performed to assess possible factors influencing the QoL outcome. Each questionnaire scale was tested separately. For this purpose, the variables sex (M = 1, F = 2), age at time of QoL evaluation (in years), and height SDS or height SDS corrected for target height SDS (Ht SDS–TH SDS) at time of start GH treatment and at time of QoL evaluation, with and without SES (range 1–3), were tested. The percentages of variance explained by the model (R^2 in %) are given. $p < 0.05$ was considered significant. All calculations were performed with SPSS 10.1.

Table 1. Mean (SDS) clinical data of all adolescents who participated in the evaluation of the quality of life evaluation, at baseline (1991) and at time of evaluation (2001)

	Whole group, CHQ participants all ≤18 years		Subgroup, TACQOL-S participants all ≤15 years	
	GH-treated SGA (n = 44)	untreated SGA (n = 28)	GH-treated SGA (n = 24)	untreated SGA (n = 15)
Male:female (% male)	28:16 (64)	12:16 (43)	14:10 (58)	6:9 (40)
Gestational age	36.8 (4.0)[b]	34.3 (3.6)	36.4 (4.0)[a]	33.5 (3.0)
Birth length SDS	–3.4 (1.3)	–3.8 (1.3)	–3.4 (1.5)	–3.9 (1.5)
Birth weight SDS	–2.5 (1.1)[a]	–3.0 (0.8)	–2.5 (1.2)[a]	–3.1 (0.8)
Target height SDS	–0.7 (0.9)	–0.5 (1.0)	–0.7 (0.8)	–0.5 (0.9)
Age				
At time of start study	6.6 (2.0)[c]	5.9 (2.3)[c]	5.0 (1.1)	4.4 (1.4)
At QoL evaluation	15.8 (2.1)[c]	15.8 (2.1)[c]	14.2 (1.2)	14.2 (1.1)
Height SDS				
At time of start study	–3.1 (0.7)[b]	–2.3 (0.7)	–3.1 (0.7)[a]	–2.5 (0.7)
At QoL evaluation	–0.6 (1.2)[b]	–1.8 (0.8)	–0.1 (1.1)[b]	–1.7 (0.8)
Height SDS gain	2.4 (1.1)[b]	0.5 (0.6)	2.9 (1.1)[b]	0.8 (0.5)
Corrected height SDS (Hsds-THsds)				
At time of start study	–2.4 (0.8)[a]	–1.8 (0.9)	–2.3 (0.7)	–2.0 (0.8)
At QoL evaluation	–0.1 (1.2)[b]	–1.3 (0.7)	0.6 (1.1)[b]	–1.3 (0.7)
Duration of GHRx at QoL evaluation	8.8 (1.7)[b]	–	10.1 (1.2)[b]	–

Data are expressed as the mean (±SD).

Independent t test: [a] $p < 0.05$; [b] $p < 0.01$; GH-treated compared to untreated group; [c] $p < 0.01$, CHQ participants compared to TACQOL-S participants.

Ethical Considerations

The Medical Ethics Committees approved the evaluation of QoL. Due to ethical considerations, the Medical Ethics Committees did not allow a randomized control group for the long-term dose response GH trial. Written informed consent was obtained from the parents or custodians and from each adolescent.

Results

Clinical Data

Table 1 shows the clinical characteristics of the participating adolescents at baseline and at time of the QoL evaluation. The mean (SD) height SDS gain was significantly higher in the GH-treated group (2.4 (1.1)) versus the untreated group (0.5 (0.6)). Mean (SD) height SDS was in 2001 significantly higher in the GH-treated group (–0.6 (1.2)), than in the untreated group (–1.8 (0.8)). This difference was larger in the subpopulation ≤15 years, who participated in the TACQOL-S. The GH group showed significantly better growth than the untreated group, resulting into better height SDS, height SDS gain and target height corrected height SDS ($p < 0.01$).

There were no significant differences in clinical characteristics between the complete group ≤18 years (CHQ group) and the subgroup ≤15 years (TACQOL-S group), apart from age. The TACQOL-S group was 1.6 year younger than the CHQ group, due to a younger age at start of the GH dose-response trial. Regarding parental occupational levels, the GH group was not significantly different compared to the untreated group.

TACQOL-Short Stature

Table 2 shows HS and HRQoL scores of the self-report TACQOL-S, measured in 2001. For 'physical abilities' and 'contact with adults', both HRQoL and HS were significantly higher in the GH group compared to the untreated group. HS of 'body image' was significantly higher in the GH group compared to the untreated group, whereas HRQoL scored also higher but this difference was not statistically significant.

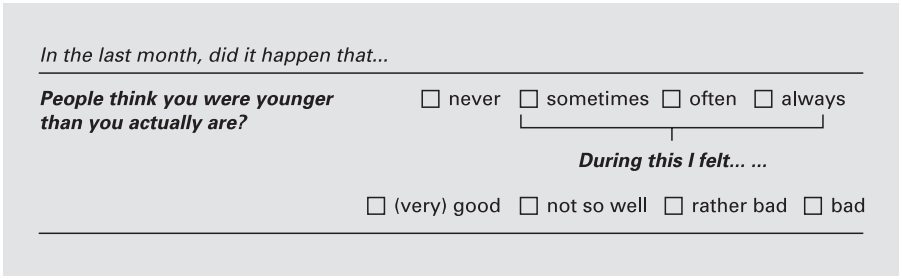

Fig. 1. Example of the format of the TAC-QOL-S.

Table 2. Results of the TACQOL-S

	GH-treated SGA group (n = 24)	Untreated SGA group (n = 15)	Effect size[1] *(d)*	p value
Physical abilities				
HS	90.8 (9.8)[b]	74.3 (19.8)	0.83	0.004
HRQoL	93.6 (7.4)[b]	78.6 (16.6)	0.90	0.002
Vitality[2]				
HS	75.0 (18.4)	65.8 (21.9)	0.42	0.234
HRQoL	79.2 (16.5)	69.6 (23.8)	0.40	0.283
Contact with peers				
HS	81.0 (18.5)	73.8 (21.9)	0.33	0.296
HRQoL	85.7 (16.4)	76.3 (19.9)	0.47	0.110
Contact with adults				
HS	85.2 (10.6)[a]	70.9 (18.8)	0.76	0.017
HRQoL	92.9 (4.4)[b]	80.0 (15.1)	0.85	0.002
Body image				
HS	88.4 (8.0)[a]	74.1 (24.1)	0.59	0.038
HRQoL	91.2 (6.9)	81.8 (20.1)	0.47	0.191

Data are expressed as the mean (± SD). There were no differences between the 2 dosage groups. [a] $p < 0.05$; [b] $p < 0.01$, compared to the untreated group (0 mg/m^2/day). Higher scores = Better health-related QoL (HRQoL)/health status (HS).

[1] Effect size = Positive effect size indicate better QoL in the GH-treated SGA group: $0.2 \leq d < 0.5$ = small effect; $0.5 \leq d < 0.8$ = moderate effect; $d \geq 0.8$ = large effect. Negative effect size (not present) indicates better QoL in the untreated SGA group.

[2] Cronbach's alpha was 0.57.

Figure 1 shows the effect sizes of the differences in HS and HRQoL between the GH group and the untreated group, as reported by the children. A positive effect size indicates better QoL scores in the GH group, whereas a negative effect size, which did not occur, indicates better QoL scores in the untreated group. The effect size of the difference between the GH-treated group and the untreated group regarding 'physical abilities' was 0.83 (p = 0.004) for HS and 0.9 (p = 0.002) for HRQoL, which indicates a large effect. The effect size of the difference between the GH-treated group and the untreated group regarding 'contact with adults' was 0.76 (p = 0.02) for HS and 0.85 (p = 0.002) for HRQoL. This indicates a large effect in quantity of problems (HS), and an even larger effect on the emotional impact (HRQoL). The effect size of HS on 'body image' was 0.59 (p = 0.04) and the effect size of HRQoL of 'body image' was 0.47 (p = 0.2).

CHQ Data

As shown in table 3, the children of the untreated group scored significantly lower on 'family cohesion' than their normal peers, 64.6 (26.9) vs. 75.7 (23.2), respec-

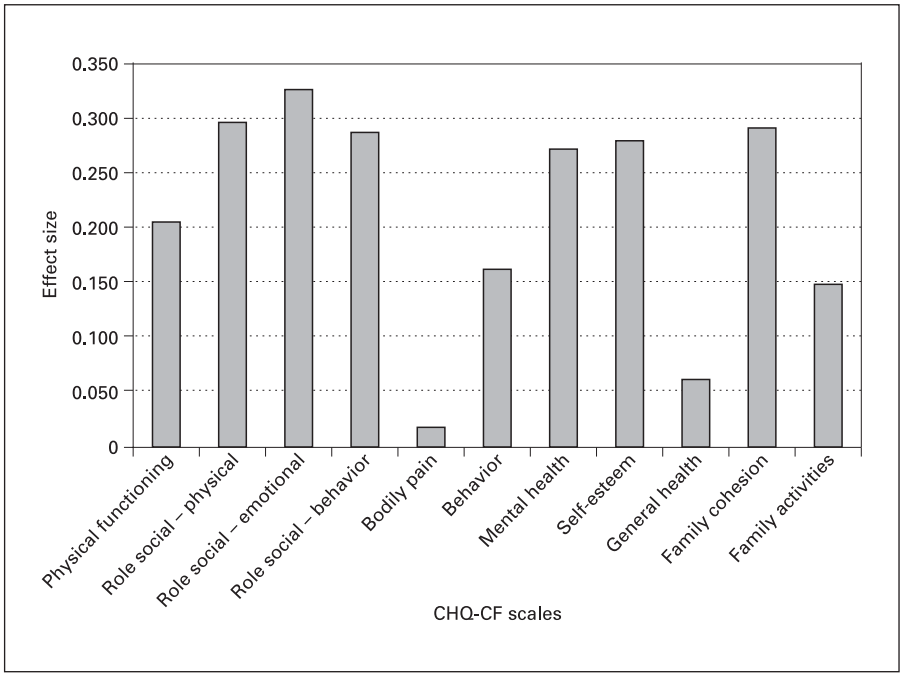

Fig. 2. Effect sizes of the differences on the QoL scales between the GH-treated SGA group and the untreated SGA group as measured with the CHQ and reported by the children. Higher score indicates better QoL in the GH-group. Effect size *(d)*: $0.2 \leq d < 0.5$ = small effect; $0.5 \leq d < 0.8$ = moderate effect; $d \geq 0.8$ = large effect.

Table 3. Results of the CHQ (CF87)

	GH-treated SGA (1 or 2 mg/m^2/day) (n = 44)	Untreated SGA (0 mg/m^2/day) (n = 28)	Reference population[1] (n = 441)
Physical functioning	95.5 (6.4)	93.0 (12.2)	96.8 (5.4)
Role social			
Physical	96.0 (9.6)	90.5 (18.6)	96.5 (11.6)
Emotion	88.4 (16.2)[a]	82.7 (17.5)[b]	92.3 (16.8)
Behavior	93.4 (14.8)	88.9 (15.7)	91.4 (13.7)
Bodily pain	75.0 (20.9)	74.6 (23.0)	78.2 (19.5)
Behavior	84.8 (9.4)	82.8 (12.4)	83.6 (10.2)
Mental health	79.2 (11.3)	75.1 (15.1)	78.2 (13.0)
Self-esteem	77.6 (11.3)	74.0 (12.9)	75.4 (12.5)
General health	73.2 (11.9)	72.2 (16.4)	74.6 (15.9)
Family			
Activities	80.0 (15.0)	77.1 (19.7)	ND
Cohesion	72.4 (20.4)	64.6 (26.9)[1]	75.7(23.1)

Data are expressed as mean (SD). No significant differences between the GH-treated and the untreated groups: [a] $p < 0.05$, [b] $p < 0.01$, compared to reference values. ND = Not done, this scale was not fielded in this study.

[1] 'Reliability and validity of the child health questionnaire-child form (CHQ-CF87) in a Dutch adolescent population', by Raat et al. [21].

tively, whereas those of the GH group were not significantly different from their normal peers. The children of both SGA groups (GH-treated and untreated) scored significantly lower than their normal peers on 'role social-emotional', 88.4 (16.2) and 82.7 (17.5), respectively, vs. 92.3 (16.8). There were no significant differences between the GH group and the untreated group.

As shown in figure 2, the GH group showed on all the scales of the CHQ higher scores than the untreated group; however, these differences between the GH-treated and untreated groups did not reach statistical significance.

Factors Influencing QoL Outcome

TACQOL-S. Using multiple regression, the HRQoL score in the GH group for the scale 'contact with adults' increased with 3.0 units per 1 SDS of the current height, adjusted for sex, age and height SDS at start GH treatment (R^2 = 43.5%). This means the taller they were, the more they felt age-appropriately treated by adults. In the same GH group, the HRQoL score of 'body image' increased with 5.3 units per 1 height SDS corrected for target height (Ht SDS–TH SDS), after adjustment for sex, age and height SDS corrected for TH SDS at start (R^2 29.4%). This indicates the taller they were compared to their parents, the more they felt satisfied and happy with their own body. Lastly, in the GH group the HS score of 'vitality' decreased with 14.7 units per 1 height SDS cor-

rected for TH SDS at start of the GH therapy, adjusted for sex, age and current height SDS corrected for TH SDS (R^2 44.3%). This indicates that the shorter they were at start of the GH therapy compared to their parents, the more vital they currently felt. In the untreated adolescents, height SDS or height SDS corrected for TH SDS were not associated with QoL, measured with the TACQOL-S. Socio-economic status was not of significant influence.

CHQ. In the adolescent reports of the CHQ, the QoL score on the scale 'role social behavior' increased with 6.8 units and 12.6 units per 1 SDS of the current height in the GH group and untreated group, respectively (R^2 18.1% and R^2 29.8%). This means the taller the adolescents were, the less problems they experienced in daily life with their behavior (like doing schoolwork or sports with friends). In addition, the QoL score of 'family cohesion' in the GH group increased with 11 units per 1 height SDS at the start, adjusted for sex, age and current height SDS (R^2 14.5%). None of the CHQ scales were affected by height SDS corrected for TH SDS.

Discussion

This study delineates various aspects of QoL in short children born SGA after long-term GH treatment. Although generic instruments are widely used, they may include irrelevant aspects or miss certain aspects of importance for specific groups of patients, here with short stature, and therefore being insensitive when measuring the effect of short stature on QoL. We therefore included a QoL questionnaire specially developed for children and adolescents with short stature, the TACQOL-S.

Before reviewing these results one has to consider the following issues to appreciate the outcome. As we do not have baseline data, QoL was not evaluated longitudinally. The GH trial started in 1991, when QoL was not as much recognized as an important measure outcome as it is today. Moreover, the QoL questionnaires were developed in the early and mid-1990s, after the start of this GH trial. Due to the lack of information about QoL before GH treatment, possible influencing factors on QoL outcome were analyzed. Second, subjects were not randomized, but from 2 separate studies, with similar inclusion criteria and age. It appeared that the untreated group had a higher height SDS than the GH group at the start of the GH study. This might have positively influenced their QoL during childhood, as their height was always nearer to the normal range. Despite a shorter height at start of study, the GH-treated group reported a better QoL, after 10 years of GH treatment, on several domains of the disorder-specific questionnaire compared to the untreated group. Third, there is a limited experience with the disorder specific questionnaire the TACQOL-S. However, the TACQOL-S is constructed from the generic TACQOL, which is broadly validated and used. The items were based on years of clinical and research experience and interviews with children with short stature. Fourth, a placebo effect could be argued. It is well known that a placebo effect on growth in GH-controlled trials only lasts for 3 months after start of GH treatment [25, 26]. As our study analyzed the long-term effect, after nearly 9 years of GH treatment, we do not expect any placebo effect. Finally, in the GH-treated SGA group, 62 of 79 enrolled in the early 1990s, were eligible for the health-related QoL evaluation, of which 44 (71%) completed the questionnaires. While clinical characteristics of the 44 responders did not differ significantly from nonresponders, we are unaware of other potential sources of selection bias. In the untreated SGA group 57 of 107 enrolled in the early 1990s, were eligible for health-related QoL evaluation, of which 28 (49%) completed the questionnaires. GH therapy that was applied outside the context of clinical studies (n = 19) was a source of not being eligible for QoL evaluation; although to our knowledge (psychological) problems did not correlate to GH therapy in that subgroup, drop-out as well as nonresponders may have introduced bias of which we are unaware.

The specific self-report questionnaire, the TACQOL-S, showed that the GH-treated SGA adolescents had a significantly better HS and HRQoL regarding 'physical abilities' and 'contact with adults' and 'body image' HS compared to untreated SGA adolescents. The better QoL in 'physical abilities' means that the adolescents in the GH group had experienced an improvement in sports, in reaching things that are high up, were able to sit comfortable at tables and in chairs at school without experiencing them too high. The 'contact with adults' was better in the GH group than in the untreated group. The GH group reported a positive influence of height on the 'contact with adults', indicating that the taller they were, the better they felt age-appropriately treated by adults. The effect size of the quantity of problems in contact with adults was moderate, but the emotional impact was large. This means that the adolescents in the GH group were more age-appropriately treated than the adolescents in the untreated group, and the adolescents experienced this respect for age by the adults as very positive. The problems the SGA adolescents experienced with 'body image' was

positively influenced by their height corrected for target height, meaning the closer the height was to that of their parents, the more happy they were with their bodies. The influences of height were not found in the untreated group. This might be related to the smaller variation in height SDS and smaller group size of the untreated group.

Our study shows effect sizes which were moderately to markedly better in the GH group compared to the untreated group on all scales of the TACQOL-S, both with respect to HS as well as the HRQoL, although some did not reach a significant difference. This might be due to the limited size of our study population. In this respect it is interesting that Kazis et al. [24] reported that not only statistical outcome, but also the effect size contribute to an understanding of the differences between groups. The authors demonstrated that statistically significant differences might not be synonymous with what is clinically important.

The generic self-report questionnaire, the CHQ, showed a near-normal QoL in SGA adolescents after long-term GH treatment. The GH group was extremely short at the start with a height SDS far below the normal range and had normalized its height at the time of QoL evaluation. For the CHQ results, no significant differences were shown between the GH group and the untreated group. We have to realize, however, that the untreated group had never been as extremely short as the GH group, and always had a height SDS just below the normal range for many years and at time of QoL evaluation just within the normal range. In both groups, GH and untreated, height influenced their 'role social behavior' positively, meaning they experienced less social problems related to behavior when they were taller. These findings are in line with a recent paper by our group, revealing a significant decline in problem behavior in SGA children during GH treatment [27].

Several studies have previously shown that using a generic questionnaire for a special disorder or disease, one might miss relevant QoL issues [28–31]. Not only the most obvious daily life issues, like being able to walk up the stairs, closing the buttons on your shirt, are relevant for an optimal QoL, also less obvious daily life issues, like reaching up for kitchen cupboards, going shopping for clothes or hanging out with friends are important. These issues might seem less obvious to someone who has a chronic disease or handicap, but their contribution to a person's QoL can be of great merit. A generic questionnaire focuses mainly on daily life issues, which are limited in case of a chronic disease or handicap. The items of the TACQOL-S are more sensitive for effects of stature on QoL outcome. So, in addition to generic QoL measurements, height-specific QoL measurements should be applied in growth studies.

It has been suggested that psychological training in coping with the psychosocial problems related to short stature would be a less-invasive alternative for GH treatment. Regarding QoL, it would have been appropriate to test the difference in QoL outcome in a prospective randomized study model. Unfortunately, to date no structural psychological program has been evaluated to be effective and of practical use. Recently, it has been shown that GH-treated children had significantly reduced total problem behavior, externalizing behavior and a better self-perception after 10 years of GH treatment compared to pretreatment [27, 32]. Taller children had less problem behavior over time. These findings were parallel to their height improvement [27]. This indicates that GH treatment is capable of improving several aspects of short SGA children, not only height. GH may improve QoL in children or adolescents by mechanisms unrelated to growth.

In conclusion, our study shows that children born SGA, when treated with long-term GH therapy, show significantly better QoL on physical abilities and contact with adults than untreated children born SGA, when measured with the disorder-specific TACQOL-S. Additionally, also fewer problems with body image were reported in the GH group. Furthermore, our study shows a larger effect size of QoL in the GH-treated versus the untreated group when tested with the disorder-specific TACQOL-S. The generic CHQ did not reveal such significant differences. Our results are, however, preliminary and need to be verified in a larger randomized, placebo-controlled study design. Furthermore, we advise to use, in addition to a generic questionnaire, a height-specific questionnaire for measuring the influence of GH treatment on QoL.

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