Birth prevalence of achondroplasia: A systematic literature review and meta-analysis

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Abstract
Achondroplasia is a genetic disorder that results in disproportionate short stature. The true prevalence of achondroplasia is unknown as estimates vary widely. This systematic literature review and meta-analysis was conducted to better estimate worldwide achondroplasia birth prevalence. PubMed, Embase, Scielo, and Google Scholar were searched, complemented by manual searching, for peer-reviewed articles published between 1950 and 2019. Eligible articles were identified by two independent researchers using predefined selection criteria. Birth prevalence estimates were extracted for analysis, and the quality of evidence was assessed. A meta-analysis using a quality effects approach based on the inverse variance fixed effect model was conducted. The search identified 955 unique articles, of which 52 were eligible and included. Based on the meta-analysis, the worldwide birth prevalence of achondroplasia was estimated to be 4.6 per 100,000. Substantial regional variation was observed with a considerably higher birth prevalence reported in North Africa and the Middle East compared to other regions, particularly Europe and the Americas. Higher birth prevalence was also reported in specialized care settings. Significant heterogeneity (Higgins $I^2$ of 84.3) was present and some indication of publication bias was detected, based on visual asymmetry of the Doi plot with a Furuya-Kanamori index of 2.73. Analysis of pooled data from the current literature yields a worldwide achondroplasia birth prevalence of approximately 4.6 per 100,000, with considerable regional variation. Careful interpretation of these findings is advised as included studies are of broadly varying methodological quality.

KEYWORDS
achondroplasia, birth prevalence, epidemiology, meta-analysis, systematic review

1 | INTRODUCTION

Achondroplasia (OMIM 100800), the most common form of disproportionate short stature, is caused by a variant in the fibroblast growth factor receptor 3 (FGFR3) gene, which leads to inhibition of endochondral bone development (Horton, Hall, & Hecht, 2007;...
Achondroplasia is a rare disease. In the United States, a rare disease is defined as a condition that affects fewer than 200,000 people (Orphan Drug Act of 1983), and in the European Union, a disease is defined as rare when it affects fewer than 200,000 people (Orphan Drug Act of 1983), and in the European Union, a disease is defined as rare when it affects fewer than 200,000 people (Orphan Drug Act of 1983) and a disease is defined as rare when it affects fewer than 200,000 people (Orphan Drug Act of 1983) for in the epidemiologic literature. Reported estimates of achondroplasia studied, geography, year of birth and the method of diagnosis, and these elements are not always robustly reported and accounted for in the epidemiologic literature. Reported estimates of achondroplasia birth prevalence vary widely, ranging from 1 in 10,000 to 40,000 newborns worldwide (GARD, 2019; Horton et al., 2007; Ornitz & Legeai-Mallet, 2017; Orphanet, 2019; Pauli, 2019; Unger, Bonafé, & Gouze, 2017) and reports are often based on a few selected references (Horton et al., 2007; Pauli, 2019; Unger et al., 2017). Accurate prevalence rates are critical for health economics, public health, and research purposes. This systematic literature review with meta-analysis aims to provide a pooled estimate of achondroplasia birth prevalence in the general population. A secondary objective is to gain insight into the distribution of the birth prevalence of achondroplasia across regions of the world.

2 | METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used as a guidance for the reporting of this systematic review. The study protocol was registered to Prospero, (van den Bosch et al., PROSPERO 2020 CRD42020148316).

2.1 | Identification of eligible publications

PubMed (MEDLINE) and Embase were searched for articles reporting on the birth prevalence of achondroplasia between January 1950 up to and including July 29, 2019. PubMed was searched using the following search strategy: "Achondroplasia"[MeSH Terms] OR "Achondroplasia"[All Fields] OR Achondroplastic[All Fields] OR "Skeletal dysplasia[all fields] AND "Prevalence"[Mesh] OR Prevalen*[tiab] OR "Epidemiology"[Mesh] OR "Epidemiology"[subheading] OR Epidemiol*[tiab] OR Burden*[tiab] OR "Incidence"[Mesh] OR Inciden* [tiab]. A comparable search strategy was formulated for Embase. The complete search queries can be found in Appendix I. Additional relevant articles were identified in Scielo and Google Scholar using the terms "Achondroplasia" AND "Prevalence" OR "Incidence." The reference lists of narrative and systematic reviews with focus on achondroplasia prevalence and the reference lists of eligible articles were checked for additional eligible articles. Articles were considered eligible if they were peer-reviewed and had an abstract available in the English language. Only articles that reported the birth prevalence of achondroplasia in an unselected population (i.e., individuals captured in a study setting that is likely representative for the general population) were included. The following exclusion criteria were applied: Did not report primary data, presented overlapping results from identical datasets (in which case only one report was included), review article, letter, comment or conference abstract, animal study, case report or case series, or clinical trial. Case series and clinical trials were excluded since they risked representing selected populations rather than the population at large.

2.2 | Study screening

Selection of peer-reviewed articles was based on title and abstract screening, followed by screening of the full-text in potentially eligible articles. The title and abstract selection and the full-text screening were done in duplicate by two independent reviewers (FK and JB).
After the screening process there was less than 5% discrepancy between the two researchers. The results were compared and discussed, and any disagreements were adjudicated by a third researcher (PKF) until consensus was reached.

2.3 Data extraction and quality assessment

Data from eligible studies were extracted into Microsoft Excel by two researchers (FK, PKF). Data extraction tables were then reviewed by a second researcher (JB). Information identified from the studies included geographical region, country, birth period, study design, setting, (i.e., specialized care, defined as a referral hospital or tertiary care center, versus other settings, such as community hospitals), study population characteristics, and study outcomes (i.e., sample size, birth prevalence). When studies included multiple study estimates (e.g., birth prevalence estimates stratified by birth year or country), data-extraction was performed separately for each study estimate.

As studies varied dramatically with respect to study methodology and the completeness of reporting, a quality assessment tool was devised to assist in evaluating the quality of the evidence presented in each study. The quality of evidence was assessed across five domains: Data source (i.e., context of case ascertainment), diagnostic method, appropriateness of the numerator and of the dominator used in determining birth prevalence, and the statistical adequacy of population size surveyed (95% confidence) (Naing, Winn, & Rusli, 2006). The quality assessment tool is detailed in Table 1. No studies were excluded based on study quality.

2.4 Statistical analysis

Birth prevalence was defined as the total number of achondroplasia cases among births in a predefined population, divided by the sample size of the predefined population, multiplied by 100,000. A meta-analysis was performed to assess the overall birth prevalence of achondroplasia, as well as birth prevalence stratified by region (North America, South America, Europe, North Africa/Middle East, Sub-Saharan Africa and South Asia, South-East Asia/Oceania) and by study setting. For study setting a distinction was made between specialized care (i.e., women who gave birth in a tertiary hospital or referral center) and other settings. A meta-analysis was performed only when at least three estimates were available per stratification category.

Meta-analyses were performed using raw data reported in the articles. To prevent bias resulting from small values where variance approaches zero, prevalence estimates were transformed using the double arcsine method (Barendregt, Doi, Lee, Norman, & Vos, 2013). Using this method, confidence intervals (CIs) are forced within the 0%

### Table 1 Quality of evidence scoring tool

| Scoring domain         | Score Strong                                                                 | Score Moderate                                      | Score Weak                                           |
|------------------------|------------------------------------------------------------------------------|-----------------------------------------------------|------------------------------------------------------|
| Data source            | Was the data source complete and representative of the population as a whole? | Community/population-based screening/newborn screening | Hospital-based records                               | Survey by query (e.g., postcards)                    |
|                        |                                                                              | Disease registry                                     | Laboratory-based records                             | Personal communication                                |
|                        |                                                                              |                                                     | General practice-based records                        | NR, unclear, other                                   |
| Diagnostic method      | Was the method(s) used for the case definition definitive?^a                  | Radiographic                                         | Clinical presentation only                           | NR                                                   |
|                        |                                                                              | Autopsy                                              |                                                     | Too vague to determine                               |
|                        |                                                                              | Positive mutational analysis                         |                                                     |                                                      |
| Numerator              | Was reporting of the numerator sufficient (describes any combination of live births, still born, spontaneous abortions/pregnancy terminations)? | The numerator is well described                       | Not applicable                                       | Numerator is not sufficiently described              |
| Denominator            | Was reporting of the denominator sufficient and appropriate?                 | The denominator is congruent with the numerator in terms of setting and pregnancy outcome | Not applicable                                       | The denominator is not congruent with the numerator  |
| Population size        | Was the population size adequate to estimate birth prevalence with 95% confidence? (Naing et al., 2006) | Adequate (≥170,000)                                  | Not adequate for this certainty level (≥100,000–170,000) | <100,000, NR                                        |

Abbreviation: NR, not reported.

^a When methods varied among sites or across time, the study was assigned the value of the lowest scoring method.
and 100% range. The final pooled result and 95% CIs were back-transformed for ease of interpretation (Barendregt et al., 2013; Schwarzer, Chemaitelly, Abu-Raddad, & Rucker, 2019).

A quality effects approach based on the inverse variance fixed effect model was used for the main analysis. In this model, the redistribution of inverse variance weights is done using a quality parameter between zero (lowest quality) and one (highest quality) (Al Khalaf, Thalib, & Doi, 2011; Deeks, Altman, & Bradburn, 2001; Doi & Thalib, 2008; Doi & Thalib, 2009). The rating of the study quality for the quality effects model was performed as follows: For each question of the quality assessment tool two points were allocated when the study scored “strong,” one point when the study scored “moderate” and zero points when the study scored “weak.” The sum of the individual scores was determined and normalized to a value between 0 and 1 by dividing by the maximum possible score (8). Question Q5 (regarding population size) was omitted from the quality scoring for the meta-analysis, as the study population size is included in the weights using the inverse variance method. The quality index, which is computed for each analysis (Table 3), expresses the extent (%) to which the weights are redistributed by the application of the quality effect weights.

The more commonly used random effects inverse variance model (DerSimonian & Laird, 1986) was also conducted.

The level of study heterogeneity was assessed by computing the Higgins $I^2$ statistic, along with a visual assessment using forest plots (Higgins, Thompson, Deeks, & Altman, 2003). A $p$-value for the chi-square test of less than .05 was considered statistically significant. $I^2$ values of less than 25%, 25–50%, 50–75%, and more than 75% were considered as very low, low, medium, and high heterogeneity, respectively (Huedo-Medina, Sanchez-Meca, Marin-Martinez, & Botella, 2006). Heterogeneity was assessed for $I^2$ values of 75% or higher using sensitivity analysis.

Publication bias was investigated by assessment of the Doi plot along with the interpretation of the Luis Furuya-Kanamori (LFK) index.

FIGURE 1  Flow chart of selection process (Moher, Liberati, Tetzlaff, & Altman, 2009). † For example, Modeling study, no original data, no English abstract [Color figure can be viewed at wileyonlinelibrary.com]
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(Furuya-Kanamori, Barendregt, & Doi, 2018). When a symmetrical Doi plot is presented, no publication bias is expected. The LFK-index quantifies the differences between the two sides of the plot. An index within ±1 was associated with no asymmetry, an index between ±1 and ±2 indicated minor asymmetry, and an index above ±2 was interpreted as the presence of major asymmetry (Barendregt & Doi, 2011–2016; Furuya-Kanamori et al., 2018). All analyses were conducted using the MetaXL version 5.3 (www.epigear.com) add-in for Microsoft Excel.

3 | RESULTS

The combined PubMed and Embase search yielded 866 unique hits, of which 68 were selected for full text evaluation (Figure 1). In addition, 65 articles from Google Scholar and Scielo, and 24 articles identified by hand searching the reference lists of eligible articles or systematic reviews were identified for the full text evaluation. From these 156 articles, 52 articles were eligible for inclusion (Figure 1). The 52 included studies reported 101 achondroplasia birth prevalence estimates. Eleven study estimates were excluded, because of double inclusion of data, or lack of reporting of numerator and denominator (further details can be found in Table 2).

3.1 | Characteristics of studies

Table 2 summarizes the birth prevalence estimates and the main characteristics of the included studies. The included studies spanned six geographical regions and 90 estimates comprising births between 1951 and 2015. In total, outcomes from 48,453,349 births were reported, with 1896 reported cases of achondroplasia (Table 2). The median birth prevalence worldwide was 4.7 cases per 100,000 births. Substantial regional variation was observed with a considerably higher birth prevalence reported in North Africa and the Middle East than in other regions, particularly Europe and the Americas. The reported birth prevalence was also notably higher in reports deriving data from specialized care settings (referral centers/tertiary hospitals), compared with other settings. Individual data for each birth prevalence estimate are shown in Table 3. More than half of the birth prevalence estimates represented births from 1990 to 2015 (Table 3). Almost half of the total population surveyed were in Europe, followed by North America and South America. Sub-Saharan Africa, North Africa/Middle East, Asia/Oceania combined represented less than 7% of the total population surveyed. Approximately 16% of the birth prevalence estimates were retrieved from studies conducted in specialized care settings (1.1% of the total included study population). For 68 of 90 estimates (75.5%) the study population comprised of a combination of live born and still born infants. More than half of these estimates (n = 35) included pregnancy terminations (Coi et al., 2019; Jaruratanasirikul et al., 2016; Langlois & Scheuerle, 2015; Rasmussen et al., 1996; Stevenson, 1957; Waller et al., 2008). For the remaining estimates it was unclear whether pregnancy terminations were considered. Fifteen estimates (16.7%) were based on livebirths and for seven estimates (7.8%) it was unclear whether livebirths, stillbirths and/or terminations were taken into account.

Only three studies (Camera & Mastroiacovo, 1988; Orioli et al., 1995; Stevenson et al., 2012) scored strong across all four domains of the quality assessment tool (Table 3). As shown in

| Region                      | Birth prevalence per 100,000 median (IQR)$^a$ | Number of studies; number of estimates (% of total estimates) | Population size (% of overall population surveyed in the included studies) |
|-----------------------------|-----------------------------------------------|---------------------------------------------------------------|----------------------------------------------------------------------------|
| Worldwide                   | 4.73 (3.10–10.83)                             | 52; 90 (100%)                                                | 48,453,349 (100%)                                                          |
| North America               | 4.00 (3.57–4.95)                             | 9; 15 (16.7%)                                               | 16,748,130 (34.57%)                                                       |
| South America               | 3.20 (1.95–4.66)                             | 5; 6 (6.7%)                                                 | 8,463,833 (17.47%)                                                        |
| Europe$^d$                  | 3.62 (2.71–5.54)                             | 13; 40 (44.4%)                                              | 19,945,267 (41.16%)                                                       |
| North Africa/Middle East    | 34.31 (16.53–52.25)                          | 13; 13 (14.4%)                                              | 218,831 (0.45%)                                                           |
| Sub-Saharan Africa          | 12.60 (7.47–16.53)                           | 5; 5 (5.6%)                                                 | 224,680 (0.46%)                                                           |
| South and South-East Asia/Oceania | 10.58 (4.39–12.82)                        | 11; 11 (12.2%)                                              | 2,852,608 (5.89%)                                                         |

Abbreviation: IQR, interquartile range.

$^a$Birth prevalence rates based on the numerator and denominators reported in the articles (i.e., number of cases/population size × 100,000).

$^d$Two studies reported results stratified for multiple regions (Kallen et al., 1993; Orioli et al., 1995). Eleven study estimates were excluded, all extracted from the study of Coi et al. (2019): four because numerator and denominator were not reported, and seven to prevent double inclusion of data (i.e., the overall data from all regions were excluded because that data were also included separately per region).

$^d$For the study of Coi et al., 2019 the data from the separate European countries are included in the analysis, instead of data of the countries combined.

$^d$Referral center/tertiary hospital.
| Author(s), year | Country | Sub-National | Birth prevalence | Birth period | Study design/data source | Study population | Specialized care | Sample size | Study quality |
|----------------|---------|--------------|------------------|--------------|--------------------------|-----------------|----------------|-------------|--------------|
|                |         |              |                  |              |                          |                 |                |             | Data source | Diagnostic method | Numerator | Denominator | Population size |             |
| Alonso Lotti et al., 1998 | Cuba | 13 of the 15 regions | 4.42 | 1985/03–1996/12 | RECUMAC | Live births, stillbirths | No | 520,578 | Strong | Moderate | Strong | Strong | Strong |             |
| Guzmán-Huerta et al., 2012 | Mexico | UNIMEF | 10.99a | 1995/01–2009/12 | Review of hospital charts of patients seen at the National Institute of Perinatal Medicine | Live births, stillbirths | Yes | 81,892 | Moderate | Strong | Strong | Strong | Weak |             |
| Kallen et al., 1993 | Mexico | NR | 2.51b | 1978–1988 | Programa Mexicano de Registro y vigilancia epidemiológica de malformaciones congénitas externas | Live births, stillbirths | No | 359,000 | Strong | Weak | Strong | Strong | Strong |             |
| Curran, Signon, & Opitz, 1974 | USA | New Jersey | 4.00b | NR ("past 10 years," <1973) | Records from the Margaret Hague Maternity Hospital | Live births | No | 75,000 | Moderate | Strong | Strong | Strong | Weak |             |
| Langlois & Scheuerle, 2015 | USA | Texas | 2.66b | 1999–2009 | Records in the Texas Birth Defects Registry | Live births, stillbirths, elective terminations | No | 4,207,898 | Strong | Weak | Strong | Weak | Strong |             |
| Rasmussen et al., 1996 | USA | Boston, Massachusetts | 2.37 | 1972/01–1975/02, 1979/01–1990/12 | Brigham and Women’s Hospital active malformation surveillance system | Live births, stillbirths >20 w, elective terminations | Yes | 126,316 | Moderate | Strong | Strong | Strong | Moderate |             |
| Stevenson, Carey, Byrne, Srisukhumbowonchai, & Fekdamp, 2012 | USA | Utah | 3.53 | 1999–2008 | UBDN | Live births, stillbirths, elective terminations | No | 509,286 | Strong | Moderate | Strong | Strong | Strong |             |
| Waller et al., 2008 | USA | Arkansas | 5.20 | 1993–1999 | Arkansas Reproductive Health Monitoring System | Live births, stillbirths >20 w, elective terminations >20 w | No | 250,000 | Strong | Moderate | Strong | Weak | Strong |             |
|                      |        | Atlanta | 3.89 | 1968–2001 | Attina Congenital Defects Program |                      |                | 1.129,972 | Strong | Moderate | Strong | Weak | Strong |             |
|                      |        | California | 4.70 | 1983–1997 | California Birth Defects Monitoring System |                      |                | 3,572,233 | Strong | Moderate | Strong | Weak | Strong |             |
|                      |        | Iowa | 4.09 | 1983–2001 | Iowa Register for Congenital and Inherited Disorders |                      |                | 733,196 | Strong | Moderate | Strong | Weak | Strong |             |
|                      |        | New York | 3.60 | 1992–2001 | New York State Congenital Malformations Registry |                      |                | 2,664,131 | Strong | Moderate | Strong | Strong | Strong |             |
|                      |        | Oklahoma | 5.99 | 1994–2003 | Oklahoma Birth Defects Registry |                      |                | 484,013 | Strong | Moderate | Strong | Weak | Strong |             |
|                      |        | Texas | 3.87 | 1996–2002 | Texas Birth Defects Epidemiology and Surveillance Branch |                      |                | 2,042,554 | Strong | Moderate | Strong | Weak | Strong |             |
| Study quality | Author(s), year | Country | Sub-National | Birth prevalence | Birth period | Study design/data source | Study population | Specialized carea | Sample size | Diagnostic method | Numerator | Denominator | Population size |
|---------------|----------------|---------|--------------|------------------|--------------|--------------------------|-----------------|-----------------|-------------|-----------------|-----------|-------------|----------------|
| (Woolf & Turner, 1969) | USA | Salt Lake City, Utah | 13.43b | 1951–1961 | Retrospective review of nursery records in the Latter-day Saints Hospital | Live births | No | 59,561 | Moderate | Weak | Strong | Strong | Weak |
| South America | (Barbosa-Buck et al., 2012) | Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Paraguay, Uruguay, and Venezuela | NR | 4.40 | 2000/01–2007/12 | ECLAMC | Live births, stillbirths > 500 g | No | 1,544,496 | Strong | Moderate | Strong | Strong | Strong |
| | (Duarte et al., 2018) | Argentina | 24 jurisdictions | 4.75 | 2009/11–2016/12 | RENAC | Live births, stillbirths > 500 g | No | 1,663,610 | Strong | Moderate | Strong | Strong | Strong |
| | (Kallen et al., 1993) | All South American Countries | NR | 1.93b | 1967–1989 | ECLAMC | Live births, stillbirths | No | 2,278,000 | Strong | Weak | Strong | Strong | Strong |
| | (Orioli et al., 1995) | South America | NR | 1.64 | 1967–1981 | ECLAMC | Live births | No | 852,893 | Strong | Strong | Strong | Strong | Strong |
| | | South America | NR | 2.00 | 1982–1992 | ECLAMC | Live births | No | 2,054,682 | Strong | Strong | Strong | Strong | Strong |
| | (Sánchez, Brito-Arreaza, Alvarez-Arratia, & Ramírez, 1991) | Venezuela | Ciudad Bolívar | 14.25 | 1978/04–1990/08 | Congenital malformations surveillance program at Ruiz y Paez Hospital | Live births until 1979-12, live births, stillbirths thereafter | No | 70,152 | Moderate | Strong | Strong | Strong | Weak |
| Europe | (Coi et al., 2019) | Austria | Styria | 1.62 | 1991–2012 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 247,210 | Strong | Moderate | Strong | Strong | Strong |
| | | Belgium | Antwerp | 5.49 | 1991–2014 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 400,634 | Strong | Moderate | Strong | Strong | Strong |
| | | Croatia | Zagreb | 3.73 | 1991–2015 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 160,988 | Strong | Moderate | Strong | Strong | Moderate |
| | (Andersen Jr & Haage, 1989) | Denmark | Fyn | 1.28 | 1970/01–1983/12/31 | County hospital records | Live births, stillbirths | No | 77,977 | Moderate | Moderate | Strong | Strong | Weak |
| | (Coi et al., 2019) | Denmark | Odense | 5.22 | 2000–2014 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 76,625 | Strong | Moderate | Strong | Strong | Weak |
| | (Kallen et al., 1993) | Denmark | NR | 0.61b | 1983–1988 | Danish National Board of Health Registry of Congenital Malformations | Live births, stillbirths | No | 328,000 | Strong | Weak | Strong | Strong | Strong |
| | (Coi et al., 2019) | France | Auvergne | 3.89 | 1991–2015 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 334,612 | Strong | Moderate | Strong | Strong | Strong |
| | | France | Isle de Reunion | 5.94 | 2001–2015 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 218,796 | Strong | Moderate | Strong | Strong | Strong |
| | | France | Paris | 6.11 | 1991–2015 | EUROCAT | Live births, stillbirths ≥ 20 w, elective terminations | No | 768,885 | Strong | Moderate | Strong | Strong | Strong |

(Continues)
| Author(s), year | Country | Sub-National | Birth prevalence | Birth period | Study design/data source | Study population | Specialized care | Sample size | Study quality |
|----------------|---------|--------------|------------------|--------------|--------------------------|-----------------|----------------|-------------|--------------|
| (Stoll, Dott, Roth, & Alembik, 1989) | France | City of Strasbourg (urban area) and “Département du Bas-Rhin” (rural area) | 6.64 | 1979/01-1986/12 | Registry of all newborn children in Strasbourg and Department du Bas-Rhin | Live births, stillbirths | No | 105,374 | Strong, Strong, Strong, Strong, Moderate |
| (Coi et al., 2019) | Germany | Saxony-Anhalt | 4.76 | 1991-2015 | EUROCAT | Live births, stillbirths ≥20 w, elective terminations | No | 357,516 | Strong, Moderate, Strong, Strong, Strong |
| (Kallen et al., 1993) | Italy | NR | 3.42 | 1978-1988 | Italian birth defects monitoring system (IPIMC) | Live births, stillbirths | No | 1,256,000 | Strong, Weak, Strong, Strong, Strong |
| (Camera, 1980) | Italy | Genoa | 1.86 | 1960-1980/02 | Records of osteochondroplasias encountered in the maternity ward of a single hospital | NR | No | 53,700 | Moderate, Weak, Weak, Weak, Weak |
| (Camera & Mastroiacovo, 1988) | Italy | NR | 3.70 | 1978-1985 | IMMSBD | Live births, stillbirths | No | 838,717 | Strong, Strong, Strong, Strong, Strong |
| (Coi et al., 2019) | Italy | Emilia Romagna | 5.70 | 1991-2015 | EUROCAT | Live births, stillbirths ≥20 w, elective terminations | No | 806,485 | Strong, Moderate, Strong, Strong, Strong |
| (Coi et al., 2019) | Tuscany | 5.06 | 1991-2015 | IPIMC | Live births, stillbirths | No | 672,268 | Strong, Moderate, Strong, Strong, Strong |
| (Orioli et al., 1995) | Italy | NR | 3.61 | 1978-1991 | IPIMC | Live births, stillbirths | No | 1,494,756 | Strong, Weak, Strong, Strong, Strong |
| (Coi et al., 1991) | Ireland | Cork & Kerry | 3.34 | 1996-2015 | EUROCAT | Live births, stillbirths ≥20 w, elective terminations | No | 179,563 | Strong, Moderate, Strong, Strong, Strong |
| Malta | NR | 6.35 | 1991-2015 | No | Strong, Moderate, Strong, Strong, Moderate |
| Netherlands | Northern region | 3.01 | 1991-2015 | No | Strong, Moderate, Strong, Strong, Strong |
| Norway | NR | 2.39 | 1999-2012 | No | Strong, Moderate, Strong, Strong, Strong |
| Poland | Wielkopolska | 4.47 | 1999-2015 | No | Strong, Moderate, Strong, Strong, Strong |
| Spain | Basque Country | 2.72 | 1991-2015 | No | Strong, Moderate, Strong, Strong, Strong |
| Spain | Valencia region | 2.69 | 2007-2015 | No | Strong, Moderate, Strong, Strong, Strong |
| (Martínez-Friás et al., 1991) | Spain | 16 of the 17 Spanish Regions (Comunidades Autónomas) | 2.53 | 1976/04-1988/12 | ECBMC | Live births | No | 710,815 | Strong, Moderate, Strong, Strong, Strong |
| (Gustavsson & Jonulf, 1975) | Sweden | Uppsala | 6.75 | 1970/02-1974/08 | Prospective collection of neonatal disorders and anomalies of the skeleton at the University Hospital in Uppsala | Live births, stillbirths | No | 14,816 | Moderate, Strong, Strong, Strong, Weak |
| Author(s), Year | Country | Sub-National | Birth Prevalence | Birth Period | Study Design/Data Source | Study Population | Specialized Care\(^\text{a}\) | Sample Size | Data Quality | Study Quality |
|----------------|---------|--------------|------------------|--------------|-------------------------|----------------|----------------|-------------|--------------|---------------|
| (Kallen et al., 1993) | Sweden | NR | 1.64\(^\text{b}\) | 1965–1989 | Swedish register of congenital malformations | Live births, stillbirths | No | 2,375,000 | Strong | Weak | Strong | Strong | Strong |
| (Coi et al., 2019) | Switzerland | Vaud | 3.63 | 1991–2015 | EUROCAT | Live births, stillbirths ≥20 w, elective terminations | No | 192,684 | Strong | Moderate | Strong | Strong | Strong |
| UK | Wessex | 4.07 | 1994–2015 | Strong | Moderate | Strong | Strong | Strong | Weak |
| UK | Wales | 3.48 | 1998–2015 | No | No | No | No | No | No | No |
| UK | South West England | 3.12 | 2005–2015 | Strong | Moderate | Strong | Strong | Strong | Strong | Strong |
| UK | Northern England | 3.03 | 1991–2015 | No | No | No | No | Strong | Moderate | Strong | Strong | Strong | Strong |
| UK | Thames Valley | 1.94 | 1991–2015 | No | No | No | No | Strong | Moderate | Strong | Strong | Strong | Strong |
| (Gardner, 1977) | UK | Edinburgh | 1.93 | 1964/04–1968/10 | Edinburgh Register of the Newborn | Live births, stillbirths | No | 51,836 | Strong | Strong | Strong | Strong | Weak |
| | | | 2.73\(^\text{b}\) | 1968/11–1972/12, 1968/11–1972/11 | Birth records at the Simpson Memorial Maternity Pavilion of the Royal Infirmary and at the Eastern General Hospital | Live births, stillbirths | No | 36,569 | Moderate | Strong | Strong | Strong | Weak |
| (Harris & Patton, 1971) | UK | Manchester | 6.26\(^\text{b}\) | 1951–1969 | Reassessment of cases of achondroplasia from birth records at St. Mary’s Hospital, Manchester | Live births, stillbirths | No | 63,934 | Moderate | Moderate | Strong | Strong | Weak |
| (Sokal, Taf, & Fleming, 2014) | UK | Whole Country | 7.56\(^\text{b}\) | 1990–2009 | Prospectively collected primary care data from THIN | Live births | No | 794,169 | Moderate | Weak | Strong | Strong | Strong |
| (Stevenson, 1957) | UK | Belfast | 28.34 | 1938/01–1956/06 | Records of the Royal Maternity Hospital | Live births, stillbirths | No | 31,753 | Moderate | Moderate | Strong | Strong | Weak |
| (Coi et al., 2019) | Ukraine | OMNI-net | 6.00 | 2005–2015 | EUROCAT | Live births, stillbirths ≥20 w, elective terminations | No | 333,189 | Strong | Moderate | Strong | Strong | Strong |

(Continues)
| Author(s), year            | Country       | Sub-National           | Birth prevalence | Birth period       | Study design/data source                                      | Study population | Specialized care? | Sample size | Study quality | Data source | Diagnostic method | Numerator | Denominator | Population size |
|---------------------------|---------------|------------------------|------------------|-------------------|----------------------------------------------------------------|-----------------|--------------------|-------------|---------------|-------------|------------------|------------|-------------|-----------------|
| (Alaani, Al-Fallouji, Busby, & Hamdan, 2012) | Iraq          | Fallujah               | 16.53b           | 2009/11-2010/09   | Records from a single pediatric clinic                         | Live births     | Yes                 | 6,049       | Moderate     | Weak        | Strong           | Strong     | Strong       | Weak            |
| (Al-Ani et al., 2012)     | Iraq          | Al-Anbar governorate   | 52.25            | 2010/10-2011/10   | WICCAFS                                                        | Live births     | Yes                 | 5,742       | Strong       | Moderate   | Strong           | Strong     | Strong       | Weak            |
| (Al-Janabi, 2007)         | Iraq          | Al-Anbar governorate   | 241.60           | 2000/07-2002/06   | Prospective collection of congenital malformation frequency at the Maternal and Children Hospital in Al-Anbar governorate | Live births, stillbirths | No                  | 12,831      | Moderate     | Strong     | Strong           | Strong     | Strong       | Weak            |
| (Al-Obaidi, Mahmood, & Al-Dalla Ali, 2013) | Iraq          | Ramadi                 | 66.93            | 2009/02-2009/10   | Prospective collection of congenital malformation frequency at the Maternal and Children Teaching Hospital in Ramadi | Live births, stillbirths | No                  | 1,494       | Moderate     | Moderate   | Strong           | Strong     | Strong       | Weak            |
| (Al-Rubaili, Al-Tufaily, & Fakhri, 2009) | Iraq          | Babylon                | 62.82b           | 2007/01-2008/01   | Records from Babylon Maternity and Pediatrics Teaching Hospital | Live births     | No                  | 9,551       | Moderate     | Moderate   | Strong           | Strong     | Strong       | Weak            |
| (Tabou, 2012)             | Iraq          | Mosul                  | 34.21b           | 2009/01-2010/12   | Prospective study of congenital abnormalities at Lahore General Hospital | Live births, stillbirths | No                  | 46,775      | Moderate     | Moderate   | Strong           | Strong     | Strong       | Weak            |
| (Madi, Al Naggar, Al Awadi, & Bastaki, 2005) | Kuwait        | Al-Jahra Region        | 12.92b           | 2000/01-2001/12   | Data from the newborn register at AL-Jahra Hospital            | Live births, stillbirths | No                  | 7,739       | Moderate     | Strong     | Strong           | Strong     | Strong       | Weak            |
| (Bittar, 1998)            | Lebanon       | Southern sector of Beirut, Baalbak, Hermel and South Lebanon | 25.87            | 1991/02-1993/07   | Prospective collection of congenital malformation frequency at a large hospital in south Beirut | Live births, stillbirths | No                  | 3,865       | Moderate     | Moderate   | Strong           | Strong     | Strong       | Weak            |
| (Al-Jama, 2001)           | Saudi Arabia  | Al-Khobar              | 6.77             | 1992/01-1997/12   | Retrospective examination of delivery room records             | Singleton live births | Yes                 | 14,762      | Moderate     | Strong     | Strong           | Strong     | Strong       | Weak            |
| (Sallout et al., 2015)    | Saudi Arabia  | Riyadh                 | 48.14            | 2007/01-2012/12   | Prospective collection of data on congenital anomalies in the obstetrics and gynecology ultrasound unit King Fahad Medical City | Live births     | Yes                 | 29,084      | Moderate     | Moderate   | Strong           | Strong     | Strong       | Weak            |
| Author(s), year | Country       | Sub-National                  | Birth prevalence | Birth period          | Study design/data source                                                                 | Study population              | Specialized care | Sample size | Study quality |
|--------------|--------------|-------------------------------|------------------|-----------------------|------------------------------------------------------------------------------------------|------------------------------|------------------|-------------|----------------|----------------|
| (Al-Gazali et al., 2003) | UAE          | Al Ain Medical District       | 10.51            | 1996/01-2000/12       | Active malformation surveillance system in Al Ain Medical District                         | Live births, stillbirths     | No               | 38,048      | Strong         | Strong         | Strong         | Strong         | Weak          |

Sub-Saharan Africa

| Author(s), year | Country       | Sub-National                  | Birth prevalence | Birth period          | Study design/data source                                                                 | Study population              | Specialized care | Sample size | Study quality |
|----------------|--------------|-------------------------------|------------------|-----------------------|------------------------------------------------------------------------------------------|------------------------------|------------------|-------------|----------------|----------------|
| (Charlotte, Aurore, Charlotte, Esther, & Eugene, 2015) | Camaroon     | NR                            | 16.53            | 2008/01-2012/06       | Prospective collection of congenital malformation frequency at Doala General Hospital     | Live births, stillbirths     | Yes              | 6,048       | Moderate       | Moderate       | Strong         | Strong         | Weak          |

South-East Asia/Oceania

| Author(s), year | Country       | Sub-National                  | Birth prevalence | Birth period          | Study design/data source                                                                 | Study population              | Specialized care | Sample size | Study quality |
|----------------|--------------|-------------------------------|------------------|-----------------------|------------------------------------------------------------------------------------------|------------------------------|------------------|-------------|----------------|----------------|
| (Oberklaid, Danks, & Jensen, 1979) | Australia    | Victoria                      | 3.85             | 1969-1975             | Royal Children's Hospital records and surveys of all pediatricians, radiologists, orthopedic surgeons in Victoria (1968-1970), Newspaper and television publicity, Little Peoples' Association of Australasia, and personal visits to rural areas to ascertain additional cases. | NR                           | No               | 492,889     | Weak          | Weak          | Weak          | Weak          | Strong        |

(Continues)
| Author(s), year | Country | Sub-National | Birth prevalence | Birth period | Study design/data source | Study population | Specialized care¹ | Sample size | Data source | Diagnostic method | Numerator | Denominator | Population size |
|----------------|---------|--------------|------------------|--------------|--------------------------|-----------------|-----------------|-------------|-------------|------------------|-----------|-------------|-----------------|
| (Kallen et al., 1993) | Australia | NR | 4.93³ | 1981-1989 | Data from Australian National data systems for (1) congenital malformations and (2) for pregnancies resulting from in vitro fertilization. | Live births, stillbirths | No | 1,946,000 | Strong | Weak | Strong | Strong | Strong |
| (Jaiikrishan et al., 2013) | India | NR | 11.38 | 1995/08-2011/06 | Prospective collection of congenital malformation frequency in 7 government hospitals serving people from high and normal national radiation areas | Live births, stillbirths >28 w | No | 140,558 | Moderate | Moderate | Strong | Strong | Moderate |
| (Kusumalatha et al., 2017) | India | Kakinada | 14.40⁴ | 2016/01-2016/12 | Hospital-based cross-sectional study | Live births, stillbirths | No | 13,893 | Moderate | Moderate | Strong | Strong | Weak |
| (Rasheed & Haseeb, 2016) | India | Maharashtra | 14.26 | 1994/03-1995/04 | Prospective collection of frequencies of congenital anomalies at Marden Medical Complex | Live births, stillbirths | Yes | 7,012 | Moderate | Moderate | Strong | Strong | Weak |
| (Higurashi et al., 1990) | Japan | Tokyo | 10.92 | 1972/07-1985/12 | Records from consecutive births in a single large maternity hospital in Tokyo | Live births | No | 27,472 | Moderate | Moderate | Strong | Strong | Weak |
| (Peng, 1988) | Malaysia | State of Kedah | 10.12 | 1984/04-1987/03 | Records of live births occurring in Alor Setar General Hospital | Live births | Yes | 19,769 | Moderate | Moderate | Strong | Strong | Weak |
| (Qadir, Amir, & Bano, 2017) | Pakistan | Mardan | 10.58⁵ | 2016/05-2017/04 | Prospective collection of frequencies of congenital anomalies at Government Medical College and Hospital | NR | No | 9,453 | Moderate | Moderate | Weak | Weak | Weak |
| (Tariq, 2010) | Pakistan | Lahore | 34.82⁶ | 2007/01-2007/12 | Prospective study of congenital abnormalities at Al-Batool Teaching Hospital of Obstetrics and Gynecology | NR | No | 2,872 | Moderate | Moderate | Weak | Weak | Weak |
Figure 2, the most common domain (40% of estimates) on which an estimate may have received a weak score was population size (i.e., the investigated population was too small to estimate birth prevalence with 95% confidence). The description of the numerator was weak (it was unclear if the numerator included still births and/or elective terminations) in 15.5% of all estimates and the denominator was not congruent to the numerator (e.g., numerator included still births and/or elective terminations and the denominator included only livebirths) in 16.7%. Case definition method was weak in 17.8% of all estimates. Only one study scored weak on data source (1.1%).

3.2 | Meta-analyses

Pooled analysis based on the quality effects model showed a worldwide achondroplasia birth prevalence of 4.6 cases per 100,000 births (Table 4). Figure 3 shows an overview of the global pooled prevalence of achondroplasia and the pooled estimate per region using the quality effects model.

The pooled birth prevalence estimate was substantially higher in North Africa/Middle East (35.1 per 100,000, based on 13 estimates) and Sub-Saharan Africa (17.9 per 100,000, based on five estimates), compared with other regions. All of the studies conducted in these regions were relatively small, resulting in very large confidence intervals (Figure 3). One study conducted in North Africa/Middle East (N = 12,831) (Al-Janabi, 2007) reported a birth prevalence of 240.6 cases per 100,000 births. When this study was omitted from the regional analysis, the estimated $I^2$ changed to 54.5% ($p = .052$) and the pooled birth prevalence changed to 24.4 cases (95%CI 9.1–46.5) per 100,000 births, which is still higher than observed in other regions. The lowest pooled prevalence estimates were found in South America (3.5 per 100,000, based on six estimates) and Europe (3.5 per 100,000, based on 40 estimates). Results were generally similar to those obtained in the random effects model.

The pooled birth prevalence differed by the setting in which subjects gave birth with a 3-fold higher birth prevalence (13.3 cases per 100,000 births) in specialized care settings compared with other settings (4.2 cases per 100,000 births). Results obtained using the fixed effects model were generally similar to those obtained in the quality effects model (Table 4).

3.3 | Heterogeneity and bias

A high level of heterogeneity was observed among the studies (Table 4). Heterogeneity persisted even after stratification by region and study date (e.g., omitting papers conducted on or before 1975, data not shown).

The visual asymmetry of the Doi plot suggested publication bias, where smaller studies reported higher birth prevalence estimates (Figure 4). The LFK index of 3.78 suggested positive asymmetry of the
plot. However, when stratifying the results by region, major asymmetry suggesting publication bias was only present for reports of birth prevalence in North America, Sub-Saharan Africa and the Asia/Oceania region, with LFK indexes of 2.73, 2.56 and 7.23, respectively. Minor asymmetry was detected in South America, Europe, North Africa/Middle East, with LFK indexes of 1.02, 1.18, and 1.37, respectively.

**TABLE 4** Meta-analysis of reported achondroplasia birth prevalence stratified by study setting and by region

| Region                        | Pooled birth prevalence per 100,000 | Higgins $I^2$ test (95% CI) | $N$ studies; $N$ estimates | Quality index $^a$ |
|-------------------------------|-------------------------------------|-----------------------------|----------------------------|-------------------|
|                               | Quality effects model (95% CI)      | Random effects model (95% CI) | $p$ value$^b$               |                   |
| Worldwide                     | 4.6 (3.9–5.4)                       | 4.5 (4.1–5.0)               | 84.3 (81.3–86.9)            | 52; 90            | 23.0 |
| Specialized care$^c$          | 13.3 (5.3–24.6)                     | 16.4 (8.8–26.3)             | 78.4 (64.3–87.0)            | 14; 14            | 30.2 |
| Other settings$^d$            | 4.2 (3.5–4.9)                       | 4.2 (3.7–4.6)               | 84.2 (80.8–87.0)            | 38; 76            | 18.8 |
| North America                 | 4.2 (3.5–5.0)                       | 4.2 (3.5–4.9)               | 71.18 (51.3–82.9)           | 9; 15             | 52.5 |
| South America                 | 3.5 (2.1–5.3)                       | 3.9 (2.5–5.7)               | 91.4 (84.1–95.4)            | 5; 6              | 11.0 |
| Europe                        | 3.5 (3.0–4.2)                       | 3.6 (3.2–4.0)               | 76.2 (67.9–82.4)            | 13; 40            | 14.5 |
| North Africa and Middle east  | 35.1 (14.9–63.0)                    | 43.1 (23.0–69.3)            | 82.6 (71.5–89.4)            | 13; 13            | 18.6 |
| Sub-Saharan Africa            | 17.9 (3.0–42.8)                     | 12.8 (2.2–30.6)             | 82.7 (60.5–92.5)            | 5; 5              | 65.4 |
| South and Southeast Asia/Oceania | 5.9 (2.9–10.0)                     | 6.3 (3.8–9.4)               | 61.9 (26.7–80.3)            | 11;11             | 33.1 |

Abbreviation: CI, confidence intervals.

$^a$The quality index represents the extent to which (percent) the weights of the inverse variance fixed effect model are redistributed by the application of the quality effect weights.

$^b$Chi$^2$ $p$-value.

$^c$Women who gave birth in a specialized care setting (i.e., referral center or tertiary hospital).

$^d$Women who gave birth in other settings (not a referral center or tertiary hospital).

**FIGURE 2** Quality assessment of included estimates ($N = 90$). For numerator and denominator a moderate score was not an option (Table 1) [Color figure can be viewed at wileyonlinelibrary.com]
DISCUSSION

Meta-analysis of the studies included in this systematic literature review estimated the pooled birth prevalence of achondroplasia in the general population worldwide to be 4.6 cases (95% CI 3.9–5.4) per 100,000 births, based on 52 studies and 90 study estimates.

A high degree of heterogeneity was observed among estimates of birth prevalence. Several factors may contribute to this heterogeneity, including reporting of birth prevalence in all pregnancies vs. restricted to live births (18%). In the article by Coi et al., 18.9% of diagnosed cases resulted in terminations of pregnancy for fetal anomaly, a factor that may apply in other studies as well (Coi et al., 2019). The inclusion of stillbirths and elective terminations in some of the studies may have led to some degree of overestimation of achondroplasia birth prevalence. In addition, reported birth prevalence tended to be higher in smaller studies and in those reporting data deriving from specialized care settings. This latter observation may reflect the fact that mothers in whom fetal anomalies are suspected may be more likely to give birth in these centers, especially in regions (or in past eras) where home-births are more common. Other factors that could account, in part, for discrepancies among the reports include completeness of ascertainment and diagnostic accuracy; however, these could not be readily assessed.

The birth prevalence appeared substantially higher in North Africa and the Middle East, and in Sub-Saharan Africa than in other regions. These large regional variances were not in accordance with our expectations, as the preponderance of achondroplasia cases arise from spontaneous dominant mutations (Horton et al., 2007), which would not necessarily be expected to give rise to isolated “hotspots.” The studies that reported unusually high birth prevalence tended to be smaller studies (scoring weak on the population size domain of the quality assessment tool, Table 3) and did not provide evidence-based explanations for the high number of congenital malformation cases.
observed. Because of the small population sizes surveyed, the precision of the estimate for these regions is notably lower (i.e., the confidence intervals are larger, see Figure 3) than for other regions. In addition, the proportion of estimates for which data were derived from specialized care settings was substantially higher in North Africa and the Middle East, and in Sub-Saharan Africa compared with other regions (80% for Sub-Saharan Africa and 46% for North Africa and Middle East, as compared to 18% for South and Southeast Asia/Oceania, 13% for North America, and 0% for South America and Europe), which may also contribute to higher apparent prevalence. While the estimates for North Africa and the Middle East, and for Sub-Saharan Africa may reflect the genuine birth prevalence, they should be interpreted in the context of these limitations. However, achondroplasia birth prevalence has been linked to race, ethnicity, and social factors (Orioli et al., 1995; Waller et al., 2008; Wilkin et al., 1998), such as advanced paternal age (Duarte et al., 2018). Also, there is growing (though inconclusive) evidence that higher incidences of congenital abnormalities can be due to prenatal exposure to environmental pollution (e.g., air- and water-pollution as a result of urbanization and industrialization; Dolk & Vrijheid, 2003; Vrijheid et al., 2011). Such factors may have the potential to have contributed to a truly elevated birth prevalence in these regions.

The visual assessment of the Doi plot and the positive LFK index indicated major asymmetry, suggesting that the pooled birth prevalence resulting from our analysis may be slightly overestimated (Furuya-Kanamori et al., 2018). However, the asymmetry could arise from sources other than publication bias (e.g., data irregularities and/or heterogeneity; Egger, Davey Smith, Schneider, & Minder, 1997; Sterne, Egger, & Smith, 2001; Sterne & Harbord, 2004). When publication bias was assessed by region, major asymmetry was only detected in North America, Sub-Saharan Africa and Asia/Oceania.

In the course of developing this systematic literature review, it became apparent that there were deficiencies both in the way studies were conducted as well as in the way in which results were reported, which undoubtedly contributed to the heterogeneity discussed previously. The fact that only three of the reports scored strongly across all domains in our quality rating scale reflects a need for better study design and reporting in the epidemiological literature.

In an attempt to compensate for some of the quality differences, a quality effects model was used as the primary model for meta-analysis in this study. This model was designed to take differences in study quality into account, by giving lower weights to studies of lower quality (Doi & Thalib, 2008). However, one limitation of this approach is that the mean quality over all domains was used in the calculations implying that each domain was of equal importance. In addition, the model did not necessarily distinguish deficiencies in the quality in the reporting from the quality of the study design and execution. As the random effects model is also a well-known and widely used approach, results are also presented using this model (Table 4). For most analyses, no large differences in pooled birth prevalence were observed between the models and confidence intervals were overlapping. Thus, while we feel the quality evaluation was worthwhile and informative, it clearly does not account for all for the heterogeneity among the studies.

5 CONCLUSION

Based on 52 studies and 90 prevalence estimates, this systematic review and meta-analysis estimated the achondroplasia birth prevalence worldwide, as well as for different regions of the world. The worldwide pooled birth prevalence using a quality effects model was 4.6 cases (95% CI 3.9–5.4) per 100,000 births or 1 in 22,000 births (95% CI 18,500 to 26,000). To our knowledge this is the most comprehensive estimate of achondroplasia birth prevalence available. Careful interpretation of these results is advised, as most reports lacked key study design and/or reporting elements and moderate to high heterogeneity was present.

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CONFLICT OF INTEREST

The review team members P. K. F., S. L., and R. S. are employed by BioMarin Pharmaceutical, Inc.

AUTHOR CONTRIBUTIONS

Pamela K. Foreman, Renée Shediac, Sarah Landis, Judith van den Bosch, and Femke van Kesse involved in conception and design of the work. Pamela K. Foreman, Judith van den Bosch, Femke van Kesse, and Rosa van Hoorn involved in acquisition, analysis of the data. Pamela K. Foreman, Judith van den Bosch, Femke van Kesse, Rosa van Hoorn, Renée Shediac, and Sarah Landis involved in interpretation of the data. Pamela K. Foreman, Renée Shediac, Sarah Landis, Judith van den Bosch, and Femke van Kesse involved in development of the quality of evidence tool. Pamela K. Foreman, Renée Shediac, Sarah Landis, Judith van den Bosch, Femke van Kesse, and Rosa van Hoorn involved in drafting and revising the article.

DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated.

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APPENDIX I

SEARCH STRINGS

PubMed (MEDLINE)

#1 Achondroplasia
("achondroplasia"[MeSH Terms] OR "achondroplasia"[All Fields])
OR achondroplastic[All Fields] OR "skeletal dysplasia"[all fields]

#2 Birth prevalence

"Prevalence"[Mesh] OR prevalen*[tiab] OR "epidemiology"[Mesh] OR "epidemiology"[subheading] OR epidemiol*[tiab] OR burden*[tiab] OR "Incidence"[Mesh] OR inciden*[tiab]

Limits:
• Publication date: from first release date to 29-07-2019.
• Language: all languages with abstract in English

#1 and #2 yielded 421 hits.

Embase

#1 Achondroplasia
‘achondroplasia’/exp OR ‘achondroplasia’ OR achondroplastic or ‘skeletal dysplasia’

#2 Birth prevalence

‘prevalence’/exp OR ‘prevalen’*:ab, ti OR ‘epidemiology’/exp OR epidemiol*:lnk OR epidemiol*:ab, ti OR ‘incidence’/exp OR inciden*:ab, ti

Limits:
• Publication date: from first release date to 29-07-2019.
• Language: all languages with abstract in English

#1 and #2 yields 746 hits.