Impact of achondroplasia on Latin American patients: a systematic review and meta-analysis of observational studies

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Abstract

Background: Achondroplasia (ACH), the most common form of disproportionate short stature, is caused by a pathogenic variant in the fibroblast growth factor receptor 3 gene. Recent advances in drug therapy for ACH have highlighted the importance of elucidating the natural history and socioeconomic burden of this condition. Recognition that there are many potential issues for the patient with ACH is the first step in planning cost-effective interventions in Latin America (LATAM), a vast geographic territory comprising countries with multicultural characteristics and wide socioeconomic differences. We conducted a systematic literature review to characterize the impact of ACH on affected individuals and on healthcare resources in LATAM countries.

Methods: Searches of the global medical literature as well as regional and local medical literature up to August 2020. Observational studies on patients with ACH from any LATAM country. Pairs of reviewers independently screened eligible articles, extracted data from included studies, and assessed their risk of bias.

Results: Fifty-three unique studies (28 case series and cross-sectional studies and 25 case reports) including data on 1604 patients were eligible. Of these studies, 11 had data available for meta-analysis. Both premature mortality and all-cause mortality in the pooled studies was 15% [95% Confidence Interval (CI) 1.0E−3 to 0.47; I² = 82.9%, p = 0.0029; three studies, n = 99 patients]. Frequency of cardio-respiratory-metabolic disorders was 17% [95% CI 0.04–0.37; I² = 90.3%, p < 0.0001; four studies, n = 230 patients]; nervous system disorders was 18% [95% CI 0.07–0.33; I² = 84.6%, p < 0.0001; six studies, n = 262 patients]; ear, nose, throat and speech disorders was 32% [95% CI 0.18–0.48; I² = 73.4%, p = 0.0046; five studies, n = 183 patients]; and spinal issues including stenosis, compression and associated pain was 24% [95% CI 0.07–0.47; I² = 91.3%, p < 0.0001; five studies, n = 235 patients].

Conclusions: There is currently evidence of high clinical burden in ACH patients in LATAM countries. Establishing the impact of ACH provides the necessary foundation for planning tailored and effective public health interventions.

Keywords: Achondroplasia, Skeletal dysplasia, Latin America

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However, data from the Latin American Collaborative Study of Congenital Malformations (ECLAMC) estimates a similar incidence in non-LATAM countries of 0.43 in 10,000 or 0.45 in 10,000 [8].

In LATAM countries, ACH is often assumed to be compatible with a healthy and productive life. However, current evidence indicates that ACH is associated with a range of medical complications including obstructive sleep apnea, spinal stenosis, chronic pain, and cervicomedullary compression with subsequent risk of high surgical burden and death [9, 10]. In addition, ACH patients may experience a number of socioeconomic issues such as social isolation, lower self-esteem, less education, and lack of employment opportunities [11–15]. Management of all these complications can be challenging as it requires multidisciplinary intervention.

Recognition that there are many potential issues for the patient with ACH is the first step in planning cost-effective interventions in LATAM, a vast geographic territory comprising countries with distinct cultures, socioeconomic structures, and public healthcare systems. However, due to the paucity of published studies on LATAM patients with ACH, particularly in the English-language medical literature, there is currently limited understanding of the impact of ACH on affected individuals and on healthcare systems in this region of the world. Moreover, of the published studies, the majority have stemmed from single centres with small patient cohorts. Furthermore, despite the growing evidence in the English-language medical literature of the clinical and psychosocial burden among patients with ACH, published studies are not exclusively based on LATAM populations and therefore the findings may not necessarily be generalizable to LATAM patients, and the experiences of living with ACH may not be the same across different regions of the world. We therefore conducted a systematic literature review and meta-analysis to better specifically characterize the impact of ACH in LATAM countries at the level of patient-important outcomes as well as at the economic (socioeconomic, healthcare utilization) level.

Eligibility criteria
We included any epidemiological observational study (e.g., cohort, case-control, nested case-control, cross-sectional studies, prospective case series, case report) on patients with ACH from any LATAM country (e.g., Brazil, Argentina, Colombia, Mexico, Costa Rica, Peru), regardless of whether they reported our pre-defined patient-important outcomes and/or economic burden outcomes defined below. A diagnosis of ACH in patients in the included studies was based on genetic confirmation and/or clinical diagnosis of ACH (clinical examination and/or radiological assessment).

We excluded studies that evaluated patients with only hypochondroplasia as well as commentaries, reviews, off-topic studies, and those with co-occurrence of ACH and another syndrome.

For patient-important outcomes, we were interested in investigating the following:

- Mortality:
  - Premature mortality defined as sudden death within 1 year of age;
  - All-cause mortality; and
  - Cardiovascular mortality.

- Physical comorbidities:
  - Cardio-respiratory-metabolic disorders (e.g., cardiovascular diseases, obstructive sleep apnea, obesity).
  - Nervous system disorders (e.g., cervicomedullary compression, gross motor delay);
  - Ear, nose, throat and speech disorders (e.g., otitis media, hearing loss, upper airway obstruction, speech delay);
  - Spinal issues including stenosis, compression and associated pain (e.g., chronic back pain, symptomatic spinal stenosis, thoracolumbar kyphosis, lumbar hyperlordosis);
  - Orthopedic complications (e.g., chronic leg pain, wheelchair bound, limited elbow extension);
  - Pain;
  - Perinatal complications (e.g., premature birth, hospitalization); and
  - Others (e.g., hypothyroidism, difficulty in performing epidural anesthesia for cesarean delivery, tumours, blood transfusion, length of hospitalization).

- Humanistic:

Materials and methods
Our review followed recommendations for systematic reviews and meta-analyses (PRISMA) [16] of observational studies in epidemiology (MOOSE) [17] statements. This systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42020204963.
- Psychosocial disorders: depression, anxiety, bullying, isolation, hopelessness, somatization, humiliation, stigma, perception about their psychosocial life, etc., measured by non-validated and validated questionnaires as defined by the included studies;
- Delayed self-care skills (e.g., toileting, cup-drinking);
- Suicide attempts, and/or suicide rates; and
- Social adaptation challenges;
- Impact of the disease on patient and/or caregiver health-related quality of life, activities of daily living, work productivity, education, employment, social, and so forth; and
- Quality of life measured by non-validated and validated questionnaires, as defined by the included studies, such as the Brief Pain Inventory-Short Form (BPI-SF) Questionnaire, the Quality of Life Short Stature Youth (QoLiSSY) Questionnaire, and the Pediatric Quality of Life Inventory (Ped-QL).

At the economic level, we were interested in investigating the following outcomes:

- Socioeconomic burden (e.g., securing employment) measured by non-validated and validated questionnaires, as defined by the included studies such as the Work and Productivity and Activity Impairment (WPAI-SHP).
- Environmental burden:
  - Lack of equipment, furniture, toys, shoes, etc., matching anthropometric limitations;
  - Limitation of physical access to transportation modalities;
  - Adaptation to standard transport equipment and;
  - Challenges in physical activity.
- Health economic impact:
  - Direct and/or indirect costs, treatment costs, health care resource use, cost of comediations, hospitalizations.

**Data source and searches**

Using Medical Subject Headings (MeSH) based on the terms “achondroplasia” and “skeletal dysplasia” (Additional file 1: Table S1) we performed the search in the global medical literature using the Medical Literature Analysis and Retrieval System Online (MEDLINE, via PubMed, from 1946 to August 2020), Excerpta Medica Database (EMBASE, via Elsevier, from 1974 to August 2020), Cochrane Central Register of Controlled Trials (CENTRAL, via Wiley, issue 8, 2020), and Web of Science (to August 2020).

We also conducted the search using both Spanish and English terms in the regional and local medical literature using Latin American and Caribbean Health Sciences Literature (LILACS, 1982 to August 2020), Scientific Electronic Library Online (SciELO, 1997 to August 2020), SciVerse Scopus via Elsevier (to August 2020), the Spanish Bibliographic Index of the Health Sciences (IBECS, 1983 to August 2020), National Bibliography in Health Sciences Argentina (BINACIS, to August 2020), Caribbean Health Sciences Literature (MedCarib, to August 2020), National Medical Sciences Information Center of Cuba (CUMED, to August 2020), and the Brazilian Bibliography of Dentistry (BBO to August 2020). The date of the last search was August 18, 2020.

We also searched the gray literature including ProQuest Dissertations & Theses Global (1989 to 2020), the National Health Surveillance Agency (ANVISA), Brazilian Digital Library of Theses and Dissertations (BDTD), Latindex Redalyc Latam, Mexico National Institute of Pediatrics website, and conference proceedings. In addition, reference lists of relevant primary studies were hand searched and experts in the field were contacted to obtain additional unpublished data.

We did not impose any language or year restrictions. The search strategy was adapted for each database to achieve more sensitivity. Duplicate records across databases were removed.

**Selection of studies**

Reviewers independently screened all titles and abstracts identified by the literature search using online software Covidence (https://www.covidence.org), obtained full-texts articles of all potentially relevant studies, and evaluated them against the eligibility criteria. Reviewers resolved disagreements by discussion or, if necessary, with third party adjudication. We also considered studies reported as abstracts; however, those that did not contain data to extract were excluded from the review. We recorded the selection process and completed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Fig. 1).

**Data extraction**

Reviewers independently extracted the following data using a pre-standardized data extraction form: (1) first author and year of publication; (2) country; (3) study design; (4) scenario; (5) age, gender, and body mass index (BMI); (6) number of patients; (7) eligibility criteria; and (8) patient-important and economic outcomes, if available. We avoided double counting of participants where there were multiple publications in
the same population. If there was more than one published report of the same group of patients, the articles were analysed to verify whether they reported different outcomes. If they presented the same outcomes, we extracted the data from the most complete article. For studies that did not report BMI but provided height and weight we calculated this variable.
Risk of bias assessment
For cohort and case-control studies, we planned to assess risk of bias with a modified version of the Ottawa-Newcastle instrument [18] that includes confidence in assessment of exposure and outcome; however, there was no included study classified as either cohort or case-control study.

For cross-sectional studies, we assessed risk of bias with the AXIS tool [19], though we excluded some domains not applied to our review. For case series and case reports, we used the single tool from the Joanna Briggs Institute (JBI) critical appraisal checklist for case reports [20]. However, in our view, the structure of the response options in both AXIS and JBI instruments leaves much to be desired. Therefore, we modified the response options to “definitely yes” (low risk of bias), “partially yes” (not all information needed available), “unclear” (no information to judge), and “definitely no” (high risk of bias), and applied it to our form for risk of bias in both cross-sectional and case series studies.

Data synthesis and statistical analysis
We performed a systematic review of clinical studies with pooled analysis of proportions [21, 22], using the method of Stuart-Ord (inverse double arcsine square root).

Only case series and cross-sectional studies were considered for any quantitative analysis; case reports were excluded. We analyzed all outcomes as dichotomous variables with their respective confidence intervals (CI) of 95%. Since we expected that there were both clinical and methodological differences among the included studies, a random-effects model [23] was used to perform the pooled analysis of proportions. A statistically significant difference between two interventions required that their combined 95% CIs did not overlap [21, 22]. We calculated weighted mean and pooled measure of variability (standard deviation) for quality of life in the Cervan et al., 2008 [24] study as this study presented data of quality of life (QoL) for physical, psychological, social, environmental domains. The meta-analysis was performed with the StatsDirect software, version 2.8.0. (StatsDirect Ltd, Altrincham, Cheshire, UK).

Because of the very sparse data on this rare condition, when there was more than one report of the same type of burden outcome in the same study, we obtained the mean or median value from the subtype of outcome for the proportional meta-analysis to avoid selection bias. For example, on cardio-respiratory-metabolic disorders outcome, one study could report excessive snoring (number of events per number of total patients, 1/39), obesity (4/39), adenotonsillectomy (5/39), sleep disturbance (21/39), as well as sleep apnea (39/39). In this example, the median value used would be adenotonsillectomy (5/39).

Subgroup and sensitivity analyses
We planned to perform subgroup analyses if there was a minimum of two studies in each category: (1) LATAM countries (e.g., Brazil versus Argentina); (2) adults versus children; however, there was an insufficient number of studies to allow for these assessments.

We performed a sensitivity analysis to explore causes of heterogeneity of the results, excluding studies according to study designs (i.e., case series versus cross-sectional studies).

Heterogeneity assessment and publication bias
We investigated heterogeneity using the chi-square test and the I² statistic [25]. An I² value of 0–40%, 30–60%, 50–90% or 75–100% was interpreted as not important, moderate, substantial or considerable heterogeneity, respectively, and significance was assumed when I² was > than 50% with a p < 0.1.

There was an insufficient number of studies (at least 10 or more) to allow for assessment of publication bias through visual inspection of funnel plots.

Results
Study selection
Our initial searches identified 4,149 citations. All were from electronic databases, except for ten studies identified through grey literature. After we removed duplicates from different databases, we retained 3,903 potentially relevant articles for further assessment. After reading titles and abstracts, 87 articles were retrieved as full text for further assessment. After screening the full texts, we included 53 clinical studies with one further publication. We excluded 32 studies after reviewing the full papers. The reasons for exclusion are listed in the PRISMA flow diagram (Fig. 1). The total number of included studies is 53 with one further publication, and from these 11 contributed to meta-analysis.

Eight of the included studies were published only as an abstract [26–33], and five studies as theses [34–38]. The remainder of the included studies (n = 40) was published as full-text articles [5, 6, 24, 39–74]. One study [75] was published as full-text with an additional publication in abstract format [76]. When information regarding risk of bias or other aspects of methods was unavailable, we attempted to contact study authors for additional information.

Study characteristics
Tables 1 and 2 summarize the key characteristics from those studies that reported at least one patient-important or economic outcome. Regarding study design, four were case series [26, 34, 35, 73], 24 cross-sectional studies [5, 6, 24, 29, 36–38, 40, 45, 48, 50–54, 56, 58, 60, 61, 66, 69,
Table 1  LATAM ACH studies evaluating patient-important or economic burden outcomes not accountable for the meta-analysis

| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|-----------|----------------|-------------------|----------------------------------------|----------------------------|------------------|
| Cervantes [35] | Central America | Mexico | Rehabilitation service of the National Institute of Pediatrics | 7 | 9 | 42.85 | NR | Patients with previous lumbar spine instrumentation, patients with abdominal skin lesions, patients undergoing surgical procedures and abdominal exercises one month before the proposed date for starting physiotherapy | Individual | Spinal issues including stenosis, compression and associated pain | Individual |
| Dantas and Medeiros [26] | South America | Brazil | Medical Genetics Service at Alcides Caneiro University Hospital, Federal University of Campinas Grande | NR | NR | NR | NR | NR | Individual | Quality of life | Others |
| Barbosa-Buck et al. [6] | South America | Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Uruguay and Venezuela | Hospitals from nine South American countries | 68 | NR | NR | NR | NR | Individual | Premature mortality | Perinatal mortality |
| Cervan et al. [24] | South America | Brazil | Small People Association of Brazil (AGPB) | 21 | 32.70 (11.18) | 61.90 | 33 (6.96) | NR | Individual | Quality of life | Physical; psychological; social; environmental |
| Gomez et al. [58] | South America | Colombia | Leather Design and Manufacturing Center | 8 | NR | NR | NR | NR | Population | Environmental burden | Adaptation of shoes, health economic impact |
| Lima [38] | South America | Brazil | Previously agreed location in the city of Sao Paulo | 7 | NR | 14.28 | NR | NR | Population | Psychological impact | Humiliation; stigma; recognition |
| Fano et al. Orphanet Journal of Rare Diseases (2022) 17:4 | | | | | | | | | | Socioeconomic burden | Labor market |
| Author/Year | LATAM country | South or Central America | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|-------------|---------------|--------------------------|----------|---------------|------------------|-----------|----------------|-------------------|--------------------------------------|------------------------|-------------------|
| Rocha and Wagner [69] | South America | Brazil | NR | 8 | NR | NR | NR | NR | Individual / Population | Orthopedic complications | Joint mobility |
| Casereport studies | | | | | | | | | | Psychosocial complications | Perception of their psychosocial life |
| Abrão et al. [39] | South America | Brazil | NR | 1 | 29 | Female | 95.18 | NR | Individual | Cardio-respiratory-metabolic disorders, and spinal issues including stenosis, compression and associated pain, and others | Use of a bronchofibroscope |
| Arlet et al. [41] | Central America | Mexico | Orthopedic Clinic, Benemérita Universidad Autónoma de Puebla | 1 | 8 | Female | NR | NR | Individual | Others | Horizontal overlap and crossbite |
| Benavides et al., 2018 [42] | South America | Colombia | NR | 1 | 23 | Female | 36.76 | NR | Individual | Pregnant patient | Cardio-respiratory-metabolic disorders |
| | | | | | | | | | | Obesity, difficulty airway, difficulty ventilation and intubation, postoperative pulmonary complications, and cardiovascular complications such as risk of pulmonary hypertension crisis, acute heart failure, peroperative myocardial infarction during general anesthesia |
| | | | | | | | | | | Spinal issues including stenosis, compression and associated pain |
| | | | | | | | | | | Neck instability and risk of spinal cord compression with neck hyperextension, and difficult spinal and epidural puncture during regional anesthesia |
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|----------|---------------|-------------------|-----------------------|----------------------|------------------|
| Calderón et al. [43] | Central America | Cuba | University polyclinic "Ana Betancourt" | 1 | 25 | Female | NR | NR | NA | NA | NA |
| Carbia et al. [44] | South America | Argentina | Clinical Medical and Dermatology Divisions, Hospital "José María Ramos Mejía", Buenos Aires | 1 | 83 | Female | NR | NR | Individual | Others | Cicatricial metastasis as the presenting sign of squamous cell esophagus carcinoma |
| Carmen et al. [46] | South America | Chile | Obstetrics Service of the Ambato Regional Teaching Hospital | 1 | 29 | Female | 27.54 | NR | Individual | Pregnant patient | Perinatal complications | Moderate anemia and cholecystitis |
| Carolina et al. [47] | South America | Chile | | NR | 1.10 | Female | NR | NR | Individual | Spinal issues including stenosis, compression and associated pain | Nervous system disorders | Aqueductal stenosis with symptomatic spinal cord compression | Hydrocephalus |
| Castro [48] | South America | Brazil | Methodist University of Piracicaba (UNIMEP) | 1 | 28 | Female | 28.47 | NR | Individual / Population | Pain | Complaints of lower back and leg pain after a period of walking and low back pain caused by hyperlordosis | Varus foot |
| Eusebio and Vidal [55] | Central America | Dominican Republic | | NR | 4 | Female | NR | NR | Individual | Spinal issues including stenosis, compression and associated pain | Orthopedic complications | Lumbar hyperlordosis | Bilateral femoral elongation surgery |
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|-----------|----------------|------------------|---------------------------------------|------------------------|-----------------|
| Frade et al. [57] | South America | Brazil | University Hospital of Brasilia | 1 | 0.1* | Female | 18.5 | NR | Individual | Perinatal complications | Needed positive pressure ventilation during birth, and during hospitalization, jaundice occurred |
| Galego et al. [27] | South America | Brazil | NR | 1 | 32 | Female | 41.6 | NR | Individual | Perinatal complications | Emergency cesarean section due to umbilical cord prolapse |
| Hernández-Motino et al. [59] | Central America | Mexico | Children's Hospital of Mexico Federico Gómez | 1 | 5 | Female | NR | NR | Individual | Cardio-respiratory-metabolic | Pulmonary arterial hypertension, apnea, and respiratory arrest, necessitating mechanical ventilation, making extubation impossible due to weakness of chest muscles |
| Jesus et al. [28] | South America | Brazil | Charitable Health Association of Northeast Paraná Norospar, Umuarama, PR | 1 | 16 | Female | 37.5 | NR | Individual | Perinatal complications | Nervous system disorders, delayed psychomotor development |
| | | | | | | | | | | Orthopedic complications | Limb functional limitation |
| | | | | | | | | | Spinal issues including stenosis, compression and associated pain | Compression of the cervicospinal canal |
| | | | | | | | | | Others | Vesicostomy for neurogenic bladder |
| | | | | | | | | | Pain | Hypotension and dyspnea | Pain at birth |
Table 1 (continued)

| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|-----------|----------------|-------------------|-------------------------------|------------------------|-----------------|
| Medina et al. [62] | South America | Paraguay | Pediatric Service Hospital Central, Institute of Social Security, Pediatric Intensive Care Unit | 1 | 2.6 | Female | NR | NR | Individual | Cardio-respiratory-metabolic disorders | Hospitalized for serious respiratory symptoms, admitted to pediatric ICU with assisted ventilation |
| Morais et al. [63] | South America | Brazil | Anesthesiology Department, Hospital Lifecenter, Belo Horizonte | 1 | 47 | Male | NR | NR | Individual | Spinal issues including stenosis, compression and associated pain | Thoracic kyphosis and severe lumbar lordosis, in addition to surgical scar on the lumbar region |
| Muratore and Viollaz [64] | South America | Argentina | Britânico Hospital, Buenos Aires | 1 | 21 | Female | 37.19 | NR | Individual | Orthopedic complications | Bilateral femoral elongation surgery |
| Nascimento et al. [30] | South America | Brazil | Federal Hospital of Lagoa | 1 | 51 | Female | 48.6 | NR | Individual | Cardio-respiratory-metabolic disorders | Obesity and video-laparoscopic gastroplasty |
| Oliveira et al. [31] | South America | Brazil | Vera Cruz Hospital, Campinas / SP | 1 | 33 | Female | 37.72 | NR | Individual | Pregnant patient | Peritoneal plane pain at birth |

 Others: Hypothyroidism and difficulty in epidural anesthesia for cesarean
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|--------------|----------------|-----------|---------------|-----------------|---------------------|---------------------|------------------|
| Palmira et al. [65] | Central America | Cuba | Gyneco-obstetric University Hospital “Ana Betancourt de Mora” Camagüey | 1 | 20 | Female | NR | NR | Individual | Pregnant patient | Cardio-respiratory-metabolic disorders | Obesity, bronchial asthma, and respiratory difficulty during pregnancy |
| | | | | | | | | | | Lumbar hyperlordosis | |
| | | | | | | | | | Others | Twin pregnancy of 34 weeks preventing the patient to walk, to stand up, and no tolerance of supine decubitus, 10 days of hospitalization after complications at birth with cesarean section |
| Pimentel and Figueredo [67] | South America | Brazil | Professor Edgard Santos University Hospital Complex, Salvador | 1 | 73 | Male | 46.82 | NR | Individual | Others | Surgical treatment of colon adenocarcinoma, after surgery the patient was diagnosed with septic shock with an abdominal focus which required a new surgical approach, deep venous thrombosis, 30th day of hospitalization |
| Author, year                  | South or Central America | LATAM country                  | Scenario                                                                 | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria                                                                 | Individual and/or population outcomes                                                                 | Type of burden outcomes                                                                 | Specify outcomes                                                                 |
|------------------------------|--------------------------|--------------------------------|--------------------------------------------------------------------------|---------------|------------------|-----------|----------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Posada et al. [68]           | South America            | Colombia                       | NR                                                                       | 1             | 0.8*             | Male      | NR             | NR                                                                                   | Individual                                                                              | Pregnant patient                                                                 | Apnea, Spinal issues including stenosis, compression and associated pain          |
| Rudas et al. [71]            | South America            | Colombia                       | NR                                                                       | 1             | 29               | Female    | 33.9           | NR                                                                                   | Individual                                                                              | Pregnant patient, Nervous system disorders                                          |
| Tosato and Alves [32]        | South America            | Brazil                         | Hospital da Sagrada Familia, Salvador, Bahia                            | 1             | 22               | Female    | NR             | NR                                                                                   | Individual                                                                              | Orthopedic complications                                                          |
| Uemura et al. [74]           | South America            | Brazil                         | Ambulatory of the Specialization Course in Pediatric Dentistry of the Union of Dentists of the State of São Paulo (SOESP) | 1             | 4                | Female    | NR             | NR                                                                                   | Individual                                                                              | Psychosocial complications, Others                                                 |
| Werb et al. [33]             | South America            | Brazil                         | Getúlio Vargas State Hospital, Rio de Janeiro                          | 1             | 79               | Female    | NR             | NR                                                                                   | Individual                                                                              | Blood coagulation disorders with indication of suprapatellar amputation of lower limb |

ACH: achondroplasia; ICU: intensive care unit; LATAM: Latin America; NR: not reported; NA: not applicable; SD: standard deviation; BMI: body mass index

*a* Hypochromic microcytic anemia (hematocrit 30) with hypoferremia and hypoproteinemia

* months

* number

* Case report study that did not evaluate any pre-defined burden outcomes

* Comparative cross-sectional studies
Twenty-four of the included studies were conducted in Brazil [5, 24, 26–34, 36, 38–40, 45, 49, 57, 63, 66, 67, 69, 74, 75], nine in Argentina [44, 50–54, 56, 64, 73], five in Colombia [42, 48, 58, 68, 71], four in Mexico [35, 37, 41, 59], three in Chile [46, 47, 61], three in Cuba [43, 60, 65], one each in Dominican Republic [55], in Paraguay [41, 59], three in the Dominican Republic [55], in Paraguay [62], in Venezuela [72], and in Puerto Rico [70]. Only one article [6] was a multicenter cross-sectional study, which involved nine countries (i.e., Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Uruguay, and Venezuela) [6]. Sample sizes from these studies ranged from four [61] to 357 patients [53]. Study participants ranged in age, from a mean age of 3.07 [56] to 40.24 [40] years (Tables 1 and 2).

The type of burden outcome most frequently reported among the cross-sectional and case series studies was nervous system disorders (28.66%, n = 8) [5, 29, 34, 37, 56, 70, 72, 73], followed by spinal issues including stenosis, compression and associated pain (25.00%, n = 7) [34, 35, 37, 40, 56, 70, 73], and then ear, nose, throat and speech disorders (21.42%, n = 6) [5, 37, 40, 56, 70, 75]. The majority of the cross-sectional, case series, and case reports studies (86.36%, n = 38) reported only on patient-important outcomes (Tables 1 and 2).

Additional file 2: Table S2 describes study characteristics related to LATAM countries only from those that reported other than patient-important or economic outcome. Ten studies [36, 45, 48, 50–54, 60, 61] evaluated in addition to burden outcomes, such factors as mutations in the fibroblast growth factor receptor 3 gene [48, 61]; growth velocity [52, 54]; and body proportions references [53].

Additional file 3: Table S3 describes the burden outcomes on 25 LATAM case reports studies. With regards the case reports studies, the majority (68.0%, n = 17) [27, 28, 30, 39, 42, 44, 46, 47, 49, 55, 57, 59, 62–65, 68] assessed some physical comorbidities such as apnea [59, 68], lower back and leg pain [49], and obesity [65]. Ten case report studies evaluated other outcomes such as hemorroidectomy [63] and vesicostomy for neurogenic bladder [59]. Only one study [49] reported on environmental burden (i.e., difficulty getting on the bus because of the distance from the sidewalk to the step and the height of the steps).

Risk of bias assessment

Figure 2 and Additional files 4, 5: Tables S4 and S5 describe the risk of bias assessment. In the cross-sectional studies (Fig. 2, panel A), at least one of the following domains of sample size, statistical significance, statistics methods, or demographic data were rated as “high risk of bias” in 13 studies (54.16%) [5, 24, 29, 37, 38, 40, 56, 58, 66, 69, 70, 72, 75]. In the case series studies (Fig. 2, panel B), only two domains (i.e., clear description of both patient’s history and post-intervention clinical condition) were rated as “high risk of bias” in three studies (75.00%) [34, 35, 73].

Outcomes

The results were pooled from studies that reported available data. Therefore, out of 54 included studies [5, 6, 24, 26–76], only 11 [5, 29, 34, 37, 40, 56, 66, 70, 72, 73, 75, 76] were used for the quantitative analysis described below as they presented available data (Table 2).

Mortality

The pooled proportion for mortality (i.e., sudden death [37] and death due to respiratory complications [56, 72]) was 15% [95% CI 1.0E−3 to 0.47; I2 = 82.9%, p = 0.0029] from three studies [37, 56, 72] with a total of 99 patients (Fig. 3). There was significant statistical heterogeneity in the analyses.

Cardio-respiratory-metabolic disorders

The pooled proportion for cardio-respiratory-metabolic disorders was 17% [95% CI 0.04 to 0.37; I2 = 90.3%, p < 0.0001] from four studies [5, 37, 56, 75, 76] with a total of 230 patients (Fig. 3). There was significant statistical heterogeneity in the analyses. The outcomes used to calculate the mean or median of the cardio-respiratory-metabolic disorders among the studies included in the analysis were: adenotonsillectomy [5]; apnea followed by death [37]; pneumonia [56]; apnea index slightly and moderately increased [75]; desaturations during sleep [75]; and apnea [75]. There was no outcome directly related to cardiac to be included in this category.

Nervous system disorders

The pooled proportion for nervous system disorders was 18% [95% CI 0.07 to 0.33; I2 = 84.6%, p < 0.0001] from six studies [5, 29, 37, 56, 72, 73] with a total of 262 patients (Fig. 3). There was significant statistical heterogeneity in the analyses. A sensitivity analysis excluding case series studies from the cross-sectional studies yielded results that were consistent with the primary analysis of 27% [95% CI 0.09 to 0.50; I2 = 87.2%, p < 0.0001] from five studies [5, 29, 37, 56, 72] with a total of 165 patients (Fig. 4). There was no statistically significant difference between the primary analysis (i.e., all the studies) and the sensitivity analysis (i.e., only cross-sectional studies), as their CIs overlapped. The outcomes used to calculate the
mean or median of the nervous system disorders among the studies included in the analysis were: hydrocephalus [5, 37]; convulsive crises [72]; epilepsy [5]; paresthesias and paresias [37]; hypotonia [37]; neurological manifestations [56]; decompressive surgery for foramen magnum [56]; mental retardation [72]; and neurological problems [73].

Ear, nose, throat and speech disorders
The pooled proportion for ear, nose, throat and speech disorders was 32% [95% CI 0.18 to 0.48; \( I^2 = 73.4\% \), \( p = 0.0046 \)] from five studies [5, 37, 40, 56, 75, 76] with a total of 183 patients (Fig. 3). There was significant statistical heterogeneity in the analyses. The outcomes used to calculate the mean or median of the ear, nose, throat and speech disorders among the studies included in the analysis were: hearing loss [5, 56, 75]; recurrent otitis media [37, 56, 75]; required surgical treatment (i.e., placement of ventilation tubes) [37]; delay in speech development [56]; hypotonia [56]; hypertrophy of adenoids [75]; snoring; tonsillectomy; and thickening of the tympanic membrane [75].

Spinal issues including stenosis, compression and associated pain
The pooled proportion for spinal issues including stenosis, compression and associated pain was 24% [95% CI 0.07 to 0.47; \( I^2 = 91.3\% \), \( p < 0.0001 \)] from five studies [34, 37, 40, 56, 73] with a total of 235 patients (Fig. 3). There was significant statistical heterogeneity in the analyses. A sensitivity analysis excluding case series studies from the cross-sectional studies yielded results that were consistent with the primary analysis of 17% [95% CI 0.01 to 0.45; \( I^2 = 93.4\% \), \( p < 0.0001 \)] from three studies [37, 40, 56] with a total of 194 patients (Fig. 4). There was no statistically significant difference between the primary analysis (i.e., all the studies) and the sensitivity analysis (i.e., only cross-sectional studies), as their CIs overlapped. The outcomes used to calculate the mean or median of the spinal disorders among the studies included in the analysis were: osteopenia or osteoporosis [40]; posterior laminectomy [37]; craniocervical compression [34, 37, 56, 73]; spinal compression requiring laminectomy [56]; spinal cord liberation alone [73]; anterior arthrodesis plus posterior instrumented arthrodesis [73]; anterior arthrodesis, associated with fibular grafting followed by posterior simple arthrodesis [73]; posterior arthrodesis instrumented with pedicural screws [73].

Psychosocial disorders
The pooled proportion for psychosocial complications was 19% [95% CI 0.02 to 0.48; \( I^2 = 80.8\% \), \( p = 0.0054 \)] from three studies [5, 66, 70] with a total of 66 patients (Fig. 3). There was significant statistical heterogeneity in the analyses. The outcomes used to calculate the mean or median of the psychosocial disorders among the studies included in the analysis were: depression [5], perception of their body image [66], and mild somatization [70].

Descriptive analysis
Four studies [38, 58, 69, 75, 76] reported on economic burden outcomes. Gomez et al., 2017 [58] reported on the adaptation of shoes for the ACH patients and the costs associated with the anthropometric and baropodometric analyses of the foot. This study addressed the design of a footwear system that fulfills form, function and usage of eight persons with ACH patients. The most relevant information was that footwear should have a low heel (about 2 cm) as there is a greater risk of falling due to the instability associated with wearing higher heels (7 1/2 cm and above), considering the lower center of gravity for ACH patients; however, patients want to have comfort and elegant heels and shoes (Table 1).

The Lima, 2019 [38] study sought to identify the consequences of stigmatization on social life, including work. The results indicate that people with ACH experience humiliation and disrespect due to associations made with the stereotype built about them. The authors found this stereotype is commonly used by comedians for entertainment purposes (Table 1).

Medeiros et al., 2017; Medeiros et al., 2019 [75, 76] and Rocha & Wagner, 2018 [69] describe the challenges associated with physical activities (Table 1). Patients reported that while physical activities can be difficult to perform [75, 76], though the regular practice of physical activity improves their self-esteem and confidence which in turn contributes to their sense of social inclusion [69].

None of the included studies reported on the following patient-important outcomes: suicide attempts, and suicide rates; impact of the disease on caregivers, such as health-related quality of life, activities of daily living, work productivity, education, employment, social, and so forth; and social adaptation challenges. Furthermore, none of the included studies reported on the following economic burden outcomes: limitation of physical access to transportation modalities; and adaptation to standard transport equipment.

Discussion
Main findings
Based on pooled data from 11 clinical studies [5, 29, 34, 37, 40, 56, 66, 70, 72, 73, 75, 76] with 409 participants, we
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|----------|----------------|-------------------|--------------------------------------|------------------------|------------------|
| Alves [34]   | South America            | Brazil        | Neurosurgery Outpatient Clinic of Instituto Fernandes Figueira / Fiocruz | 31             | 3.23             | 45.17    | NR             | Achondroplasia associated with other genetic diseases | Individual Spinal issues including stenosis, compression and associated pain | Craniocervical decompression surgery after displaying signs of medullary suffering and alteration of tendon reflexes; surgical intervention (craniocervical decompression surgery and endoscopic third ventriculostomy) |
|              |                          |               |          |               |                  |          |                | Nervous system disorders | Hydrocephalus as a neurosurgical complication; endoscopic third ventriculostomy was performed on one patient, successfully, that presented alterations of eye background with optic papilla edema, arterial hypertension, and convulsive crises; neurosurgical complications; accidental dural opening need for reoperation to correct CSF fistula; surgical intervention (craniocervical decompression surgery and endoscopic third ventriculostomy) | Others | Blood transfusion; length of ICU; length of hospitalization |
| Author, year     | South or Central America | LATAM country   | Scenario                          | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria                                                                 | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes                                                                 |
|------------------|--------------------------|-----------------|-----------------------------------|---------------|------------------|-----------|----------------|------------------------------------------------------------------------------------|----------------------------------------|-------------------------|--------------------------------------------------------------------------------|
| Tello et al. [73] | South America            | Argentina       | Dr. Juan P. Garrahan Pediatric Hospital | 76            | NR               | NR        | NR             | Individual                                                                          | Spinal issues including stenosis, compression and associated pain | Needed surgical procedure, given the poor spinal cord compliance to deformations; dorso-lumbar kyphosis; posterior fossa decompression; spinal cord liberation alone; anterior arthrodesis plus posterior instrumented arthrodesis; anterior arthrodesis, associated with fibular grafting followed by posterior simple arthrodesis; the same technique was employed on 2 other patients, followed by posterior arthrodesis instrumented with pedicular screws | Nervous system disorders | Neurological problems |
| Arita et al. [40] | South America            | Brazil          | Heliopolis Hospital, Sao Paulo     | 11            | 40.27 (8.019)    | 45.45     | 33.75 (7.94)   | Spinal issues including stenosis, compression and associated pain                  | Individual                             | Mean number of teeth, bone fracture, mean cortical width, Klemetti index | Normal density; osteopenia/osteoporosis; mandibular cortical erosion in all sample |

*Cross-sectional studies*
| Author, year  | South or Central America | LATAM country | Scenario                                                                 | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria                                                                 |
|---------------|-------------------------|---------------|--------------------------------------------------------------------------|---------------|-----------------|-----------|----------------|------------------------------------------------------------------------------------|
| Ceroni et al. [5] | South America           | Brazil        | Medical School of the University of Sao Paulo (HC-FMUSP)                 | 39            | 10.2            | NR        | NR             | Patients who did not present a molecular study                                      |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Individual outcomes: Ear, nose, throat and speech disorders                      |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Type of burden outcomes: Motor developmental delay; speech delay; recurrent infection of the middle ear; persistent middle ear fluid; hearing loss; ventilation tube insertion                          |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Specify outcomes: Sleep disturbance; sleep apnea; adenotonsillectomy; excessive snoring; obesity                       |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Nervous system disorders: Hydrocephalus; epilepsy                                |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Perinatal complications: Perinatal incurrance; premature, presenting respiratory distress, pathological jaundice and deglution disturbance; required three months of hospitalization |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Other: Bilateral Wilms' tumor                                                   |
| Escobar [37]  | Central America         | Mexico        | National Institute of Pediatrics of the Ministry of Health              | 87            | NR              | 39        | NR             | Patients with other achondroplasias                                               |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Individual outcomes: Nervous system disorders                                   |
|               |                         |               |                                                                          |               |                 |           |                |                                                    | Specify outcomes: Hydrocephalus; paresthesias; paresthesia; hypotonia             |
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|-------------|--------------------------|---------------|----------|---------------|------------------|---------|---------------|-----------------|---------------------------------------|-------------------------|------------------|
| Fano and Lejarraga [56] | South America | Argentina | Consultancy services for the growth and development of the National Hospital of Pediatrics "Prof. Dr. J. P. Garrahan" | 96 | 3.07 | 47.91 | NR | NR | Individual | Spinal issues including stenosis, compression and associated pain | Spinal compression; surgical treatment, with posterior laminectomy being the procedure performed |
| | | | | | | | | | | | Cardio-respiratory-metabolic disorders | Apnea followed by death; neuromuscular blockers |
| | | | | | | | | | | Ear, nose, throat and speech disorders | Recurrent otitis media; required surgical treatment (placement of ventilation tubes) |
| | | | | | | | | | | Orthopedic complications | Orthopedic complication; corrective treatment; lengthening treatment |
| | | | | | | | | | | All-cause mortality | Sudden death |
| | | | | | | | | | | Others | Eye complications |
| | | | | | | | | | | Ear, nose, throat and speech disorders | Relapsing otitis media; any degree of hearing loss; delay in speech development; hipotonia |
| | | | | | | | | | | Cardio-respiratory-metabolic disorders | Recurrent bronchitis; pneumonia; snoring during sleep; surgical requirement for presenting signs of cervicomedullary compression plus coexistence with severe respiratory illness; obesity |
Table 2 (continued)

| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|-----------|----------------|-------------------|----------------------------------------|------------------------|-----------------|
| Senior [28]  | South America            | Brazil        | Rehabilitation hospital in Minas Gerais | 24  | NR             | 54.16      | NR             | NR                | Individual Nervous system disorders | Nervous system disorders | Neurological manifestations; myeloradiculopathy |
| Junior [29]  | South America            | Brazil        | Rehabilitation hospital in Minas Gerais | 24  | NR             | 54.16      | NR             | NR                | Individual Nervous system disorders | Nervous system disorders | Neurological manifestations; myeloradiculopathy |
|              |                          |               |          |               |                  |            |                |                   | Individual Nervous system disorders | Nervous system disorders | Neurological manifestations; myeloradiculopathy |

Individual Nervous system disorders

- Rigid kyphosis; spinal compression requiring laminectomy
- Any neurological complications; surgical requirement for presenting signs of cervicomedullary compression (decompressive surgery of foramen magnum); surgical requirement for presenting signs of cervicomedullary compression plus coexistence with severe respiratory illness; delay in motor development; hydrocephalus that required ventriculoperitoneal shunt
- Premature mortality
- Others Sustained hypoxemia requiring home oxygen supply due to sequelae of lung disease after infection

Specify outcomes

- Spinal issues including stenosis, compression and associated pain
- Nervous system disorders

Type of burden outcomes

- Premature mortality
- Others

Exclusion criteria

- Individual

Individual and/or population outcomes

- Nervous system disorders

BMI, Mean (SD)

- 54.16

# of patients

- 24

Age, Mean (SD), y

- 54.16

Female, %

- NR

BMI, Mean (SD)

- 54.16

Exclusion criteria

- Individual

Type of burden outcomes

- Nervous system disorders

Specify outcomes

- Neurological manifestations; myeloradiculopathy
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|-------------|--------------------------|---------------|----------|---------------|------------------|-----------|---------------|------------------|-----------------------------------------|------------------------|-----------------|
| Medeiros et al., Meideiros et al. [75, 76] | South America | Brazil | Medical Genetics outpatient clinic at Hospital Universitário Alcides Carneiro (HUAC) from the Federal University of Campinas Grande | 8 | NR | 37.5 | NR | NR | Individual / Population | Ear, nose, throat and speech disorders | Hypertrophy of adenoids; snoring; tonsillectomy; thickening of the tympanic membrane; hearing loss; recurrent otitis media |
| | | | | | | | | | | Cardio-respiratory-metabolic disorders | Apnea index moderately highly increased; desaturations during sleep, but not accompanied by electrocardiographic change |
| Petitto and Baumote [66] | South America | Brazil | Participants’ home | 5 | 25 | NR | 33.66 | NR | Individual | Psychosocial complications (i.e., impact of the disease on patient) | Challenges in physical activity | Body image |
Table 2 (continued)

| Author, year | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|---------------|----------|---------------|------------------|-----------|----------------|--------------------|----------------------------------------|-------------------------|-----------------|
| Rodriguez-Gomez et al. [70] | Central America | Puerto Rico | Residents of Puerto Rico | 22 | 39.6 | 68.2 | NR | NR | Individual | Depression, anxiety, bullying, isolation, somatization, etc | Mild to severe depressive symptoms; mild to severe symptoms associated to anxiety; mild to severe symptoms associated with hopelessness; mild to severe symptoms in at least one of the sub-scales in Dero-gatis Symptom Checklist-90-Revisited (SCL-90-R) particularly the obsessive-compulsive, paranoid and depressive subscales; mild somatization; mild interpersonal sensitivity; mild hostility; mild to severe paranoid ideation; mild to moderate psychoticism |

- Cardio-respiratory-metabolic disorders: At least one complication (hypertension, diabetes, rheumatoid arthritis, asthma, scoliosis, thyroid problems, neuropathy, psoriasis, gastritis and/or sleep apnea)
- Nervous system disorders
- Ear, nose, throat and speech disorders
| Author, year | South or Central America | LATAM country | Scenario | # of patients | Age, Mean (SD), y | Female, % | BMI, Mean (SD) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specify outcomes |
|--------------|--------------------------|---------------|----------|---------------|------------------|-----------|---------------|-----------------|----------------------------------------|------------------------|-----------------|
| Sanchez et al. [72] | South America | Venezuela | Ruiz y Páez Hospital in Ciudad Bolívar | 10 | NR | NR | NR | NR | Individual Premature mortality | Spinal issues including stenosis, compression and associated pain | Diabetes, rheumatoid arthritis, thyroid problems, neuropathy, psoriasis, and gastritis | Acanthosis Nigricans |

ACH: achondroplasia; ICU: intensive care unit; LATAM: Latin America; NR: not reported; NA: not applicable SD: standard deviation; BMI: body mass index

* Number

1 Comparative cross-sectional studies
found evidence of the impact of ACH on affected individuals in LATAM. Case-series and cross-sectional studies provide pooled proportions of burden ranging from 15% (mortality) to 32% (for ear, nose, throat and speech disorders outcomes).

We have now applied a methodology [21, 22] to evaluate the proportions of clinical burden outcomes in the LATAM ACH population. The proportions of pooled case series and cross-sectional studies were consistent with results from only pooled cross-sectional studies in the outcomes of nervous system disorders and spinal issues including stenosis, compression and associated pain, meaning that the assumed proportions lie in a high probability of a true value. To the best of our knowledge, this is the first study to clearly demonstrate the burden of LATAM ACH patients, an observation that should be taken into account in regional health policy debates regarding management of ACH disease. Of note, while limb lengthening procedures are frequently performed on ACH patients in LATAM, we were not able to find any data on these procedures in the included studies.

**Strengths and limitations**

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias and data abstraction independently and in duplicate; and an assessment of risk of bias that included a sensitivity analysis addressing homogeneity of study designs.

The primary limitation of our study is related to the rare disease nature of ACH. The population available to study was limited and the study designs presented some flaws.

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**Fig. 2** Risk of bias assessment of the included studies. **a** Cross-sectional studies. **b** Case series studies.
Fig. 3 Pooled analysis of proportions for burden outcomes in LATAM ACH patients. **a** Mortality. **b** Cardio-respiratory-metabolic disorders. **c** Nervous system disorders. **d** Ear, nose, throat and speech disorders. **e** Spinal issues including stenosis, compression and associated pain. **f** Psychosocial complications. **g** Others
Another limitation is that our analysis demonstrates a significant heterogeneity (I²) in all studied clinical burden outcomes. Explanations for this heterogeneity could be both clinical and methodological diversities. The studies differed considerably in their mean age of patient selection, study designs (i.e., case series, cross-sectional, and case reports), and type of burden outcomes (e.g., nervous system disorders, one study could report hydrocephalus, while another reports epilepsy).

Furthermore, out of the 53 clinical studies we were only able to include data in the meta-analysis from 11 of them (20.4%). The majority of the studies were difficult to decipher, and they did not provide all burden pre-defined outcomes.

A further limitation was the insufficient number of studies, which prevented completing statistical analyses that had initially been planned. We were unable to assess publication bias because there were less than 10 eligible studies addressing the same outcome in a meta-analysis. Subgroup analyses on LATAM countries (e.g., Brazil versus Argentina), and adults versus children were not possible since minimal criteria were not met (i.e., at least four studies available, with at least two in each sub-group).

A sensitivity analysis pooling all included studies (i.e., case series and cross-sectional studies) compared with pooling only the cross-sectional studies was only possible for nervous system disorders and spinal issues outcomes. No difference was found in the proportion of overlap CIs between both analyses.

Relation to prior research
Unfortunately, there is a dearth of information on LATAM patients in both non-English and English-language medical literature on ACH. While we found a 15% mortality rate in our review, with a wide-ranging prevalence from 0.1 to 47%, a multicenter study of mortality in ACH [77] that studied 855 USA patients presented an overall mortality rate of 99% per 1,000 person years, with an absolute number of deaths of 12 patients (n = 5, toddlers; n = 2, young children; and n = 5, young adulthood). The authors of the clinical study also found that the infant mortality rate was 3.2/1,000 person years. Although only three studies [37, 56, 72] contributed to our data on mortality, only one of them [56] reported the mean age of the population as 3.07 years old. Therefore, in our systematic review, 33.33% of the mortality data is contributed from predominantly children with a mean age of three years. Another two studies [2, 9] estimated the maximal risk of deaths in the first year of life as 7.5%; this high percentage may also be explained due to the absence of special care and surgical intervention.

Furthermore, an additional two studies [78, 79] identified in the literature corroborate with our findings showing that motor delays are common in the ACH population. In our review, we found a prevalence of nervous system disorders, which encompassed motor delay, of 26% with a reasonable CI ranging from 12 to 44%. 

Fig. 4 Sensitivity analysis excluding case series studies from the cross-sectional studies for burden outcomes in LATAM ACH patients. Panel A: Nervous system disorders. Panel B: Spinal issues including stenosis, compression and associated pain.
A high prevalence of ear, nose, and throat disorders (32%) and spinal issues (26%) were found in our review which is consistent with other studies indicating that middle ear dysfunction [80] and spinal stenosis [81] are highly common in both children and adults with ACH.

Conclusions
LATAM ACH patients presented a high prevalence of clinical complications, although the possibility of residual confounding due to lack of adequate reports in this population and high heterogeneity in the analysis cannot be ruled out. This study also highlights the need to address well-conducted clinical studies on ACH, and to alert the public health authorities. Future observational studies should have standardized outcomes measures such as mortality, physical comorbidities, humanistic outcomes, and socioeconomic and environmental burden outcomes.

Supplementary Information
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Authors’ contributions
All authors contributed to study design, interpretation, and analysis. C.A.K, P.R., RED, R.S., T.M., D.M. and J.L.J were responsible for data identification, extraction, and synthesis. V.F. was responsible for creating the first draft. All authors read and approved the final manuscript.

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Availability of data and materials
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Not applicable.

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Not applicable.

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