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ORIGINAL ARTICLE

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;

Abbreviations: CIs, confidence intervals; *FGFR3* gene, fibroblast growth factor receptor 3 gene; LFK index, Luis Furuya-Kanamori index.

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Rousseau et al., 1994; Shiang et al., 1994). Achondroplasia is inherited as an autosomal dominant condition, although it is estimated that approximately 80% of cases occur due to a de novo germ cell mutations in unaffected parents (Horton et al., 2007). In some studies, this is related to advanced paternal age (Orioli, Castilla, Scarano, & Mastroiacovo, 1995; Waller et al., 2008; Wilkin et al., 1998).

Achondroplasia can result in medical complications that significantly increase morbidity and mortality across the lifespan. Common medical complications include delayed motor and speech development in children (Hunter, Bankier, Rogers, Sillence, & Scott Jr., 1998; Ireland et al., 2010; Ireland et al., 2011; Ireland et al., 2012), otolaryngeal problems such as otitis media associated with hearing loss (Afsharpaiman, Sillence, Sheikhvatan, Ault, & Waters, 2011; Hunter et al., 1998; Tunkel et al., 2012), respiratory dysfunction including obstructive sleep apnea (Afsharpaiman et al., 2011; Hunter et al., 1998) spinal stenosis and compression (Hunter et al., 1998; Shirley & Ain, 2009), and dental malocclusions (Hunter et al., 1998). Furthermore, these medical complications can cause significant pain and diminish physical function and quality of life (Alade et al., 2013; Dhiman et al., 2017; Gollust, Thompson, Gooding, & Biesecker, 2003; Mahomed, Spellmann, & Goldberg, 1998; Matsushita et al., 2019). Mortality rates are elevated in individuals with achondroplasia at all ages due to an increased risk of sudden death in young children attributed to brainstem compression resulting from foramen magnum stenosis and greater mortality risk in adulthood related to cardiovascular disease, neurological complications, and accidents (Hashmi et al., 2018; Hecht, Francomano, Horton, & Annegers, 1987; Simmons, Hashmi, Scheuerle, Canfield, & Hecht, 2014; Wynn, King, Gambello, Waller, & Hecht, 2007). While there is currently no approved effective pharmacological treatment for skeletal dysplasias caused by variants of *FGFR3* gene, efforts to develop disease-specific therapies for achondroplasia are underway (Breinholt et al., 2019; Garcia et al., 2013; Komla-Ebri et al., 2016; Savarirayan et al., 2019). Treatment with growth hormone does not have substantial effect (Harada et al., 2017) and while limb lengthening can be successful, it is a major undertaking associated with significant complications (Donaldson, Aftab, & Bradish, 2015; Kim, Balce, Agashe, Song, & Song, 2012; Ko, Shim, Chung, & Kim, 2019; Leiva-Gea et al., 2020; Venkatesh et al., 2009).

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 1 in 2,000 people (GARD, 2019; Orphanet, 2019). Deriving accurate prevalence estimates in a rare disease is especially challenging due to small population sizes, incomplete disease characterization, and rapidly evolving diagnostic methods. Furthermore, prevalence data can vary by population 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 was 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	Moderate	Weak
Data source	Was the data source complete and representative of the population as a whole?	• Community/population-based screening/newborn screening • Disease registry	• Hospital-based records • Laboratory-based records • General practice-based records	• Survey by query (e.g., postcards) • Personal communication • NR, unclear, other
Diagnostic method	Was the method(s) used for the case definition definitive?[a]	• Radiographic • Autopsy • Positive mutational analysis	• Clinical presentation only	• NR • Too vague to determine
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 • Denominator is not sufficiently described
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

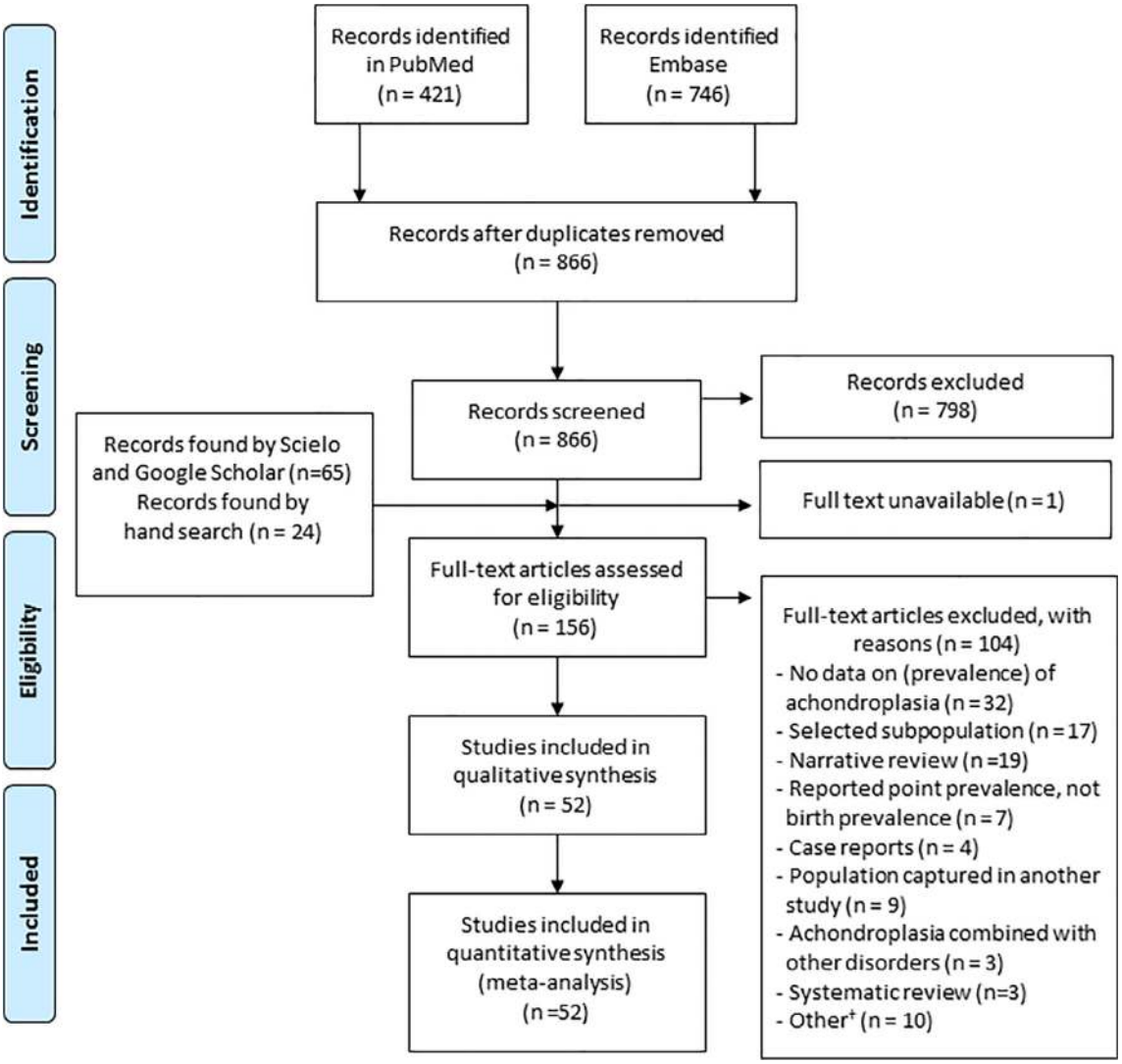

FIGURE 1 Flow chart of selection process (Moher, Liberati, Tetzlaff, & Altman, 2009). † For example, Modeling study, no original data, no English abstract [Color figure can be viewed at wileyonlinelibrary.com]

(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

TABLE 2 Summary statistics of reported achondroplasia birth prevalence

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[b]; 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[c]	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%)
Populations investigated in specialized care[d]			
Yes	13.43 (7.61–2,921)	14; 14 (15.6%)	524,538 (1.08%)
No	4.08 (2.94–6.43)	38; 76 (84.4%)	47,928,811 (98.92%)

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).

[b]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).

[c]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.

TABLE 3 Individual birth prevalence reports and study characteristics by region and by country

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
North America													
(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	10.99[b]	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	2.51[b]	1978–1988	Programa Mexicano de Registro y vigilancia epidemiogica de malformaciones congentias externas	Live births, stillbirths	No	359,000	***Strong***	*Weak*	***Strong***	***Strong***	***Strong***
(Curran, Sigmon, & Opitz, 1974)	USA	New Jersey	4.00[b]	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	2.66[b]	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	1972/02–1975/02, 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, Srisukhumbowornchai, & Feldkamp, 2012)	USA	Utah	3.53	1999–2008	UBDN	Live births, stillbirths, elective terminations	No	509,286	***Strong***	***Strong***	***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	Atlanta 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***

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Woolf & Turner, 1969)	USA	Salt Lake City, Utah	13.43[b]	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	1.93[b]	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			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 Hopital	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			No	400,634	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	Croatia	Zagreb	3.73	1991–2015			No	160,988	***Strong***	**Moderate**	***Strong***	***Strong***	**Moderate**
(Andersen Jr & Hauge, 1989)	Denmark	Fyn	1.28	1970/01/01–1983/12/31	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	0.61[b]	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			No	218,796	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	France	Paris	6.11	1991–2015			No	768,885	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***

(Continues)

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Stoll, Dott, Roth, & Alembik, 1989)	France	City of Strasbourg (urban area) and "Département du Bas-Rhin" (rural area)	6.64	19 79/01–1986/12	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[b]	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[b]	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			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., 2019)	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	110,174	***Strong***	**Moderate**	***Strong***	***Strong***	**Moderate**
	Netherlands	Northern region	3.01	1991–2015			No	465,261	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	Norway	NR	2.39	1999–2012			No	836,535	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	Poland	Wielkopolska	4.47	1999–2015			No	626,876	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	Spain	Basque County	2.72	1991–2015			No	441,896	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	Spain	Valencia region	2.69	2007–2015			No	446,903	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
(Martínez-Frías et al., 1991)	Spain	16 of the 17 Spanish Regions (Comunidades Autonomas)	2.53	1976/04–1988/12	ECEMC	Live births	No	710,815	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
(Gustavson & Jorulf, 1975)	Sweden	Uppsala	6.75[b]	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*

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Kallen et al., 1993)	Sweden	NR	1.64[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			No	615,000	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	UK	Wales	3.48	1998–2015			No	602,776	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	UK	South West England	3.12	2005–2015			No	545,302	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	UK	Northern England	3.03	1991–2015			No	824,745	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
	UK	Thames Valley	1.94	1991–2015			No	411,928	***Strong***	**Moderate**	***Strong***	***Strong***	***Strong***
(Gardner, 1977)	UK	Edinburgh	1.93[b]	1964/04–1968/10	Edinburgh Register of the Newborn	Live births, stillbirths	No	51,836	***Strong***	***Strong***	***Strong***	***Strong***	*Weak*
			2.73[b]	1968/11–1973/12, 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[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, Tata, & Fleming, 2014)	UK	Whole country	7.56[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***
Northern Africa/Middle East													
(Golalipour, Ahmadpour-Kacho, & Vakili, 2005)	Iran	Gorgan	40.02	1998/01–1999/08	Prospective collection of congenital malformation frequency at a referral hospital in Gorgan	Live births, stillbirths	Yes	9,996	**Moderate**	**Moderate**	***Strong***	***Strong***	*Weak*
(Golalipour, Kaviany, Golalipour, Mirfazeli, & Behnampour, 2018)	Iran	Gorgan, Golestan Provincein	33.44	2007/03–2011	Prospective collection of frequencies of congenital limb defects in 3 hospitals in Gorgan	Live births	Yes	32,895	***Strong***	**Moderate**	***Strong***	***Strong***	*Weak*

(Continues)

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Alaani, Al-Fallouji, Busby, & Hamdan, 2012)	Iraq	Fallujah	16.53[b]	2009/11–2010/09	Records from a single pediatric clinic	Live births	Yes	6,049	**Moderate**	*Weak*	***Strong***	***Strong***	*Weak*
(Al-Ani et al., 2012)	Iraq	Al-Anbar governorate	52.25	2010/10–2011/10	WICCARS	Live births	Yes	5,742	***Strong***	**Moderate**	***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 governate	Live births, stillbirths	No	12,831	**Moderate**	**Moderate**	***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 Maternity and Children Teaching Hospital in Ramadi	Live births, stillbirths	No	1,494	**Moderate**	**Moderate**	***Strong***	***Strong***	*Weak*
(Al-Rubaii, Al-Tufaily, & Fakhri, 2009)	Iraq	Babylon	62.82[b]	2007/01–2008/01	Records from Babylon Maternity and Pediatrics Teaching Hospital	Live births	No	9,551	**Moderate**	**Moderate**	***Strong***	*Weak*	*Weak*
(Taboo, 2012)	Iraq	Mosul	34.21[b]	2009/01–2010/12	Prospective study of congenital abnormalities at Lahore General Hospital	Live births, stillbirths	No	46,775	**Moderate**	**Moderate**	***Strong***	***Strong***	*Weak*
(Madi, Al Naggar, Al Awadi, & Bastaki, 2005)	Kuwait	Al-Jahra Region	12.92[b]	2000/01–2001/12	Data from the newborn register at AL-Jahra Hospital	Live births, stillbirths	No	7,739	**Moderate**	***Strong***	***Strong***	***Strong***	*Weak*
(Bittar, 1998)	Libanon	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***	*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***	*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***	*Weak*

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(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													
(Charlotte, Aurore, Charlotte, Esther, & Eugene, 2015)	Camaroon	NR	16.53[b]	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*
(Ekanem et al., 2008)	Nigeria	Cross River and Akwa Ibom states	3.13	1980–2003	Records from University of Calabar Teaching Hospital, St Luke's Hospital Anua, Uyo, and St Mary's Hospital Uruakpan	NR	Yes	127,929	**Moderate**	*Weak*	*Weak*	*Weak*	**Moderate**
(Ekanem, Bassey, Mesembe, Eluwa, & Ekong, 2011)	Nigeria	Port Harcourt, Rivers state	12.60[b]	1990–2003	Records from 2 major hospitals in Port Harcourt	NR	Yes	39,693	**Moderate**	*Weak*	*Weak*	*Weak*	*Weak*
(Sunday-Adeoye, Okonta, & Egwuatu, 2007)	Nigeria	Afiko, Ebonyi State	38.62[b]	1980/01–1999/12	Records births at the Mater Misericordiae Hospital	NR	No	33,659	***Strong***	**Moderate**	***Strong***	***Strong***	*Weak*
(Delport, Christianson, Van den Berg, Wolmarans, & Gericke, 1995)	South-Africa	Pretoriaz	5.76	1986/05–1989/04	Prospective collection of congenital malformation frequency at the Kalafong Hospital	Live births	Yes	17,351	**Moderate**	**Moderate**	***Strong***	***Strong***	*Weak*
South-East Asia/Oceania													
(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)

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Kallen et al., 1993)	Australia	NR	4.93[b]	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***
(Jaikrishan 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	14.40[b]	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	10.58[b]	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	34.82[b]	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*

TABLE 3 (Continued)

Author (s), year	Country	Sub-National	Birth prevalence	Birth period	Study design/data source	Study population	Specialized care[a]	Sample size	Study quality				
									Data source	Diagnostic method	Numerator	Denominator	Population size
(Nasreen, Naib, & Ibrar, 2016)	Pakistan	Peshawar	0.00[b]	2007/06–2009/06	Prospective collection of data on congenital anomalies at Khyber Teaching Hospital	NR	No	6,297	Moderate	Moderate	*Weak*	*Weak*	*Weak*
(Jaruratanasirikul et al., 2016)	Thailand	Songkhla, Trang and Phatthalung	2.68[b]	2009/01–2013/12	Records from Bureau of Policy and Strategy, Ministry of Public Health	Live births, stillbirths, elective terminations	No	186,393	*Strong*	Moderate	*Strong*	*Strong*	*Strong*

Abbreviations: ECEMC, Spanish Collaborative Study of Congenital Malformations; ECLAMC, Latin American Collaborative Study of Congenital Malformations; EUROCAT, European network of population-based registries for the epidemiological surveillance of congenital anomalies; g, grams; IMMSBD, Italian birth defects monitoring system; NR, not reported; OMNI-NET, Ukraine Birth Defects Program; RECUMAC, Registry of Congenital Malformations; RENAC, Records from National Network of Congenital Anomalies of Argentina; THIN, the Health Improvement Network; UBDN, Utah Birth Defect Network; UK, United Kingdom; UNIMEF, Department of Maternal Fetal Medicine; USA, United States of America; W, weeks; WICCARS, Western Iraq Center for Congenital Anomalies Registry and Surveillance.

[a]Yes: Women who gave birth at a referral center or tertiary hospital. No: Women who gave birth in other settings.

[b]Calculated per 100,000 births based on raw data provided in the article.

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

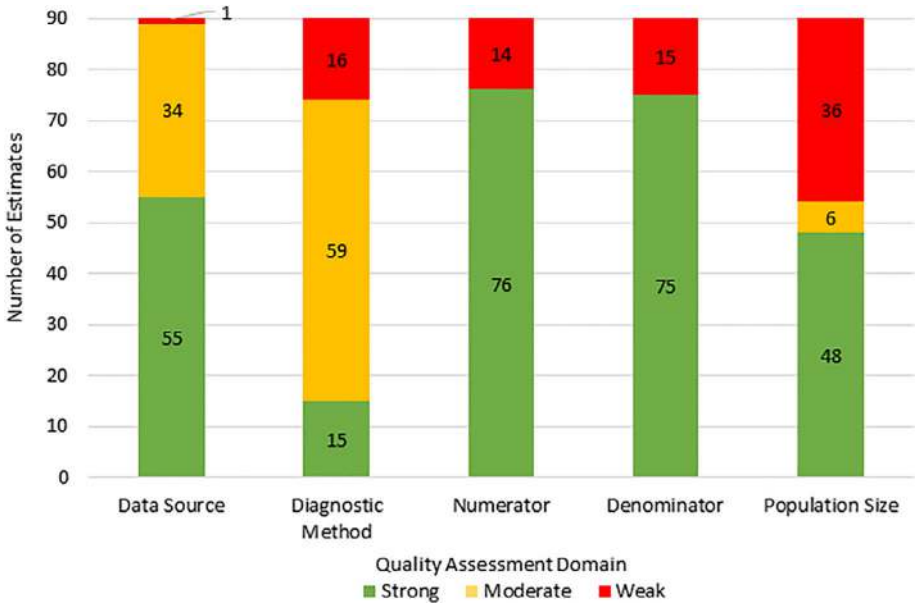

FIGURE 2 Quality assessment of included estimates (*N* = 90). For numerator and denominator a moderate score was not an option (Table 1) [Color figure can be viewed at wileyonlinelibrary.com]

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

	Pooled birth prevalence per 100,000		Higgins I^2 test (95% CI)		
	Quality effects model (95% CI)	Random effects model (95% CI)	*p* value[b]	*N* studies; *N* estimates	Quality index[a]
Worldwide	4.6 (3.9–5.4)	4.5 (4.1–5.0)	84.3 (81.3–86.9) <.001	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) <.001	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) <.001	38; 76	18.8
North America	4.2 (3.5–5.0)	4.2 (3.5–4.9)	71.18 (51.3–82.9) <.001	9; 15	52.5
South America	3.5 (2.1–5.3)	3.9 (2.5–5.7)	91.4 (84.1–95.4) <.001	5; 6	11.0
Europe	3.5 (3.0–4.2)	3.6 (3.2–4.0)	76.2 (67.9–82.4) <.001	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) <.001	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) <.001	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) <.001	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).

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 Afica/Middle East, with LFK indexes of 1.02, 1.18, and 1.37, respectively.

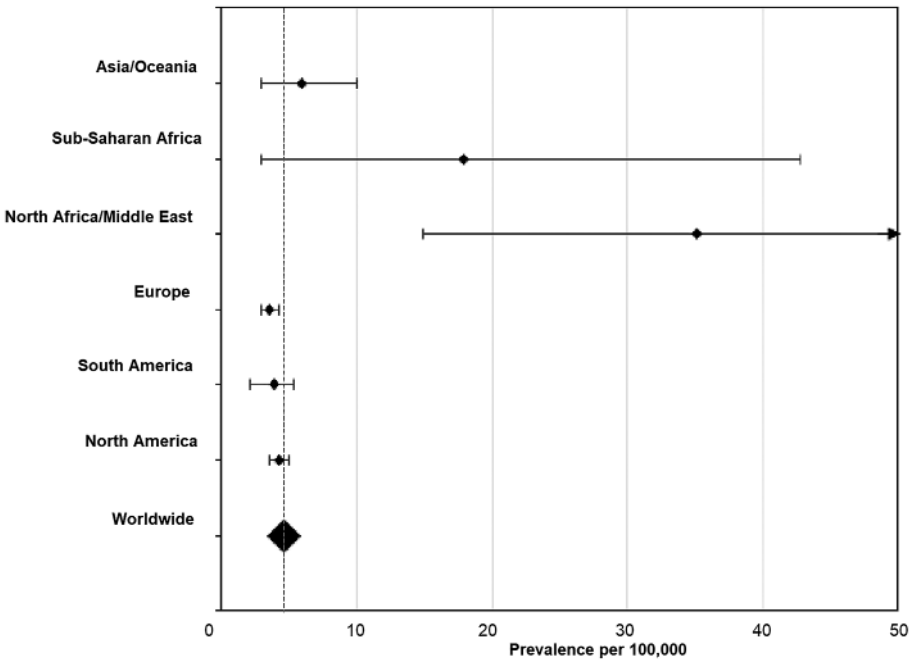

FIGURE 3 Forest plot of achondroplasia pooled birth prevalence estimates. Prevalence was estimated using the quality effects model

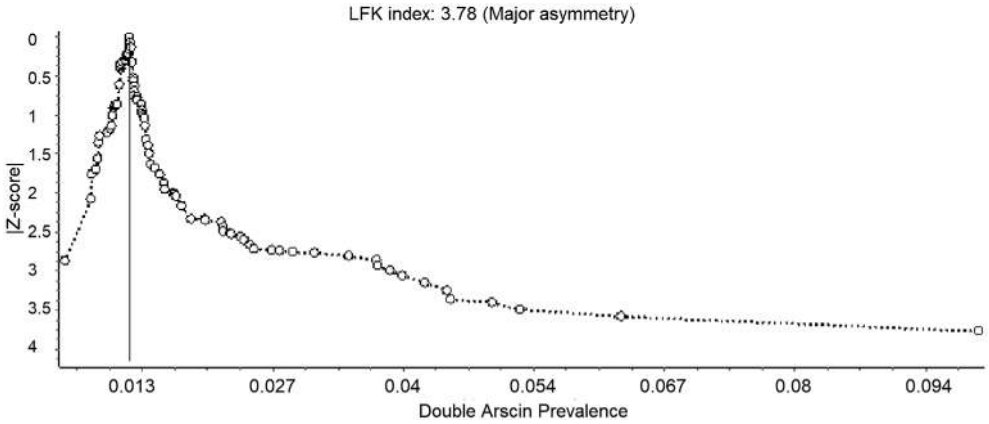

FIGURE 4 Doi plot to evaluate publication bias

4 | 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 and46% 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 for 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.

ACKNOWLEDGMENTS

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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 epidemiology:lnk OR epidemiol*:ab, ti OR burden: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.