Health-related quality of life (HRQoL) in achondroplasia: Findings from a multinational, observational study

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Background and Objectives

- Achondroplasia, caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 gene *(FGFR3)*, leads to significant multisystem complications across the lifespan and is associated with a reduced quality of life[1]
- The Lifetime Impact of Achondroplasia In Europe (LIAISE) study aimed to quantify the impact of achondroplasia by measuring the health-related quality of life (HRQoL) of affected individuals across the age spectrum and how this is impacted by disease state/clinical outcomes (https://clinicaltrials.gov/ct2/show/NCT03449368)

Methods

- LIAISE was a multinational, observational, retrospective study with a cross-sectional patient-reported outcome (PRO) component
- Individuals with achondroplasia aged ≥5 years were recruited from six European countries (Austria, Germany, Italy, Spain, Sweden, Denmark)
- Assessment of HRQoL was conducted using standardized, age-specific questionnaires at study enrollment covering a broad range of outcomes relative to achondroplasia **(Table 1)**

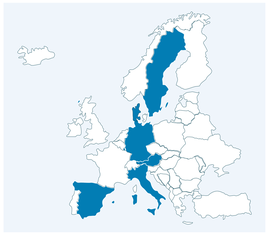


Table 1. Outcome domains assessed by questionnaire

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
PedsQL	✓	✓	✓		✓	
QoLISSY	✓	✓	✓		✓	
WeeFIM		✓				✓
APPT				✓		
EQ-5D	✓	✓		✓		
NHP	✓	✓	✓	✓	✓	
BPI				✓		
WPAI:SHP						✓

ACH: achondroplasia; APPT: adolescent paediatric pain tool; BPI: brief pain inventory; EQ-5D: EuroQoL 5-dimension QoL questionnaire; NHP: Nottingham health profile; PedsQL: Pediatric Quality of Life Inventory; PRO: patient-reported outcome; QoL: quality of life; QoLISSY: quality of life of short-stature youth; WeeFIM: paediatric functional independence measure; WPAI:SHP: work productivity and activity impairment.

- Adult participants (aged 16+ years) completed the EuroQOL 5 dimensions 5 levels (EQ-5D-5L) Questionnaire,[2,3] the Brief Pain Inventory (Short Form) (BPI-SF),[4] the Nottingham Health Profile part I (NHP),[5] and the Work Productivity and Activity Impairment Questionnaire:Specific Health Problem (WPAI:SHP)[6]
- Children/adolescents aged 5–17 years and/or their caregivers completed the Quality of Life in Short Stature module (QoLISSY),[7] the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL™ 4.0 GCS),[8] the Pediatric Functional Independence Measure questionnaire (WeeFIM),[9] and Adolescent Pediatric Pain Tool (APPT)[10]
- Tools were selected based on their content validity relative to achondroplasia and/or the availability of normative data in order to enable comparison and interpretation of results
- Medical history data was collected retrospectively from medical notes
- Analysis: Descriptive statistics of domain and total scores were examined as well as comparisons to reference populations when applicable. Correlations between HRQoL assessments and height were investigated

Results

Table 2. Participant characteristics

	Overall (N=186)	Limb Lengthening (n=40)	No Limb Lengthening (n=146)
Amount of historical medical data collected (years)			
Median (Q1,Q3)	9.4 (6.5, 15.7)	14.8 (7.7,23.5)	8.8 (6.4,14.0)
Age (years)			
Mean (SD)	21.7 (17.3)	24.2 (12.6)	21.0 (18.4)
Median (Q1,Q3)	14.9 (8.9, 30.8)	18.5 (14.7, 36.8)	13.1 (8.0, 26.8)
Age subgroups (years)			
5–10	66 (35.5%)	4 (10.0%)	62 (42.5%)
11–15	36 (19.4%)	10 (25.0%)	26 (17.8%)
16–20	17 (9.1%)	8 (20.0%)	9 (6.2%)
21–30	22 (11.8%)	5 (12.5%)	17 (11.6%)
31–40	14 (7.5%)	7 (17.5%)	7 (4.8%)
41–50	15 (8.1%)	5 (12.5%)	10 (6.8%)
51–60	8 (4.3%)	1 (2.5%)	7 (4.8%)
>60	8 (4.3%)	0 (0.0%)	8 (5.5%)
Gender			
Male	85 (45.7%)	10 (25.0%)	75 (51.4%)
Female	101 (54.3%)	30 (75.0%)	71 (48.6%)

Table 3. Participants generally reported lower scores across PROs compared to general population (where applicable)

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
PedsQL	Reduced[b]	Reduced[b]	Reduced[b]		~ Equal to population norms	
QoLISSY	Reduced[b]	Reduced[b]	Reduced[b]		~ Equal to population norms	
WeeFIM		No population norms – medium assistance				No population norms – medium assistance
APPT				Mild pain, multiple sites		
EQ-5D	Reduced[b]	Reduced[b]		37% moderate-extreme		
NHP	No population norms – moderate impact	No population norms – moderate impact	No population norms – moderate impact	No population norms – moderate impact	No population norms – moderate impact	
BPI				Mild pain, multiple sites		
WPAI:SHP						No population norms[c]

[a]Reference population consists of other short stature conditions, rather than average stature; [b]Reduced compared with population norms; [c]15% reduction in work, 27% reduction in activities. APPT: adolescent paediatric pain tool; BPI: brief pain inventory; EQ-5D: EuroQoL 5-dimension QoL questionnaire; NHP: Nottingham health profile; PRO: patient-reported outcome; QoL: quality of life; QoLISSY: quality of life of short-stature youth; WeeFIM: paediatric functional independence measure; WPAI:SHP: work productivity and activity impairment.

Children/adolescent HRQoL

- The QoLISSY questionnaire was completed by 67 children/adolescents and 108 parents, the PedsQL questionnaire by 105 children/adolescents and 97 parents, the WeeFIM for 104 subjects, and the APPT questionnaire by 50 adolescents
- In children, mean total QoLISSY and PedsQL scores were lower compared to general population
  - The mean overall (combined child and parent) QoLISSY total score (range: 0 [poor quality of life] to 100 [perfect quality of life]) was 58.0 (SD: 21.8)
  - Most impacted QoLISSY dimensions were physical score and psychosocial score **(Figure 1)**
  - The mean PedsQL total score (range: 0 [poor health-related quality of life] to 100 [perfect health-related quality of life]) was 69.3 (SD: 16.3) for the child version **(Figure 2)** and 67.6 (SD: 16.8) for the parent version

Figure 1. Child QoLISSY — mean scores

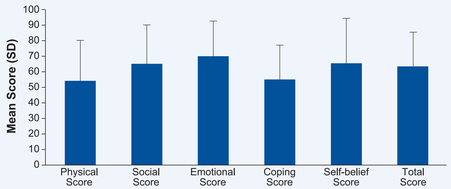
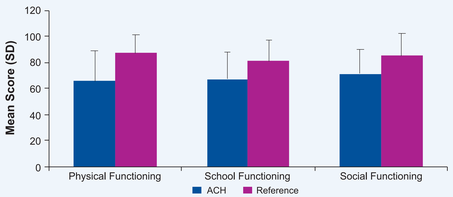


Figure 2. Child PedsQL: Dimensions with the lowest mean scores



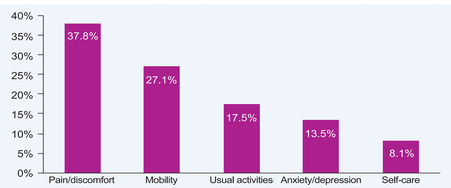
PedsQL: score ranged from 0 to 100. Child-only data presented; the same three dimensions were identified in the parent data as those with the biggest difference versus reference. ACH: achondroplasia.

- The mean WeeFIM overall total score (range: 18 [total assistance] to 126 [complete independence]) was 112.7 (SD: 13.3), indicating a moderate impact of achondroplasia on functional independence
- Per APPT questionnaire, 58.6% of adolescents reported at least 1 pain site and 32.9% reported ≥3 pain sites

Adult HRQoL

- Of 74 adult participants, 74 completed the EQ-5D-5L and NHP questionnaires, 72 completed the BPI-SF, and 73 completed the WPAI:SHP
- The mean overall HRQoL was lower than in the general population
  - EQ-5D visual analogue scale (VAS) and EQ-5D index scores (n=74) were lower than the mean values in the reference population (73.9 vs. 80.1 and 0.7 vs. 0.9, respectively)
  - The mean NHP total score (range: 0 [good subjective health status] to 100 [poor subjective health status]) was 16.0 (SD: 18.9), the most impacted domains being physical mobility (20.9 [SD: 21.7]), energy (20.9 [SD: 30.7]), and pain (18.5 [SD: 26.7])
- A high proportion of adults reported high pain burden
  - 37.8% reported moderate to extreme problems on the EQ-5D-5L pain/discomfort domain **(Figure 3)**
  - 70.3% of participants reporting at least 1 pain site and 41.9% reporting ≥3 pain sites (n=72) on the BPI
- There is a high impact on mobility, with 27.1% of adults reporting moderate to extreme problems on the EQ-5D mobility domain **(Figure 3)**

Figure 3. Proportion of adults reporting moderate or extreme problems (EQ-5D-5L)



- Work productivity and activity are impacted
  - Mean percentage of impairment while working due to achondroplasia (impact on productivity over the past week) was 15.4%
  - Mean percentage of activity impairment due to achondroplasia (impact on the ability to do regular daily activities, other than work at a job, over the past week) was 26.6%

Exploratory analysis of associations between HRQoL and clinical characteristics

- Low-moderate Pearson's correlations (0.32–0.46) were seen between QoL and height and height Z-score in 3/7 QoLISSY domains and the total score and 2/3 WeeFIM domains and the total score **(Table 4)**
  - The strongest correlations were between physical domain and height Z-score on QoLISSY and mobility and height Z-score on WeeFIM

Table 4. Summary of correlations from exploratory analysis

Disease-specific	Pearson's coefficients: Age	Pearson's coefficients: Height	Pearson's coefficients: Z-score	Point-biserial coefficients: Sex, female
QoLISSY Number of patients: Children ≤16 years of age n = 64 (95%)				
Physical score	0.223*	0.387***	0.466***	0.001
Social score	0.240*	0.366***	0.345***	-0.014
Emotional score	0.150	0.203*	0.229*	-0.049
Coping score	0.153	0.052	-0.230*	-0.050
Beliefs score	0.060	0.159	0.324***	-0.039
Future score	-0.003	0.117	0.268**	-0.112
Effects score	0.237*	0.232*	0.059	0.113
Total score	0.230*	0.361***	0.394***	-0.021
WeeFIM Number of patients: Children ≤16 years of age n = 55 (95%)				
Self-care score	0.311**	0.423***	0.339***	−0.083
Mobility score	0.273**	0.399***	0.404***	−0.093
Cognition score	0.089	0.076	0.036	−0.050
Total score	0.300**	0.407***	0.351***	−0.092

Generic	Pearson's coefficients: Age	Pearson's coefficients: Height	Pearson's coefficients: Z-score	Point-biserial coefficients: Sex, female
EQ-5D-5L Number of patients: Adults >16 years of age n = 55 (100%)				
Mobility score	0.265*	−0.002	−0.080	−0.173
Self-care score	0.107	−0.162	−0.187	−0.068
Usual activities score	0.239*	−0.139	−0.135	0.032
Pain/discomfort score	0.371***	0.110	0.058	−0.130
Anxiety/depression score	0.096	−0.239*	−0.276**	−0.075
Utility	−0.262*	0.083	0.143	0.133
VAS score	−0.292**	−0.180	−0.158	0.066
PedsQL 4.0 GCS Number of patients: Children ≤16 years of age n = 61 (97%)				
Physical score	−0.085	0.041	0.273**	−0.008
Emotional score	0.025	0.054	0.100	−0.005
Social score	0.123	0.200	0.177	−0.159
School score	−0.171	−0.054	0.255**	0.123
Psychosocial score	−0.015	0.076	0.218*	−0.011
Total score	−0.048	0.068	0.266**	−0.011

*** p<0.01, ** p<0.05, * p<0.1

Negligible correlation (0.0 to <0.3) | Low correlation (0.3 to <0.5)

N = 125. Participants with height measurement within 1 year of enrollment and medical history for past 5 years only were included in these analyses.

Conclusions

- LIAISE provides a comprehensive snapshot of quality of life/activities of daily living in the achondroplasia population across different age groups
- Participants generally rated themselves lower than general population norms (where available), especially in physical and psychosocial domains across several questionnaires
- These data suggest that achondroplasia negatively impacts HRQoL of patients and that there is a high burden of disease and unmet need
- Correlations between QoL and height Z-score indicate there may be an association between height and HRQoL
- Study limitations include: small sample sizes; participants recruited through healthcare sites, potentially excluding those with no/minimal medical conditions; results may not be representative of all individuals with achondroplasia

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