Health-related quality of life (HRQoL) in achondroplasia:

findings from LISA (Life Impact Study on Achondroplasia), a multinational and observational study in Latin America

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Commercial disclosure and conflicts of interest

- BioMarin: Consulting payments, research grants and speaker fees

Lifetime Impact Study for Achondroplasia (LISA)

4 sites

3 Latin American countries

Multinational epidemiological, observational, retrospective and cross-sectional study in 175 patients with achondroplasia.

General objective of the study:

Describe the disease's impact in individuals with achondroplasia by evaluating the health-related quality of life (HRQoL), clinical and socioeconomic burden, and healthcare resource use.

COLOMBIA (Population = 50.88 million)

Dr. Pablo Roselli, PI, Pediatric Orthopedist
Fundación Cardioinfantil (general/family practice)

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BRAZIL (Population = 212.60 million)

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Instituto Fernandes Figueira
(maternal and pediatric)

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Instituto da Criança (pediatric)

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ARGENTINA (Population = 45.38 million)

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Responsible Party: BioMarin Pharmaceutical
ClinicalTrials.gov Identifier: NCT03872531 History of Changes
Other Study ID Numbers: 111-502

Relevance of the LISA study

Achondroplasia is the most common form of short limb dwarfism[1]

Birth prevalence in South America 3.2 per 100,000[2-4]

Limitations of the existing data on health-related quality of life (HRQoL) in Latin America

- Small studies, with limited number of patients;
- Lack of information regarding the link of the clinical manifestations of disease to:
  - Impact on HRQoL over a lifetime of living with the disease;
  - Medical or social burden of disease

Specific objectives of LISA were to describe the associations between the recorded clinical characteristics of the disease and:

- Patient- and parent-reported outcome measures of HRQoL:
  - Functional impact of the disease;
  - Psychosocial impact: psychological and socialization;
  - Comorbidities, medical and surgical complications;
  - Use of health services;
  - Socio-economic impact;
- Clinical measures of pain;
- Describe the associations between recorded clinical measures of pain and HRQoL;
- Investigate the determinants of HRQoL measures with height within 1 year;

1. Horton WA, Hall JG, Hecht JT. Lancet. 2007;370(9582):162-172; 2. Foreman PK, van Kessel F, van Hoorn R, et al. Am J Med Genet A. 2020 Oct;182(10):2297-2316; 3. Barbosa-Buck CO, Orioli IM, da Graça Dutra M, et al. Am J Med Genet A. 2012 May;158A(5):1038-45; 4. Cavalcanti DP, Fano V, Mellado C, et al. Am J Med Genet C Semin Med Genet. 2020 Dec;184(4):986-995.

Study design and methods

- **Study design:**
  - Multinational and observational study with a cross-sectional component assessing HRQoL:
    - Individuals was asked to complete a booklet of standardized questionnaires at study enrollment, referring to the self-perceived impact of the disease in their Quality of Life (QoL);
    - Enrollment period: Jan/2018 to Jul/2021.
  - Analysis of retrospective data:
    - Descriptive statistics of domain and total scores were compared to reference populations.

- **Eligibility:**
  - Inclusion Criteria:
    - Individuals with achondroplasia in Latin America (Brazil, Argentina and Colombia) aged ≥ 3 years;
  - Other Criteria:
    - Enrollment limited by age groups (in years) as follows: 3-5 (n=20), 6-10 (n=30), 11-15 (n=30), 16-20 (n=20), 21-30 (n=20), 31-40 (n=20), 41 and over (n=35);
    - To minimize confounding bias, number of participants with limb lengthening surgery was capped at 20%.

Child/Adolescent and adult questionnaires applied in the study with the outcome domains assessed

	Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
Pediatric	PedsQL*	✓	✓	✓		✓	
	QoLISSY*	✓	✓	✓		✓	
	WeeFIM		✓				✓
	APPT				✓		
Adult	EQ-5D- 5L*	✓	✓	✓	✓		✓
	NHP	✓	✓	✓	✓	✓	
	BPI-SF				✓		
	WPAI						✓

QoLISSY, Quality of Life in Short Stature Youth; PedsQL, Pediatric Quality of Life Inventory Questionnaire; APPT, Adolescent Pediatric Pain Tool; WeeFIM, Pediatric Functional Independence Measure; WPAI, Work Productivity and Activity Impairment; BPI-SF, Brief Pain Inventory – Short Form; NHP, Nottingham Health Profile.

* Values for reference population available (average stature or other short stature conditions).

Demographic characteristics at time of enrollment

	Overall EAS (a), n=172
Participants per country, n (%)	
Brazil	94 (54.6)
Argentina	37 (21.5)
Colombia	41 (23.8)
Gender, n (%)	
Male	81 (47.1)
Female	91 (52.9)
Age (years)	
Median (25th, 75th Percentile)	16.0 (8.0, 31.5)
Age subgroups (years) (b), n (%)	
3-5	20 (11.6)
6-10	35 (20.3)
11-15	29 (16.9)
16-20	16 (9.3)
21-30	25 (14.5)
31-40	23 (13.4)
≥41	24 (14.0)
Limb lengthening prior to enrollment (c), n (%)	
Yes	12 (7.0)
Time since limb lengthening (years) (d)	
Median (25th, 75th Percentile)	6.4 (2.6, 10.2)

(a) Enrolled Analysis Set (EAS): included all consented subjects with a documented diagnosis of achondroplasia and medical records available for the 3 years prior to the date of enrollment;

(b) When date of birth is missing or only the year is provided, CRF collected age is used.

(c) Assessment closest to enrollment date.

(d) Time (years) since limb lengthening surgery = (date of enrollment - earliest date of limb lengthening surgery)/365.25.

Summary of the participants' reports compared to the reference population (when available)

Child/Adolescent questionnaires

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
PedsQL * [a]	Reduced [d]	Reduced [d]	Reduced [d]		Reduced [d]	
QoLISSY * [b,c]	Reduced [d]	Reduced [d]	Reduced [e]			
WeeFIM		No population norms – higher dependence in lower ages (5-7 years)				No population norms – higher dependence in lower ages (5-7 years)
APPT				Mild pain, multiple sites		

***** Present patient- and parent-reported outcomes; **a,** Reference population: average stature individuals; **b**, Reference population: other short stature conditions; **c**, Most affected domains were beliefs, coping and physical; **d**, Reduced compared with population norms; **e**, Expect in Female Child population from 8-12.

HRQoL and Psychosocial Burden are reduced in pediatric population

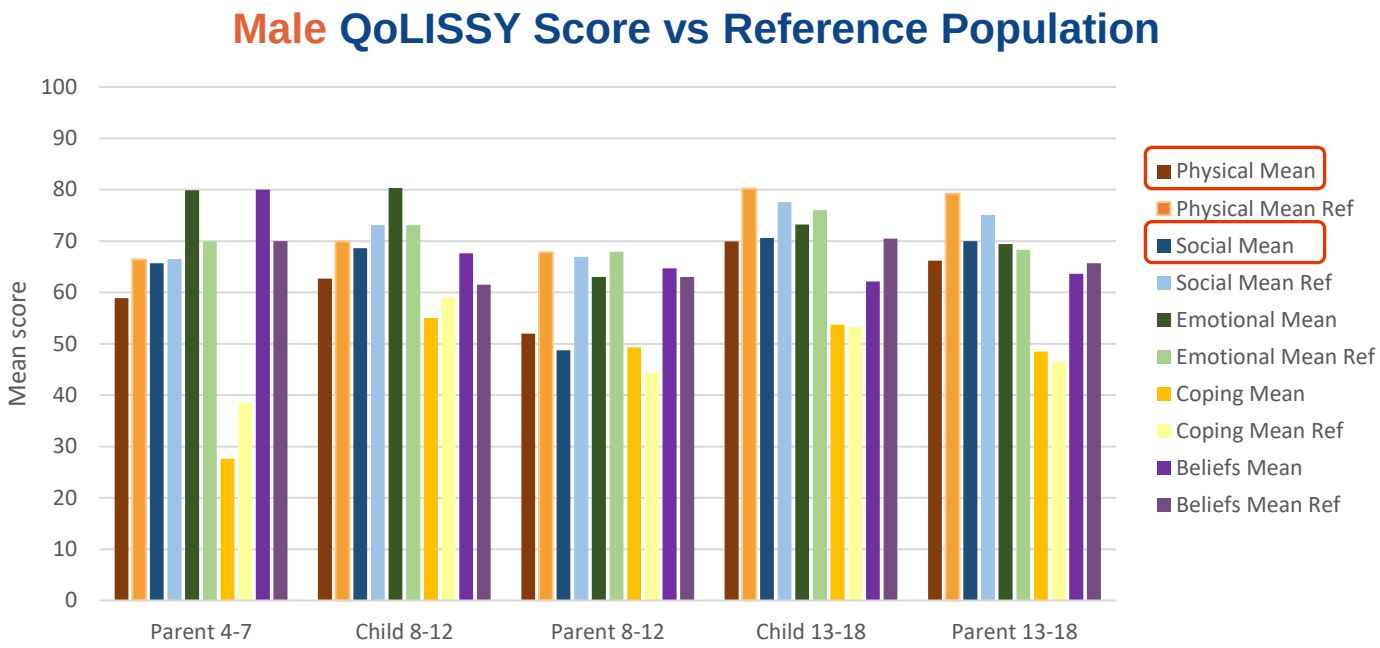
QoLISSY Mean total scores:

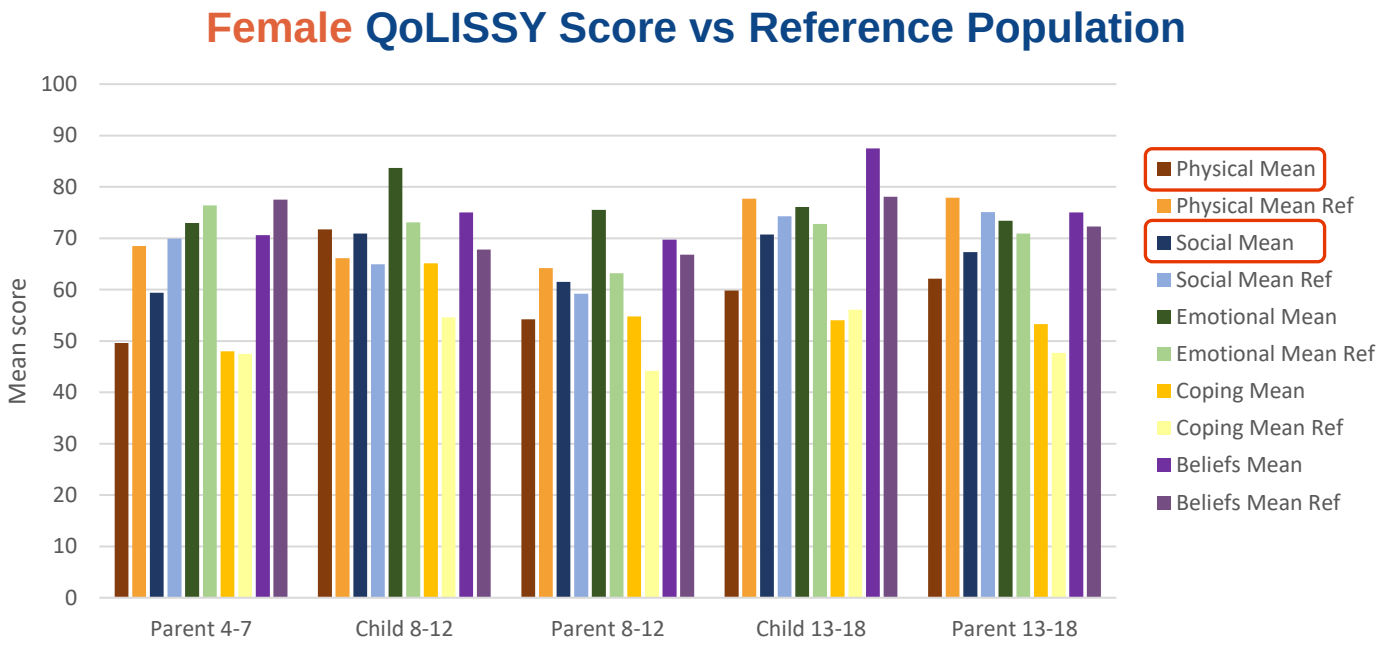
- 71.5 (SD: 17.5) for patients
  Ref mean: 83.8 (SD: 12.7)
- 63.9 (SD: 18.9) for parent proxies
  Ref mean: 82.7 (12.7)

- Most affected domains were physical, social, effect (parents) and total (child only).

➢ Reference population: average stature children;

➢ Range: 0 (Poor quality of life) to 100 (Perfect quality of life)

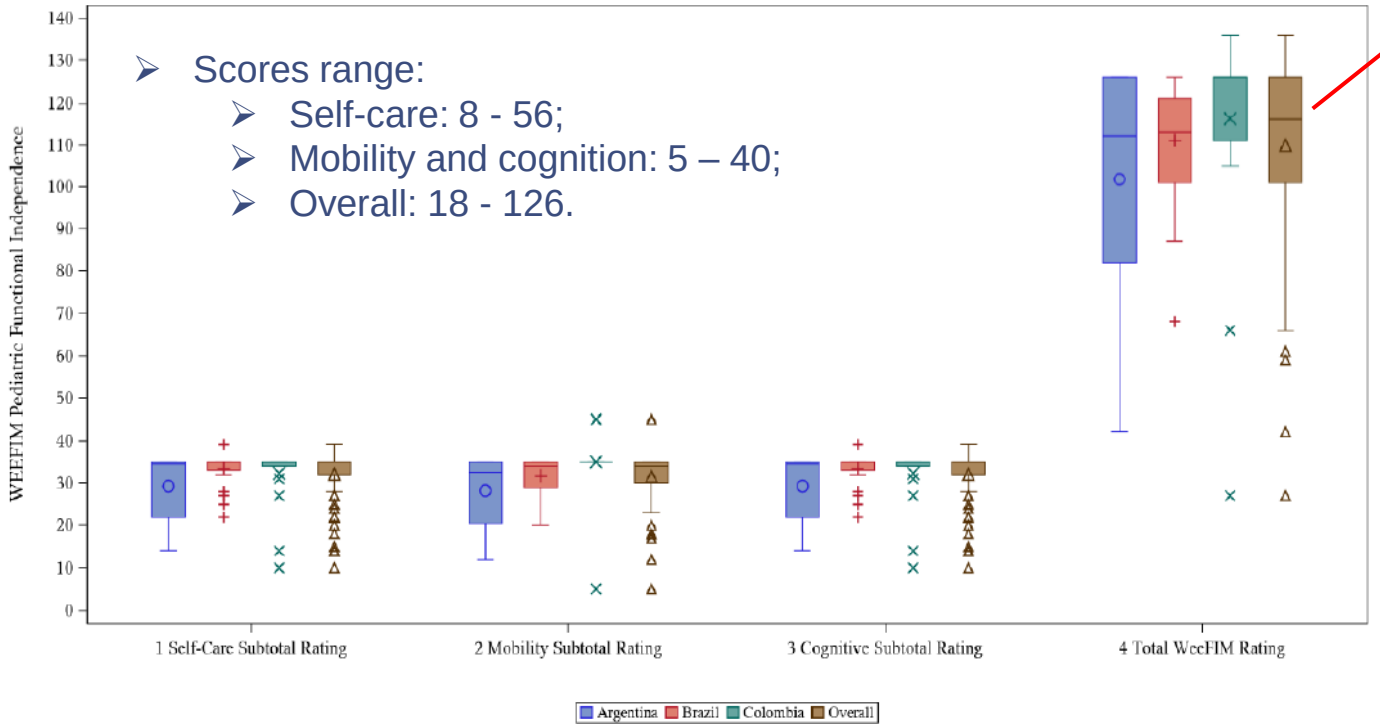




WeeFIM: Functional, independence and autonomy is negatively impacted by achondroplasia

- WeeFIM measures the functional skills and performance in daily activities in children with physical or general developmental limitations or restrictions [1];
- This questionnaire assess the need for assistance and the severity of disability.

Pediatric Functional Independence Measure



Age (n)	Overall WeeFIM score, Mean (SD)
Children and Adolescents	
5-7 (22)	95.9 (15.34)
8-12 (31)	117.2 (9.19)
13-17 (27)	124.1 (3.51)
Limb Lengthening Surgery	
5-7 (0)	-
8-12 (3)	119.0 (12.12)
13-17 (4)	126.0 (0.00)

- Low scores indicate “total assistance” while high scores indicate “complete independence”.

1. Ireland PJ, McGill J, Zankl A, et al. Dev Med Child Neurol. 2011 Oct;53(10):944-50.

Pain in adolescent pediatric population

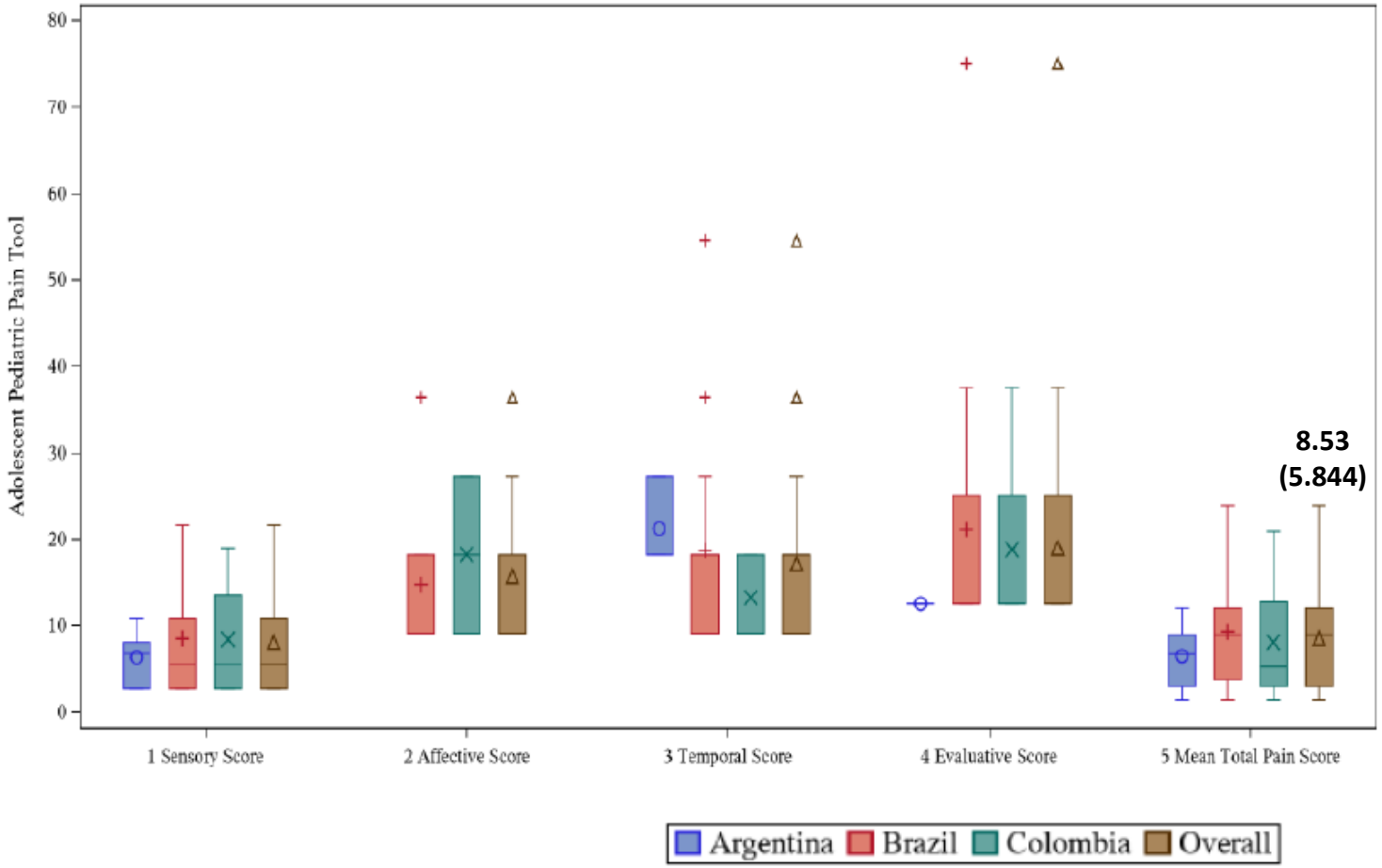
n=57 adolescent subjects (98.3%)

- 53.4% of adolescents reported at least 1 pain site;
- 10.3% reported pain in 3 sites.

- Accessed scores: sensory, affective, temporal, evaluative and mean total pain;
- Maximum score for all domains: 100
- Higher scores indicate a larger number of pain descriptors used.

Adolescent Pediatric Pain (APPT)

Questionnaire Results in Subjects Aged 8 to 17 Years, Mean (SD)



Summary of the participants' reports compared to the reference population (when available)

Adult questionnaires

Questionnaire	Quality of Life	Physical Function	Psychosocial Function	Pain	Emotional/ Coping	Activity Impact
EQ-5D- 5L[a]	Reduced [b]	20.3% Moderate to severe problems with mobility	26.6% Moderate or severe anxiety/depression	25.3% Moderate to severe pain or discomfort		17.8% Moderate to severe problems or unable to do usual activities
NHP [c]	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-SF				Mild pain, multiple sites		
WPAI						No population norms 13.8% reduction in work, 23.1% reduction in activities

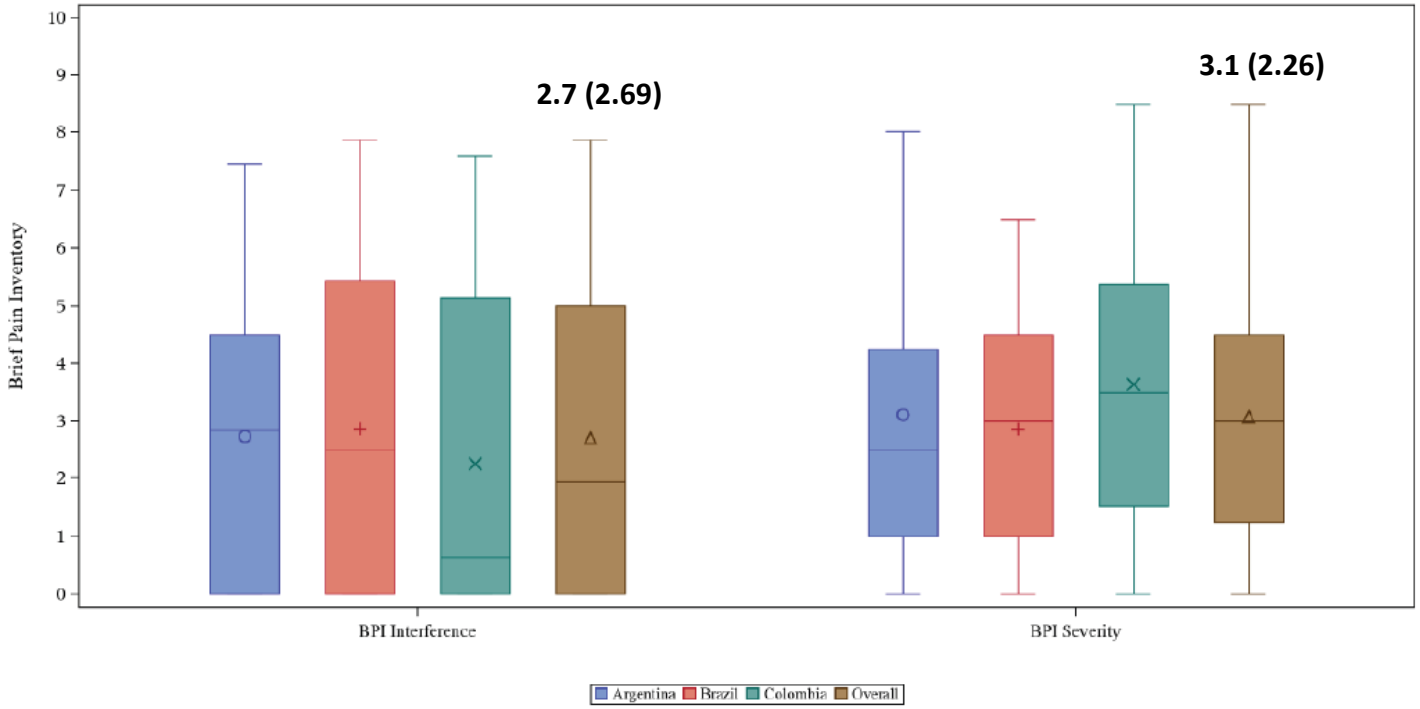
a, Reference population: average stature individuals; **b**, Reduced compared with population norms; **c**, Most negatively impacted domains were energy, pain and physical mobility.

Pain in adult population

- 73.4% of subjects reported experiencing pain not described as everyday minor aches and pain;

Brief Pain Inventory (BPI)

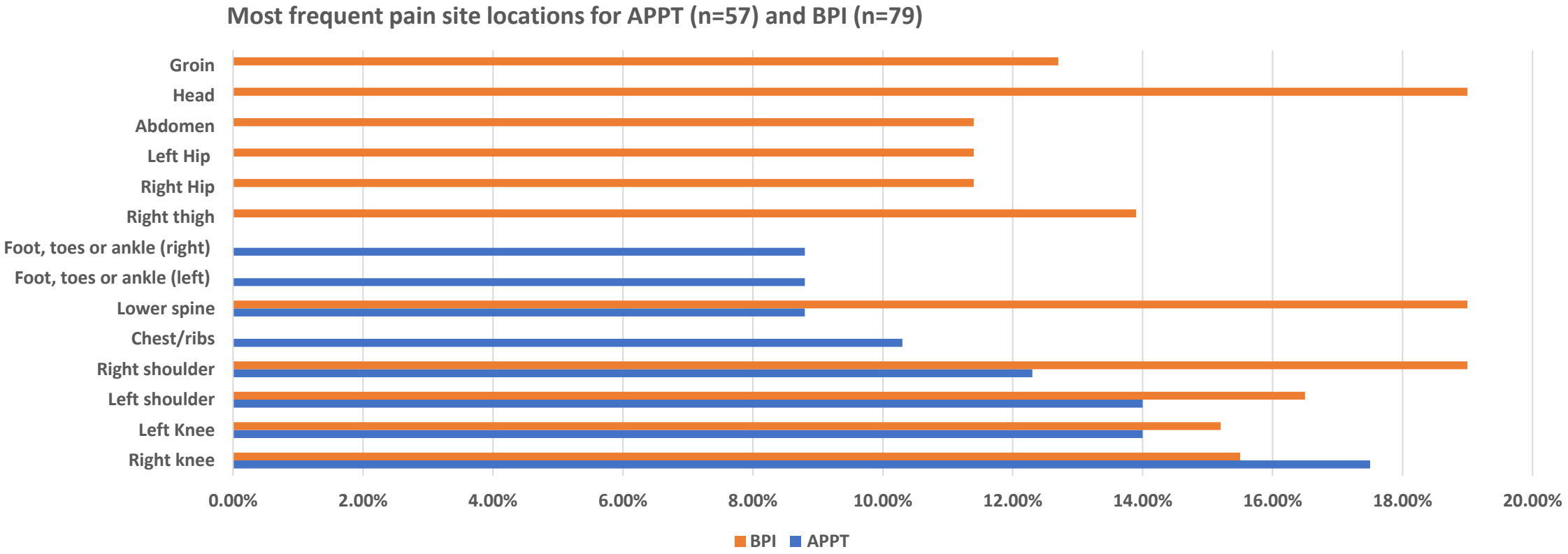
Questionnaire Severity Score and Interference Score, Mean (SD)



- Accessed scores: pain and interference;
- Pain: scores range from 0 (no pain) to 10 (pain as bad as one can imagine);
- Interference: scores range from 0 (no interference) to 10 (completely interferes);
  - Interference scores describes the impact of pain in mood, walking ability, normal work and housework, relations with other people, sleep and enjoyment of life.

Overall achondroplasia population reported mild pain

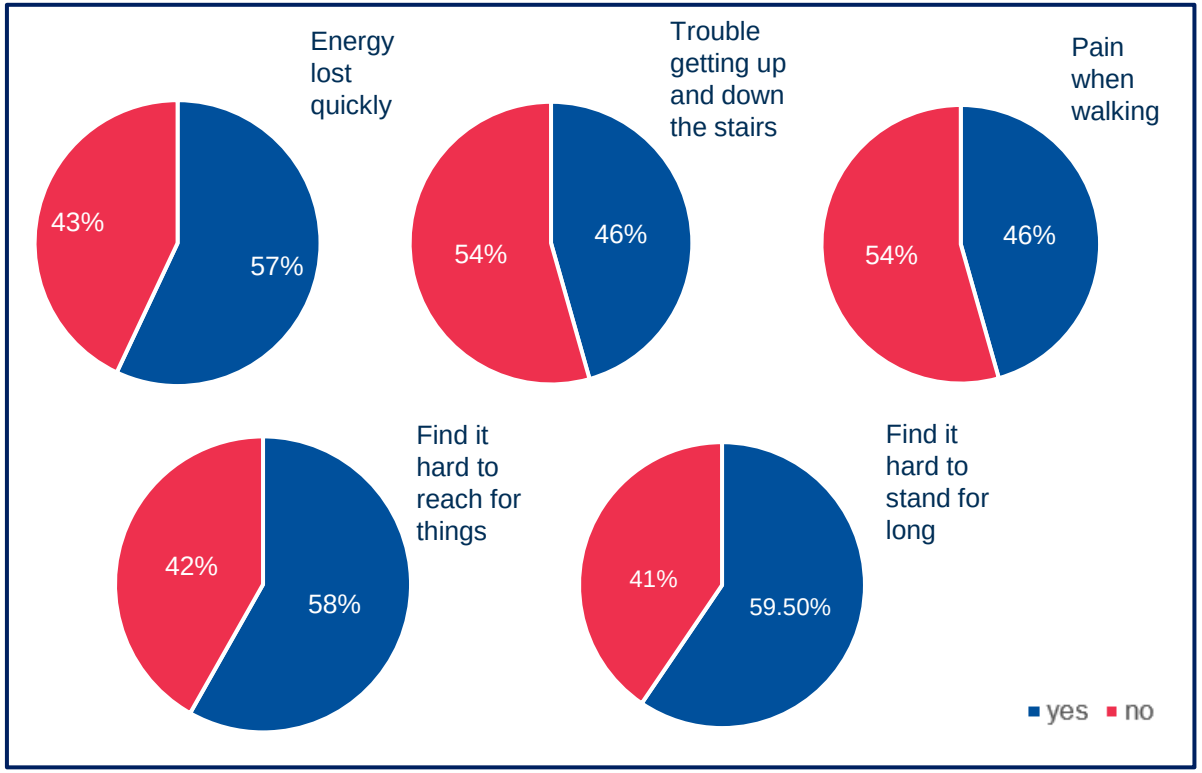
- 79 (73.4%) adult subjects reported “having pain other than everyday kinds of pain today” and mild pain regardless of age.
- 57 (98.3%) of adolescent subjects completed the APPT, reporting a mean (SD) number of pain sites of 1.9.



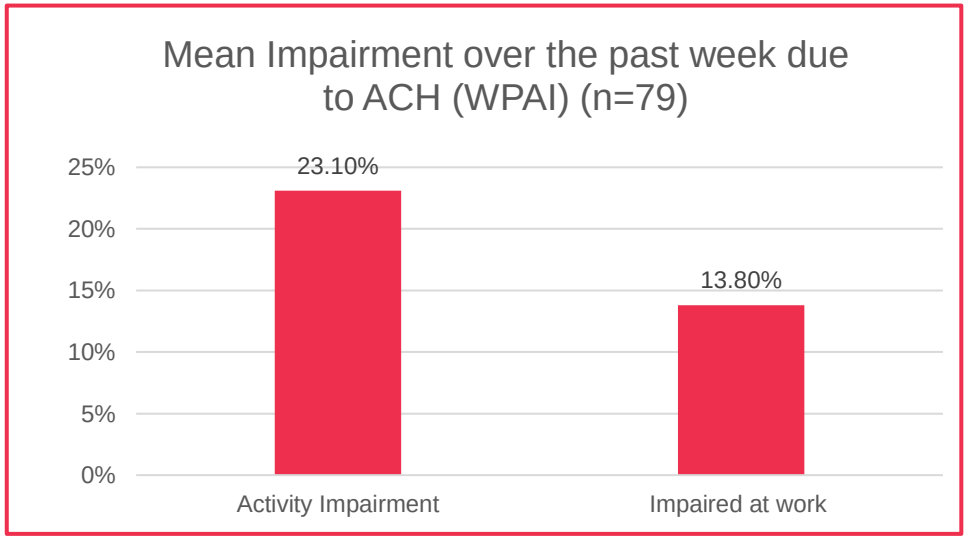
BPI mean severity score was on a scale of 0 (no pain) to 10 (pain as bad as subject can imagine). Mean interference score reports interference with general activity, mood, walking ability, normal work, social relations, sleep, and enjoyment of life on a scale of 0 (does not interfere) to 10 (completely interferes)

APPT: adolescent paediatric pain tool; BPI: brief pain inventory.

Activities of daily living and functionality of the overall achondroplasia population are restricted



- Adults and children reported reduced physical function or mobility in the EQ-5D, Peds-QL, QoLISSY, NHP and WeeFIM.
- Psychosocial function was also affected, as reported in the PEDS-QL, EQ-5D, QOLISSY and NHP.



WPAI productivity refers to the mean percent impact on productivity while working due to achondroplasia over the last week; WPAI activity refers to the mean percent impact of achondroplasia on ability to do regular daily activities, other than work at a job, over the past week.
ACH: achondroplasia; EQ-5D: EuroQoL 5-dimension QoL questionnaire; NHP: Nottingham health profile; QOLISSY: quality of life of short-stature youth; WeeFIM: paediatric functional independence measure; WPAI: work productivity and activity impairment

Limitations of LISA

- Observational and retrospective design
  - Retrospective data review revealed gaps in medical records (with exception to the Argentinean pediatric site)
    - This study may underreport the medical burden and real-life experience of achondroplasia patients in Latin America;

- The COVID-19 pandemic caused delayed and unbalanced enrollment across countries and age groups, challenges in gathering complete medical records, and disruptions in planned monitoring activities;

- Due to the small number of sites involved in the study, generalization of results to a larger population should be made with caution.

Conclusions

- LISA study provides the largest set of data to date from Latin America on the lifetime impact of achondroplasia;
  - The study addresses the gaps in knowledge about clinical and socioeconomic burden of illness, HRQoL, psychosocial impact, and healthcare resource use for individuals with achondroplasia in Latin America;
  - Despite the diversity of patients and sites across the 3 countries that participated of LISA, assessments of QoL, WeeFIM and pain questionnaires were similar.
- LISA data demonstrates that subjects experience significant burden of illness across multiple domains, in which impact the HRQoL;
  - Despite not shown in this presentation, LISA also demonstrates substantial healthcare resource use along with medical and surgical interventions in patients with achondroplasia.
- The HRQoL of individuals with achondroplasia corroborates with European subjects in the LIAISE study [1].

1. Maghnie M, Semler O, Guillen-Navarro E, et al. Health-related quality of life (HRQoL) in achondroplasia: Findings from a multinational, observational study (LIAISE). Presented at the ACMG Annual Clinical Genetics Meeting; April 13-16, 2021..

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