Children's psychosocial functioning and parents' quality of life in pediatric short stature: The mediating role of caregiving stress

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Abstract

Objectives. Based on the multidimensional model of the caregiving process, this study aimed (1) to compare the levels of quality of life (QoL) and psychological problems of children with short stature, and the levels of caregiving stress and QoL of their parents, between diagnostic, treatment and current height deviation groups; and (2) to examine the direct and indirect links, via caregiving stress, between children's psychosocial functioning and their parents' QoL. **Method.** The sample was collected in five European countries and comprised 238 dyads of 8-18 year-old children/adolescents with a clinical diagnosis of growth hormone deficiency (GHD) or idiopathic short stature (ISS) and one of their parents. The children completed self-report measures of height-related QoL (QoLISSY Core Module) and psychological problems (Strengths and Difficulties Questionnaire); the parents reported on their own QoL (EUROHIS-QOL-8 Index) and caregiving stress (QoLISSY Effects on Parents subscale). **Results.** Children who were treated and who achieved normal height reported better QoL compared to those untreated and with current short stature. Parents of children with ISS and current short stature presented greater caregiving stress than parents of children with GHD and achieved normal height. Children's better psychosocial functioning was indirectly associated with parents' better QoL, via less caregiving stress, and these links were invariant across diagnoses, treatment status and current height deviation. **Conclusions.** These results suggest that, along with GH treatments, multidisciplinary interventions in pediatric endocrinology should be family-centered, by targeting both the children's psychosocial functioning and the parents' stress, in order to improve individual and family adaptation.

Keywords: Caregiving stress, Child psychosocial functioning, Multidimensional model of caregiving process and caregiver burden, Parents' quality of life, Pediatric short stature.

Key Practitioner Message:

- Height-related quality of life impairments and more internalizing problems in children/adolescents with short stature increases caregiving stress, which in turn has a negative impact on parents' quality of life, independently of patients' diagnosis, treatment status and current height deviation.

- In addition to growth hormone treatment, multidisciplinary interventions in the context of pediatric short stature should target the children/adolescents' psychosocial functioning, as well as provide the parents with cognitive and behavioral strategies to manage their child's physical, emotional, social and behavioral problems.

- Caregiving stress should be routinely assessed and selected as a strategic intervention target for family-centered psychosocial interventions aimed at promoting parents' adaptation outcomes (e.g., quality of life).

- Psychosocial interventions should prioritize the children/adolescents who had never been treated with growth hormone and who have current short stature, as well as the parents of children with idiopathic short stature and current short stature.

Introduction

Although height is a physical trait on a continuum and the threshold between standard height and short stature is statistically set (Cousounis, Lipman, Ginsburg, Cucchiara, & Grimberg, 2014), normal growth and development are important characteristics of healthy childhood and adolescence. Short stature is conventionally defined as a body height more than two standard deviations (*SD*) below the mean for the same sex and age group (Cohen et al., 2008), occurring by definition in 2.5% of children. The etiology of short stature is associated with genetic, endocrine, environmental and psychosocial factors or could be the consequence of a primary systemic disease (Batty et al., 2009; Peck & Lundberg, 1995). Growth hormone deficiency (GHD) represents a relatively rare cause for short stature, with a prevalence rate of approximately 1/4000 children (Lindsay, Feldkamp, Harris, Robertson, & Rallison, 1994). However, most children with short stature have sufficient growth hormone (GH) secretion, normal birth size and no evidence of systemic disease or malnutrition; this heterogeneous group which lacks a specific etiology and includes 60-80% of the short-statured children is classified as idiopathic short stature (ISS). Recombinant human GH treatment by daily subcutaneous injection is the most effective option to increase growth velocity and to normalize adult height in children with GHD (Tanaka et al., 2002). Although children with ISS have normal levels of GH secretion, it may be insufficient to stimulate their GH receptors (Wit et al., 2008) and there is evidence of the effectiveness of GH treatment to improve their adult height (Bryant, Baxter, Cave, & Milne, 2007). In addition, the treatment of children with ISS is predicated on the widespread belief that being taller improves children's psychosocial wellbeing (Sandberg & Colsman, 2005).

Psychosocial Consequences of Short Stature

Children and adolescents with short stature may face difficulties in everyday life caused by height-related physical limitations and environmental barriers to their autonomy, such as difficulties in reaching objects in high places, inadequate posture and limited vision of the board due to school furniture inappropriate to their height, and inaccessibility to fairground rides and other recreation activities and sports that other children of the same age can access. In addition, children with short stature encounter significant social, academic and psychological difficulties due to their condition, such as stigmatization and being bullied, low self-esteem, body-image disturbance, lack of age-expected social competences and social withdrawal

(Gordon, Crouthamel, Post, & Richman, 1982; Holmes, Karlsson, & Thompson, 1985; Law, 1987). Some studies have reported lower health-related quality of life (HrQoL) and more internalizing problems among children with short stature, compared to normal-statured reference groups (Abe et al., 2009; Stephen et al., 2011), as well as improvement in HrQoL and psychological functioning after GH treatment in both GHD and ISS patients (Sheppard et al., 2006; Stabler et al., 1998). However, controversies still exist regarding the clinical relevance of those findings (Gardner, Boshart, Yeguez, Desai, & Sandberg, 2016; Sandberg & Gardner, 2015) and a growing set of research support the hypothesis that, despite of psychosocial disadvantages, most patients scored within the normative range in social, emotional and behavioral outcomes (Ross et al., 2004; Theunissen et al., 2002; Visser-van Balen et al., 2007).

Clinicians and researchers have long recognized that a pediatric chronic condition does not only affect the child; it also affects all family members and the relationships among them (Kazak, 1989). However, few studies have addressed the impact of pediatric short stature on the parents and on the whole family functioning and the results are inconsistent. Gordon and colleagues (1982) reported that parents of children with short stature tend to be more overprotective and permissive (i.e., they tend to set less clear limits on child behavior and expect less obedience) and have more difficulties with communication and cooperation within the family than parents of normal-statured children. In contrast, other studies found no significant differences in adaptability and cohesion between families with children of normal height and those with short children (Starke, Erling, Möller, & Wikland, 2000) or between parents of short statured children with and without GH insufficiency (Stabler et al., 1994).

This variability in individual and family adaptation trajectories may be better explained not only by the clinical characteristics of the pediatric health condition but by a complex interplay between children's and parents' risk and resource factors. Therefore, examining the links between the children's physical and psychosocial functioning and the parents' concerns about their children's short stature may contribute to a better understanding of adaptation processes and outcomes, namely the parents' quality of life (QoL).

Mapping the Caregiving Process in Pediatric Short Stature

Based on previous research and theory, Raina and colleagues (2004) have proposed a comprehensive multidimensional model of the caregiving process and caregiving burden aimed at mapping the direct, indirect and conditional links between children's characteristics (e.g., clinical features, psychosocial function and behavior), caregivers' stress and burden, coping factors and the health outcomes of the caregivers. According to this hybrid model, the disease

parameters (e.g., height deviation and GH treatment) and the children's physical and psychosocial functioning may affect the parents' QoL, not only directly but also indirectly through the perceived caregiving burden.

In fact, the burden of caregiving, broadly defined as the "caregiver's perceived responsibilities and associated limitations on self and family" (Canning, Harris, & Kelleher, 1996, p. 737), was emphasized by Raina and colleagues (2004) as a foremost predictor of parents' physical and psychological health. While providing daily care to young children is a normative assignment of parenting, the additional practical demands and concerns arising from parenting a child with a chronic condition may elicit caregiving stress related to the parent-child dyadic relationship (relationship burden), instrumental activities and consequent fatigue and time constraints (objective burden) and emotional stress, worry and anxiety (subjective or stress burden; Montgomery, Gonyea, & Hooyman, 1985; Savundranayagam, Montgomery, & Kosloski, 2011). Specifically in parents of children with short stature, these may include the objective burden of daily treatments and regular medical appointments, the disruption in the parent-child relationship due to overprotectiveness and permissive child-rearing style, and the feelings of helplessness and worry about other peoples' reactions to the child's height. Higher levels of caregiving burden, particularly its subjective dimension, have been associated with poorer QoL and psychological adjustment in the parents of children with several medical conditions (Canning et al., 1996; Carona, Pereira, Moreira, Silva, & Canavarro, 2013; Silva, Crespo, Carona, & Canavarro, 2015), but these adaptation processes and outcomes remain understudied in the context of pediatric short stature.

The Present Study: Aims and Hypotheses

Theoretically grounded on the Conceptual Model of Caregiving Process and Caregiver Burden (Raina et al., 2004), the objective of the present study was twofold. First, we intended to compare the levels of HrQoL and psychological problems of children/adolescents with short stature, as well as their parents' caregiving stress and QoL, between different clinical groups of diagnosis (i.e., GHD *vs*. ISS), treatment status (i.e., patients who were receiving or had received GH treatment *vs*. never treated patients) and current height deviation (i.e., patients who had achieved normal height due to normal growth or GH treatment *vs*. patients with current short stature). The second aim of our study was to examine the links between the children/adolescents' psychosocial functioning and the parents' QoL, both directly and indirectly via caregiving stress, as well as to ascertain the (in)variance of the mediation model between diagnoses, treatment status and current height deviation.

Accordingly, the following theoretically-driven hypotheses were formulated. First, the children/adolescents who were receiving/had received GH treatment and with achieved normal height were expected to report better HrQoL and fewer internalizing and externalizing problems, when compared to untreated patients with current short stature. In addition, we expected lower levels of caregiving stress and better QoL in the parents caring for a child with GHD, who was receiving/had received GH treatment and with achieved normal height than in the parents caring for a child with short stature of unknown etiology, untreated and with current short stature. Second, we predicted that children's better psychosocial functioning would be linked to enhanced parental QoL, and that this positive association would be mediated by the effects of pediatric short stature on the parents (i.e., caregiving stress). Given the exploratory nature of the examination of (in)variance of the mediation model across clinical groups, no predictions were made on this regard.

Methods

Participants and Procedures

The present study is part of the Quality of Life in Short Stature Youth (QoLISSY) project, which is a multicenter study conducted simultaneously in five European countries (France, Germany, Spain, Sweden and the UK) with the aim of developing a cross-cultural condition-specific HrQoL instrument for children/adolescents between 8 and 18 years of age with short stature, as well as for parents of 4-18 year-old patients. According to standardized guidelines, the development of the QoLISSY instrument was carried out in three stages: (1) focus-groups with item generation; (2) pilot-test with cognitive debriefing; and (3) field test with retest (Bullinger et al., 2013). Participants were recruited in pediatric endocrine centers of the five European countries, upon approval by the respective Ethic Committees (namely, die Ethikkommission der Ärztekammer Hamburg, Germany; the Regionala etikprövningsnämnden I Göteburg, Sweden; the Comité d'ethique de Toulouse, France; the research ethics committee, NHS Lothian, Edinburgh, UK; and the CEIC Hospital Clínic de Barcelona, Spain). The study was performed following data protection requirements of the European Parliament (Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing and free movement of personal data).

The current analyses used data from the children/adolescents between 8 and 18 years of age and from their parents, collected within the QoLISSY field test phase. Participants were

enrolled in pediatric endocrine centers of the five participating countries, if the patients met the following criteria: (1) clinical diagnosis of GHD or ISS; (2) height deviation greater than -2 *SD* from the norms for their age, gender and nationality at the time of diagnosis; (3) age between 8 and 18 years; (4) absence of comorbidities with other chronic health conditions or severe mental disorders; and (5) be accompanied by the parent currently assuming the role of primary caregiver. Eligible participants were identified by the pediatric endocrinologists based on the children's medical records. In compliance with the American Psychological Association (APA) ethical principles regarding research with human participants (APA, 2010), detailed information about the study aims and procedures was provided in the respective language when the families attended regular appointments at the clinical centers. Informed consents were obtained from the parents, together with informal assents from the children/adolescents, as well as a permission to extract clinical information from the medical records through their physicians. The field test questionnaires, to be independently completed by the patients and the parents, were given to the families who agreed to participate in the study when they visited the pediatric endocrine centers, or they were sent by mail together with a pre-stamped envelope for returning the completed questionnaires. Data was entered into a project specific database in each center, which included the computation of the children's height deviation at the time of assessment with reference to the national norms for age and gender, and was subsequently sent to the German coordinating center.

Overall, 421 families participated in the field test phase of the QoLISSY project. After excluding 145 cases (34.0%) due to missing data in a ratio greater than 20% of the data, and 38 children between 4 and 7 years of age because they were unable to provide self-reports of their HrQoL and psychological problems, the final sample for the present study included 238 dyads composed of a child/adolescent aged 8-18 years and a parent currently assuming the role of primary caregiver. The sociodemographic and clinical characteristics of the sample are presented in Table 1.

Variables and Measures

Children's health-related quality of life.

Children's and adolescents' HrQoL was measured by the self-report version of the core module of the QoLISSY questionnaire (The European QoLISSY Group, 2013), which is a condition-specific instrument targeting height-related QoL of 8-18 year-old children and adolescents with short stature. The QoLISSY core module consists of 22 items, assessing three

HrQoL domains: Physical (e.g., "My height prevents me from doing things that other children my age do"), Social (e.g., "Because of my height I get laughed at or teased"), and Emotional (e.g., "Because of my height I feel different from others my age"). The items were answered using a five-point Likert scale ranging from 1 (*never/not at all*) to 5 (*always/extremely*). Standardized scores ranging from 0 to 100 were calculated for the three QoLISSY domains, with higher scores indicating better HrQoL. Good reliability was found in the current sample, with Cronbach's alpha values ranging from .85 (Physical domain) to .88 (Emotional domain).

Table 1. *Sociodemographic and clinical characteristics of the sample (n = 238 dyads)*

		Children/ Adolescents	**Parents**
Sociodemographic characteristics			
Age (in years), *M* (*SD*)			44.89 (20.09)
Age group, *n* (%)	Children 8-12 years	112 (47.1%)	
	Adolescents 13-18 years	126 (52.9%)	
Sex, *n* (%)	Male	132 (55.5%)	31 (13.0%)
	Female	106 (44.5%)	195 (81.9%)
	Missing	-	12 (5.0%)
Country, *n* (%)	France	40 (16.8%)	
	Germany	60 (25.2%)	
	Spain	40 (16.8%)	
	Sweden	69 (29.0%)	
	UK	29 (12.2%)	
Marital status, *n* (%)	Married/living with a partner		195 (81.9%)
	Single-parent household		40 (16.8%)
	Missing		3 (1.3%)
Clinical characteristics			
Diagnosis, *n* (%)	GHD	99 (41.6%)	
	ISS	139 (58.4%)	
Treatment status, *n* (%)	Untreated	110 (46.2%)	
	GH treated	128 (53.8%)	
Duration of treatment (in years), *M* (*SD*)		5.36 (3.01)	
Current height deviation, *n* (%)	Below -2 *SD* (current short stature)	115 (48.3%)	
	Above -2 *SD* (achieved normal height)	119 (50.0%)	
	Missing	4 (1.7%)	

Children's psychological problems.

The children's and adolescents' psychological problems were measured by the child-rated Difficulties scale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001). This scale is comprised of 20 items assessing emotional symptoms (e.g., "I am often unhappy, down-hearted or tearful"), conduct problems (e.g., "I fight a lot. I can make other people do what I want"), hyperactivity/inattention (e.g., "I am easily distracted, I find it difficult to concentrate"), and peer relationship problems (e.g., "I am usually on my own. I generally play alone or keep to myself"). The 20 items were answered using a Likert-type response scale with three options (0 = *not true*, 1 = *somewhat true* and 2 = *certainly true*), and coded into Internalizing and Externalizing Problems, following recent recommendations for assessing low-risk or general population samples (Goodman, Lamping, & Ploubidis, 2010). The scores ranged from 0 to 20, with higher scores indicating more psychological problems. In the current sample, Cronbach's alpha values were .72 (Internalizing Problems) and .76 (Externalizing Problems).

Caregiving stress.

The subjective burden of caring for a child/adolescent with short stature was assessed with the Effects on Parents scale of the QoLISSY questionnaire (The European QoLISSY Group, 2013). This scale is embedded in the parent-report version and was developed as a complementary scale for assessing potential determinants of pediatric HrQoL. The Effects on Parents scale assessed the subjective burden of the child's short stature on the parents through 11 items (e.g., "My child's growth problems make me feel anxious") scored on a 5-point Likert scale ranging from 1 (*never/not at all*) to 5 (*always/extremely*) and provided a 0-100 standardized score, with higher scores indicating greater caregiving stress. In the current sample, the scale presented good reliability with a Cronbach's alpha value of .89.

Parents' quality of life.

The parents' QoL was assessed with the EUROHIS-QOL-8 Index (Schmidt, Mühlan, & Power, 2006). This unidimensional self-report questionnaire was derived from the World Health Organization Quality of Life Assessment (WHOQOL-100 and WHOQOL-Brief instruments) and includes eight items representing the physical (e.g., "Do you have enough energy for everyday life?"), psychological (e.g., "How satisfied are you with yourself?"), social (e.g., "How satisfied are you with your personal relationships?") and environmental (e.g., "How satisfied are you with the conditions of your living place?") domains of QoL. The eight

items were scored on a 5-point Likert scale ranging from 1 (not *at all/very dissatisfied*) to 5 (*completely/very satisfied*). An overall QoL standardized score ranging from 0 to 100 was calculated, with higher values indicating better QoL. In the current sample, the Cronbach's alpha coefficient for the QoL score was .84.

Sociodemographic and clinical variables.

The sociodemographic data were collected from the parents and included patients' and parents' sex, current age, nationality and parents' marital status (married/living with a partner or single-parent household). Clinical data was provided by the child's physician through their medical records, and included diagnosis (GHD or ISS), treatment status (GH treated or untreated), duration of treatment (if applicable), height at the time of diagnosis and height at the time of assessment. The group of treated patients included those who were receiving GH treatment at the time of assessment and those who had received prior treatment; the untreated group included patients who had never been treated with GH. Although a height deviation greater than -2 *SD* from the norms at the time of diagnosis was required for inclusion in the sample, some patients had achieved a height deviation of less than -2 *SD* at the time of assessment due to normal growth or GH treatment. Thus, the current height deviation was categorized into two groups: achieved normal height (height deviation above -2 *SD*) and current short stature (height deviation below -2 *SD*).

Data Analysis

The statistical analyses were conducted with the Statistical Package for Social Sciences v.20.0 (IBM Corp., Armonk, NY). Except for sociodemographic and clinical variables, missing data that were random and less than 20% of the values were replaced with the individual mean score for each variable. Multivariate analyses of covariance (one-way MANCOVA) were used to test the main effects of diagnosis (GHD *vs*. ISS), treatment (GH treated *vs*. untreated) and current height deviation (current short stature *vs*. achieved normal height) on child-reported HrQoL and psychological problems. Univariate analyses (one-way ANCOVA) were performed for caregiving stress and parents' QoL, as well as to examine which dimensions of children's HrQoL and psychological problems significantly differed between the groups when a multivariate effect was found. The remaining clinical variables, as well as the children's and parents' sociodemographic variables (children's sex and age group, parents' sex, age and marital status) that were significantly associated with the outcome variables were included as covariates. Effect-size measures were presented for the comparison analyses, considering $\eta_p^2 \geq$

0.01, $\eta_p^2 \geq 0.06$, and $\eta_p^2 \geq 0.14$ as small, medium and large effects, respectively (Cohen, 1988).

Structural equation modelling was performed with Analysis of Moment Structures (AMOS Development Corporation, Meadville, PA). The method of estimation was the maximum likelihood and the overall model fit was evaluated based on the chi-square statistic (χ^2) and on the main approximate goodness-of-fit indexes, i.e., the comparative fit index (CFI), the root mean square error of approximation (RMSEA) and the standardized root mean squared residual (SRMR). A model was considered to have a good fit when χ^2 was non-significant, the CFI $\geq$ .95, the RMSEA $\leq$ .06 and the SRMR $\leq$ .08; an acceptable fit was defined by a CFI $\geq$ .90 and a RMSEA $\leq$ .10 (Browne & Cudeck, 1993; Hu & Bentler, 1999). To ensure the pertinence of latent variables, we first examined the measurement model testing the hypothesized links between the latent variables and their observed indicators. Second, we examined the structural model testing the direct and indirect links, via caregiving stress, of the children's psychosocial functioning on the parents' QoL. The statistical significance of the indirect effects was estimated using bootstrap resampling procedures with 2,000 samples and a 95% bias-corrected confidence interval (BC 95% CI; Preacher & Hayes, 2008; Williams & MacKinnon, 2008). Finally, to ascertain that the parameters tested in the mediation model were valid for the diagnostic, treatment and current height deviation groups, we examined the baseline model for each group separately and we conducted multi-group analyses testing the invariance of the associations between the latent variables and their observed indicators (i.e., measurement invariance) and the invariance on the strength of the associations among the latent variables (i.e., structural invariance; Little, 2013). The chi-square difference method was used to compare the unconstrained model with nested models in which factor loadings and structural weights were sequentially and cumulatively fixed to be equal across groups.

Results

Descriptive Statistics and Analyses of Covariance

Preliminary correlation analyses indicated that children's male gender was associated with better social HrQoL (r = .15, p = .02) and with more externalizing problems (r = .18, p < .01); adolescent age group was associated with better physical (r = .24, p < .01) and social HrQoL (r = .17, p < .01), and caregivers' male gender was associated with better emotional HrQoL (r = .15, p = .02). In addition, lower levels of caregiving stress were associated with caring for an adolescent (r = -.22, p < .01) and caregiver's male gender (r = -.13, p = .05).

Accordingly, these variables were included as covariates in the analyses of covariance when appropriate. No significant associations were found between parents' QoL and sociodemographic variables.

The descriptive statistics for children's HrQoL and psychological problems, caregiving stress and parents' QoL are presented in Table 2. The MANCOVAs for pediatric HrQoL yielded significant multivariate main effects of treatment status, Wilks' Lambda = .96; $F_{(3, 219)}$ = 3.18, p = .03; η_p^2 = .04, and current height deviation, Wilks' Lambda = .86; $F_{(3, 219)}$ = 12.11, p < .01; η_p^2 = .14. The univariate analyses (Table 2) indicated better physical and social HrQoL for children/adolescents who were receiving or had received GH treatment than for untreated patients, and better physical, social and emotional HrQoL for patients with achieved normal height than for those with current short stature. No significant multivariate main effects of diagnosis were found on pediatric HrQoL, Wilks' Lambda = .99; $F_{(3, 219)}$ = 0.58, p = .63; η_p^2 = .01. Regarding children's psychological problems, the MANCOVAs showed no multivariate main effects of diagnosis, Wilks' Lambda = 1.00; $F_{(2, 228)}$ = 0.50, p = .61; η_p^2 < .01, treatment status, Wilks' Lambda = 1.00; $F_{(2, 228)}$ = 0.29, p = .75; η_p^2 < .01, or current height deviation, Wilks' Lambda = .99; $F_{(2, 228)}$ = 1.20, p = .30; η_p^2 = .01.

The ANCOVAs for the effects of short stature on the parents indicated significant main effects of diagnosis, $F_{(1, 222)}$ = 7.05, p < .01; η_p^2 = .03, and current height deviation, $F_{(1, 222)}$ = 8.96, p < .01; η_p^2 = .04, with parents of children/adolescents with ISS reporting greater caregiving stress than parents of GHD patients, and parents of children with current short stature reporting greater caregiving stress than parents of children with achieved normal height (Table 2). No significant main effects of diagnosis, treatment status or current height deviation were detected on parents' QoL.

The Measurement Model

For structural equation modeling, three latent variables were generated: (1) children's psychosocial functioning, which comprised the Physical, Social and Emotional domains of height-related QoL, as well as internalizing and externalizing problems as observed indicators; (2) caregiving stress, which was reflected by the 11 items of the QoLISSY Effects on Parents scale; and (3) parents' QoL, which was reflected by the EUROHIS-QOL eight items as observed indicators. The measurement model testing the hypothesized links between the latent variables and their observed indicators had a nearly acceptable fit, with $\chi^2_{(249)}$ = 599.06, p < .01; χ^2/df = 2.41; CFI = .89; RMSEA = .08 (p < .01; 90% CI = .07/.09); and SRMR = .07.

Table 2. *Descriptive statistics and univariate analyses of covariance by children's diagnosis, treatment status and current height deviation*

	Diagnosis			Treatment status			Current height deviation		
	GHD	ISS		GH treated	Untreated		Achieved normal height	Current short stature	
Children's HrQoL [a]	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,221)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,221)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,221)}$
Physical HrQoL	80.91 (20.16)	68.64 (23.59)	0.10	81.10 (19.82)	65.23 (23.56)	5.70*	83.85 (17.15)	63.45 (23.67)	36.05**
Social HrQoL	81.91 (20.96)	67.31 (22.57)	0.92	80.81 (20.04)	63.87 (22.64)	7.94**	81.96 (20.85)	63.76 (21.21)	22.85**
Emotional HrQoL	78.36 (21.95)	68.66 (25.07)	0.08	78.59 (22.27)	65.86 (24.77)	2.74	81.44 (21.19)	63.79 (24.03)	21.67**
Children's psychological problems [b]	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,229)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,229)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1,229)}$
Internalizing problems	4.03 (3.32)	4.72 (3.26)	0.30	4.10 (3.12)	4.83 (3.45)	0.32	3.99 (3.06)	4.90 (3.48)	2.31
Externalizing problems	5.77 (3.93)	5.72 (3.32)	0.30	5.64 (3.57)	5.86 (3.59)	0.49	5.66 (3.47)	5.83 (3.69)	0.11
Caregiving stress [c]	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 222)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 222)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 222)}$
	25.74 (22.03)	40.35 (23.48)	7.05**	29.29 (23.18)	40.17 (23.62)	0.02	27.88 (24.19)	40.91 (21.97)	8.96**
Parents' QoL [d]	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 230)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 230)}$	***M* (*SD*)**	***M* (*SD*)**	$F_{(1, 230)}$
	75.10 (13.22)	74.12 (14.56)	0.37	74.55 (13.46)	74.48 (14.66)	0.10	74.61 (14.48)	74.43 (13.56)	< 0.01

[a] Controlling for the remaining clinical variables, children' sex and age group and parents' sex; [b] Controlling for the remaining clinical variables and children's sex; [c] Controlling for the remaining clinical variables, parents' sex and children's age group; [d] Controlling for the remaining clinical variables.

* $p \leq .05$; ** $p \leq .01$, two tailed.

All observed indicators presented good factorial validity, with standardized regression weights above the threshold of .50 and statistically significant, except for externalizing problems (factor loading = -.23, $p < .01$) and for the item 7 of effects on parents (factor loading = -.09, $p = .20$). The inspection of modification indices suggested that items 1 and 2 of the EUROHIS-QOL 8- item Index might be correlated, as well as the pairs of items 1-3, 4-5, 5-9 and 8-9 of the QoLISSY Effects of Parents scale.

In addition to excluding externalizing problems as an observed indicator of children's psychosocial functioning, the item 7 of the QoLISSY Effects on Parents scale was also omitted because it measures parents' confidence on GH treatment, unlike the remaining items, which focus on parents' feelings and concerns about their child's growth problems. Moreover, the items 1 and 2 of the EUROHIS-QOL 8 Index were correlated because they both refer to the generic facet of QoL, as were the aforementioned pairs of items of the Effects of Parents scale. The modified model had a good fit, with $\chi^2_{(201)} = 345.84$, $p < .01$; $\chi^2/df = 1.72$; CFI = .95; RMSEA = .06 ($p = .19$; 90% CI = .05/.07); and SRMR = .06, which was significantly better than the original model, with $\Delta\chi^2_{(48)} = 253.22$, $p < .001$. The standardized regression weights ranged from .46 to .96 and were statistically significant, attesting the factorial validity of the modified measurement model. In addition, the squared multiple correlations (R^2_{smc}) between each observed indicator and all other observed indicators were lower than .90, except for the child-reported social HrQoL (range from .21 to .92) and the tolerance values (1- R^2_{smc}) were higher than .10, indicating that each variable explained a substantial proportion of the total standardized variance, and, thus, the model was not limited by multicollinearity problems (Kline, 2005). In addition, moderate to strong correlations were found between the latent variables: children's psychosocial functioning was negatively associated with caregiving stress ($r = -.57$, $p < .01$) and positively associated with parents' QoL ($r = .17$, $p = .02$), and caregiving stress was negatively associated with parents' QoL ($r = -.34$, $p < .01$).

The Mediation Model

The structural model testing the direct and indirect links, via caregiving stress, between children's psychosocial functioning and parents' QoL (Figure 1), while accounting for the effect of children's age group and parents' sex on caregiving stress, had a good fit, with $\chi^2_{(241)} = 400.00$, $p < .01$; $\chi^2/df = 1.66$; CFI = .94; RMSEA = .05 ($p = .23$; 90% CI = .05/.06); and SRMR = .06, and explained 34% of the variability on caregiving stress and 12% of the variability on parents' QoL. A significant effect of children's psychosocial functioning was found on caregiving stress ($\beta = -.53$, $p < .01$); in turn, caregiving stress had a significant direct

effect on parents' QoL, with β = -.37, $p < .01$. No direct effect of children's psychosocial functioning on parents' QoL was found (β = -.05, $p = .59$), but the indirect effect via caregiving stress was statistically significant (β = .20, $p < .01$; BC 95% CI =.11/.31).

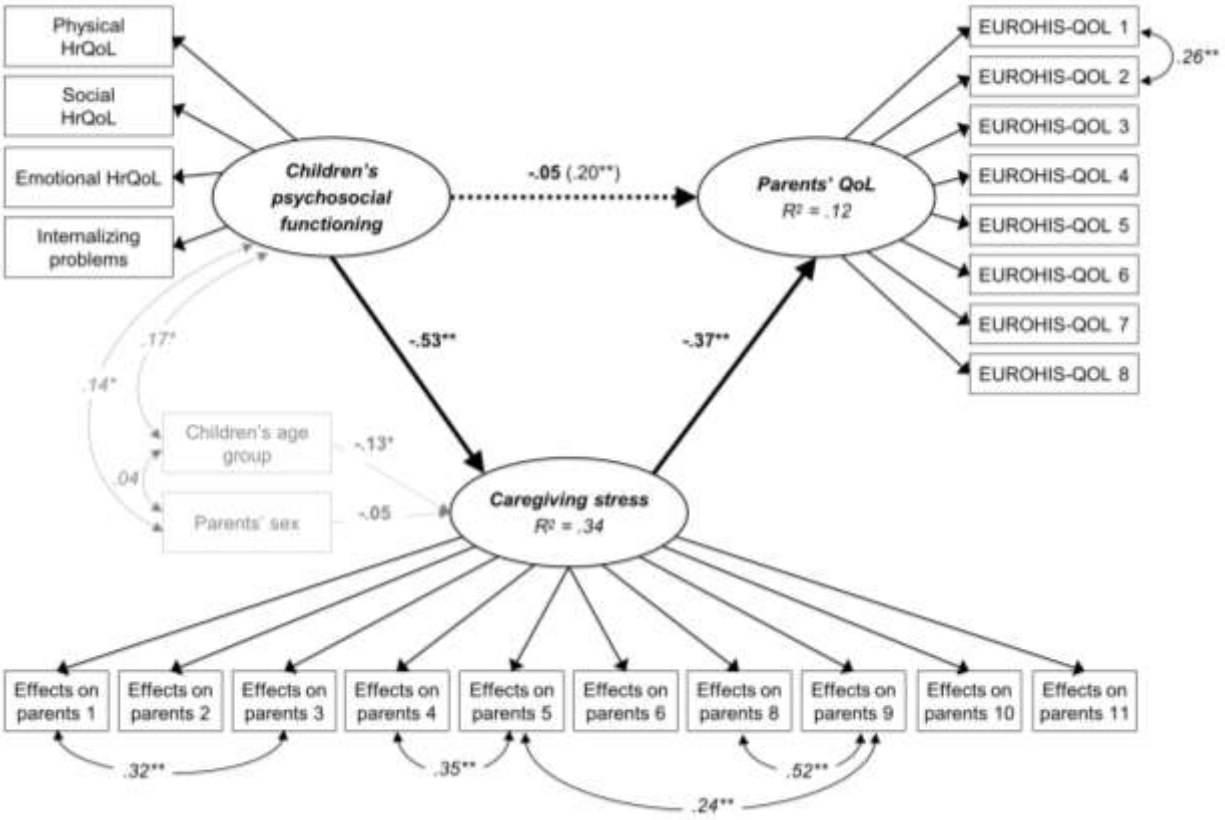

Figure 1. Structural equation model testing the direct and indirect effects, via caregiving stress, of children's psychosocial functioning on parents' quality of life, while accounting for the effect of children's age group and parents' sex on caregiving stress.

Note. Bold figures represent the standardized regression weights for the direct paths; the non-bold figure in brackets represents the standardized regression weight for the indirect path; italic non-bold figures represent the Pearson correlation coefficients. For simplicity, measurement error terms are not shown. * $p \leq .05$; ** $p \leq .01$.

Multi-Group Analyses

Table 3 presents the summary of fit statistics for the mediation model tested separately for groups with different diagnoses (i.e., GHD and ISS), treatment status (i.e., GH treated and untreated) and current height deviation (achieved normal height and current short stature), as well as the results from multi-group analyses. Regarding measurement invariance, the factor loadings of the observed indicators on their respective latent variables did not significantly

differ between patients with GHD or ISS, $\Delta\chi^2_{(19)} = 17.64$, $p = .55$, between GH treated and untreated patients, $\Delta\chi^2_{(19)} = 18.99$, $p = .46$, or between patients with current short stature and those with achieved normal height, $\Delta\chi^2_{(19)} = 26.32$, $p = .12$. Assuming that the measurement model is invariant across the groups, the results from the multi-group analyses also yielded no significant differences in the structural weights across diagnoses, $\Delta\chi^2_{(5)} = 2.12$, $p = .83$, treatment status, $\Delta\chi^2_{(5)} = 10.12$, $p = .07$, or current height deviation groups, $\Delta\chi^2_{(5)} = 8.86$, $p = .12$.

Table 3. *Multi-group analyses testing measurement and structural invariance across diagnosis, treatment status and current height deviation groups*

	χ^2	*df*	CFI	RMSEA [90% CI]	SRMR	$\Delta\chi^2$	Δdf	*p*	ΔCFI
Diagnosis									
Summary of fit statistics									
GHD	323.42**	241	.92	.06 [.04/.08]	.08				
ISS	356.51**	241	.93	.06 [.05/.07]	.07				
Multi-group analyses									
Unconstrained model	680.06**	482	.93	.04 [.04/.05]	.08	-	-	-	-
Measurement weights	697.69**	501	.93	.04 [.03/.05]	.08	17.64	19	.55	<.01
Structural weights	699.82**	506	.93	.04 [.03/.05]	.09	2.12	5	.83	<.01
Treatment status									
Summary of fit statistics									
GH treated	313.76**	241	.95	.05 [.03/.07]	.08				
Untreated	351.64**	241	.92	.07 [.05/.08]*	.08				
Multi-group analyses									
Unconstrained model	665.47**	482	.94	.04 [.03/.05]	.08	-	-	-	-
Measurement weights	684.45**	501	.94	.04 [.03/.05]	.08	18.99	19	.46	<.01
Structural weights	694.57**	506	.93	.04 [.03/.05]	.10	10.12	5	.07	.01
Current height deviation									
Summary of fit statistics									
Achieved normal height	378.94**	241	.91	.07 [.06/.09]**	.08				
Current short stature	336.36**	241	.93	.06 [.04/.07]*	.08				
Multi-group analyses									
Unconstrained model	715.30**	482	.92	.05 [.04/.05]	.08	-	-	-	-
Measurement weights	741.62**	501	.91	.05 [.04/.05]	.08	26.32	19	.12	.01
Structural weights	750.48**	506	.91	.05 [.04/.05]	.09	8.86	5	.12	<.01

* $p \leq .05$; ** $p \leq .01$, two tailed.

Discussion

The main contributions of the present study were the examination of the caregiving experiences and QoL in parents of children/adolescents with different diagnosis of short stature, different treatment status and different current height deviation, and the examination of a mediational hypothesis based on a solid theoretical background, namely the Multidimensional Model of the Caregiving Process and Caregiving Burden (Raina et al., 2004). The results, which were based on a large sample of European patients with short stature and their parents, allowed the identification of ISS and current short stature as important clinical features contributing to higher levels of caregiving stress. In addition, our findings showed that caregiving stress is an important risk factor for parent's impaired QoL and it also mediated the positive association between children's psychosocial functioning and parents' outcomes, independently of patients' clinical characteristics. To the best of our knowledge, this is the first study addressing the QoL of parents of children with clinically diagnosed GHD or ISS and the processes through which the children's health condition and psychosocial functioning may affect the parents' adaptation.

Our first set of results indicated better HrQoL for children who were receiving or had received GH treatment and who have achieved normal height, compared to children without treatment and with current short stature. Alongside with intrapersonal factors and stress processing mechanisms, the social-ecological factors, such as the feedback that children/adolescents with chronic health conditions receive from their family and extended social network, are likely to influence their psychosocial development and adaptation (Noeker, 2009; Wallander & Varni, 1998). Because of the immediate visibility of low body height and its deviation from the norms, children with short stature consistently experience negative social feedback such as stigmatization and bullying (Voss & Mulligan, 2000), which may lead to HrQoL impairments. In addition, treated children might feel they are making positive progress towards improving their height and HrQoL, as opposed to untreated children, who may feel more passive and helplessness regarding their condition. Thus, the higher HrQoL reported by treated children may be explained by this active behavior, as well as by their expectations related to GH treatments. In fact, previous studies showed that children and parents tend to be satisfied with GH treatments and have high expectations about the height that children would reach in adulthood (Leiberman, Pilpel, Carel, Levi, & Zadik, 1993; Rekers-Mombarg, Busschbach, Massa, Dicke, & Wit, 1998; Visser-van Balen, Sinnema, & Geenen, 2006).

As expected, parents of children diagnosed with ISS and with current short stature

reported greater caregiving stress than parents of children with GHD and who achieved normal height. These findings were partly supported by Glozmann (2004), who described the magnitude of caregiving burden as dependent of disease severity and suggested that the main determinant of a caregiver's decreased QoL is the care receiver's functional limitations in activities of daily living. Children with current short stature may encounter more environmental barriers to their autonomy and be more dependent on parental care, thus increasing the parents' responsibilities and worries (Bullinger et al., 2009). In addition, knowing that there exists a specific etiology and treatment for their children's short stature may contribute to alleviate the stress of parents of children with GHD, when compared to parents of children with ISS (Gordon et al., 1982). However, no significant effects of children's diagnosis, current height deviation or treatment status were found on parental QoL, suggesting that parents' adaptation outcomes would be more dependent on psychosocial risk and resistance factors than on children's clinical characteristics.

In fact, our results showed that children's psychosocial functioning was positively associated with parents' QoL, but only indirectly via decreased caregiving stress, partly confirming our second hypothesis. These results were supported by the model's invariance across children's diagnoses, treatment status and height deviation groups. Previous studies with parents of children with chronic health conditions/disabilities showed that parents' QoL depended little on medical variables and that children's psychological problems was the variable that most contributed to explain its variance (Annett, Turner, Brody, Sedillo, & Dalen, 2010; King, King, Rosenbaum, & Goffin, 1999; Vila et al., 2003). Raina and colleagues (2005) also found that fewer child behavior problems and decreased caregiving demands were associated with improvements in both physical and psychological health of the caregivers. Despite these preliminary attempts to explain the complex web of direct and indirect mechanisms underlying parents' adaptation trajectories, our study was pioneering in its examination of the mediating role of caregiving stress on the association between children's psychosocial functioning and parents' QoL in the context of pediatric short stature. The manifestations of height- and treatment-related impairments in children's physical, social, emotional and behavioral functioning require surveillance, control and exertion on the part of the parents and, thus, they constitute actual care demands (Raina et al., 2004). In turn, increased levels of caregiving stress, worry and anxiety were a main risk factor for poorer QoL in the parents, as hypothesized in the conceptual model of caregiving process and consistently ascertained in several empirical studies (Carona et al., 2013; Silva et al., 2015).

Limitations of the Study and Future Directions for Research

Some limitations in the study design and procedures should be considered when interpreting the results. A first main limitation relates to the cross-sectional design of the study, which precluded the inference of causality among the variables. Even though the directional paths tested in the mediation analysis have been hypothesized according to a widely accepted theoretical model of caregiving process (Raina et al., 2004), the negative effect of caregiving burden on children's QoL has also been described (Carona, Silva, Crespo, & Canavarro, 2014; Crespo, Carona, Silva, Canavarro, & Dattilio, 2011). In addition, the associations between children's and parents' QoL are likely to be bidirectional and further longitudinal research should be undertaken to examine the transactional paths between parent-child adaptation outcomes over time (Fiese & Sameroff, 1989) in the context of pediatric short stature. Second, the non-probabilistic sample collection method may have biased the distribution of sample characteristics and may limit the generalizability of the results. Although we intended to recruit primary caregivers regardless of their sociodemographic characteristics, our sample was mainly composed of mothers living with a partner, thus hindering the examination of model's (in)variance between caregivers' sex (i.e., fathers *vs*. mothers) and marital status (i.e., parents who were single and, thus, the only caregiver for the child *vs*. parents who could rely on a partner). Moreover, the interaction effects between diagnosis, treatment status and current height deviation on children's psychosocial functioning and on parents' caregiving stress and QoL could not be examined because more GHD patients than ISS patients were treated. Although the confounding of diagnosis and treatment status reflects the regulation for GH treatment indication in the participating countries, the sample size within each group was too small to be considered (i.e., only 12 children with GHD were untreated and 41 children with ISS were receiving or had received GH treatment). Third, no information on the time elapsed between the diagnosis of short stature and the collection of data was available, which precluded the examination of the potential effect of disease length on perceived caregiving stress. Finally, our study only assessed the caregiving burden, with a particular focus on its subjective dimension. However, caring for a child with a chronic condition is a multifaceted experience that also encompasses gratifications and positive emotions, which may buffer the deleterious effect of caregiving burden on parents' QoL (Carona et al., 2013).

Thus, future research should include both parents (primary and secondary caregiver) of children with different clinical diagnoses of short stature and to investigate other psychosocial variables and the mechanisms and conditions under which they might predict parents' QoL outcomes, to obtain a more comprehensive description of parental resources and limitations in

coping with such a chronic disease.

Clinical Implications

Two main implications for clinical practice in pediatric endocrinology settings can be drawn from the present study. First, it is important that health professionals recognize that pediatric short stature affects not only the child, but also the family as a whole. The diagnosis of short stature and its consequences may influence the daily life of all family members because they have to adapt their routines to the special needs required by the child's with short stature. Parents may be at a greater risk for experiencing higher levels of caregiving stress in response to the child's diagnosis and the loss of the "perfect child". In turn, parental concerns about their child's physical and psychosocial health may influence the clinical decision-making process, regardless of objective measures of the child's growth (Cousounis et al., 2014). In fact, short stature is the second leading cause of referrals to pediatric endocrinologists (after diabetes) and parental concerns have been reported as important factors contributing to the increase in both referrals by primary care providers to specialists and prescriptions of GH by endocrinologists (Cuttler et al., 1996; Finkelstein et al., 1999; Lee et al., 2009; Hardin, Woo, Butsch, & Huett, 2007). Thus, the caregiving stress should be routinely assessed and selected as a strategic intervention target for family-centered psychosocial interventions aimed at promoting parental participation in clinical decision-making and treatment management, thus improving both children's and parents' adaptation outcomes. Specific strategies to regulate parents' stress burden may include the fostering of positive reappraisals of caregiving demands, the search for gratifications and benefits in their caregiving experiences, and the challenging of height-related beliefs and prejudices (Carona et al., 2014; Silva et al., 2015).

A second straightforward implication of our study relates to the need of considering children's behavioral and emotional problems as important determinants of the adaptation outcomes of both children and their parents. Even if our results suggest that individual interventions focused on the children's psychosocial functioning would be effective in reducing caregiving stress and improving parents' QoL, interventions and preventive strategies should target all family members to maximize their efficacy (Kazak, 1989; Raina et al., 2005). In addition to GH treatments, multidisciplinary interventions in the context of pediatric short stature should also provide the parents with cognitive and behavioral strategies to manage their child's physical, emotional, social and behavioral problems in order to foster their ability to respond to the unique characteristics of their child and to decrease the impact of their child's short stature and consequent functional limitations on them. However, it is also worth noting

that the child's height-related limitations should not be overestimated to avoid the risk of infantilizing the child or being overprotective in their education (Noeker, 2009).

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