Title:

Birth prevalence of Congenital Talipes Equinovarus in Low and Middle Income Countries: A Systematic Review and Meta-analysis

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Abstract

Background: Congenital talipes equinovarus (CTEV), or clubfoot, is a structural malformation that develops early in gestation. Birth prevalence of clubfoot is reported to vary both between and within low and middle-income countries (LMICs) and this information is needed in order to plan treatment services. This systematic review aims to understand the birth prevalence of clubfoot in LMIC settings.

Methods: Six databases were searched for studies that reported birth prevalence of clubfoot in LMICs. Results were screened and assessed for eligibility using pre-defined criteria. Data on birth prevalence were extracted and weighted pooled estimates were calculated for different regions. Wilcoxon rank-sum test was used to examine changes in birth prevalence over time. Included studies were appraised for their methodological quality, and a narrative synthesis of findings was conducted.

Results: Forty-eight studies provided data from 13,962,989 children in 20 countries over 55 years (1960 – 2015). The pooled estimate for clubfoot birth prevalence in LMICs within the Africa region is 1.11 (0.96, 1.26); in the Americas 1.74 (1.69,1.80); in South East Asia (excluding India) 1.21 (0.73, 1.68); in India 1.19 (0.96, 1.42); in Turkey (Europe Region) 2.03 (1.54, 2.53); in Eastern Mediterranean region 1.19 (0.98, 1.40); in West Pacific (excludes China) 0.94 (0.64, 1.24) and in China 0.51 (0.50, 0.53).

Conclusion: Birth prevalence of clubfoot varies between 0.51 and 2.03/1,000 live births in LMICs. A standardised approach to the study of the epidemiology of clubfoot is required to better understand the variations of clubfoot birth prevalence and identify possible risk factors.

Background

Congenital anomalies, also known as birth defects, are one of the leading causes of disability in children (1). Clubfoot is one of the most common congenital deformities that causes mobility impairment (2). The structure and position of the foot are affected and untreated clubfoot results in pain and reduced mobility, which potentially leads to participation restrictions and activity limitation (3).

Clubfoot forms in the early weeks of gestational development, and this may be part of specific syndromes or secondary to neurologic or systemic disease. However the majority of cases occur in isolation and are termed “idiopathic” (4), the cause of which are not fully understood (5). Genetic factors have been implied (6, 7) while environmental factors, for example seasonal variation and intrauterine immobility, have been reported in some studies (5, 8). Associations with ethnicity are not clear. Other risk factors that have been reported are male gender (9-11), maternal smoking (10-15) and maternal diabetes (10, 13). However, the underlying pathogenesis for these factors remains a matter of scientific debate. A multifactorial etiologic model that involves both environmental and genetic factors is likely (8).

Epidemiological studies consistently report higher birth prevalence (16) of idiopathic clubfoot in males and in first-born children (17). The condition is bilateral in half of the cases (18). Typically a small set of statistics are routinely cited for birth prevalence of clubfoot with reports of 0.39 per 1,000 births in Chinese populations, 1.1 per 1000 in Caucasian and 6.8 per 1,000 in Polynesian populations (19). Overall, it is estimated that 80% of children born with clubfoot each year live in low and middle income countries (LMICs) (18).

Accurate collection of data on population birth rate and prevalence of birth defects is essential to plan, initiate and develop healthcare services. The aim of this study was to conduct a systematic literature review to estimate the birth prevalence of clubfoot in different World Health Organisation (WHO) regions, in order to inform planning of services and programme management in LMICs.

Methods

The systematic review was planned, conducted and reported according to established MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (20) (Web Appendix 1). A systematic literature search was conducted in January 2016 for peer-reviewed articles that presented original research findings on the birth prevalence of clubfoot in LMIC settings.

Search Strategy

EMBASE, Medline, Global Health, LLACS, Africa Wide Information and the Cumulative Index to Nursing, Allied Health Literature (CINAHL) were examined for studies published between 1960 and December 2015 to capture 55 years of data. It was hypothesised that studies that reported on several congenital birth deformities may not include clubfoot in the search terms. Consequently, in order to capture all relevant studies, a search was carried out using both birth defects and clubfoot terms, with LMIC keywords. Boolean, truncation and proximity operators were used to construct and combine searches for the key concepts as required for individual databases and an example is available as Web Appendix 2.

The articles returned by the literature search were screened by one reviewer (TS) first by title and then by abstract. Ten percent of the abstracts were reviewed by a second reviewer (HK) to check for agreement. The full text was obtained for any paper that was included at abstract screening.

Studies of all languages were included and translated as required. The reference list of all included studies were examined for further relevant studies. All full texts were reviewed independently by two reviewers (TS and either AF, CL or HK) and differences were agreed by discussion.

The search strategy is presented in Figure 1.

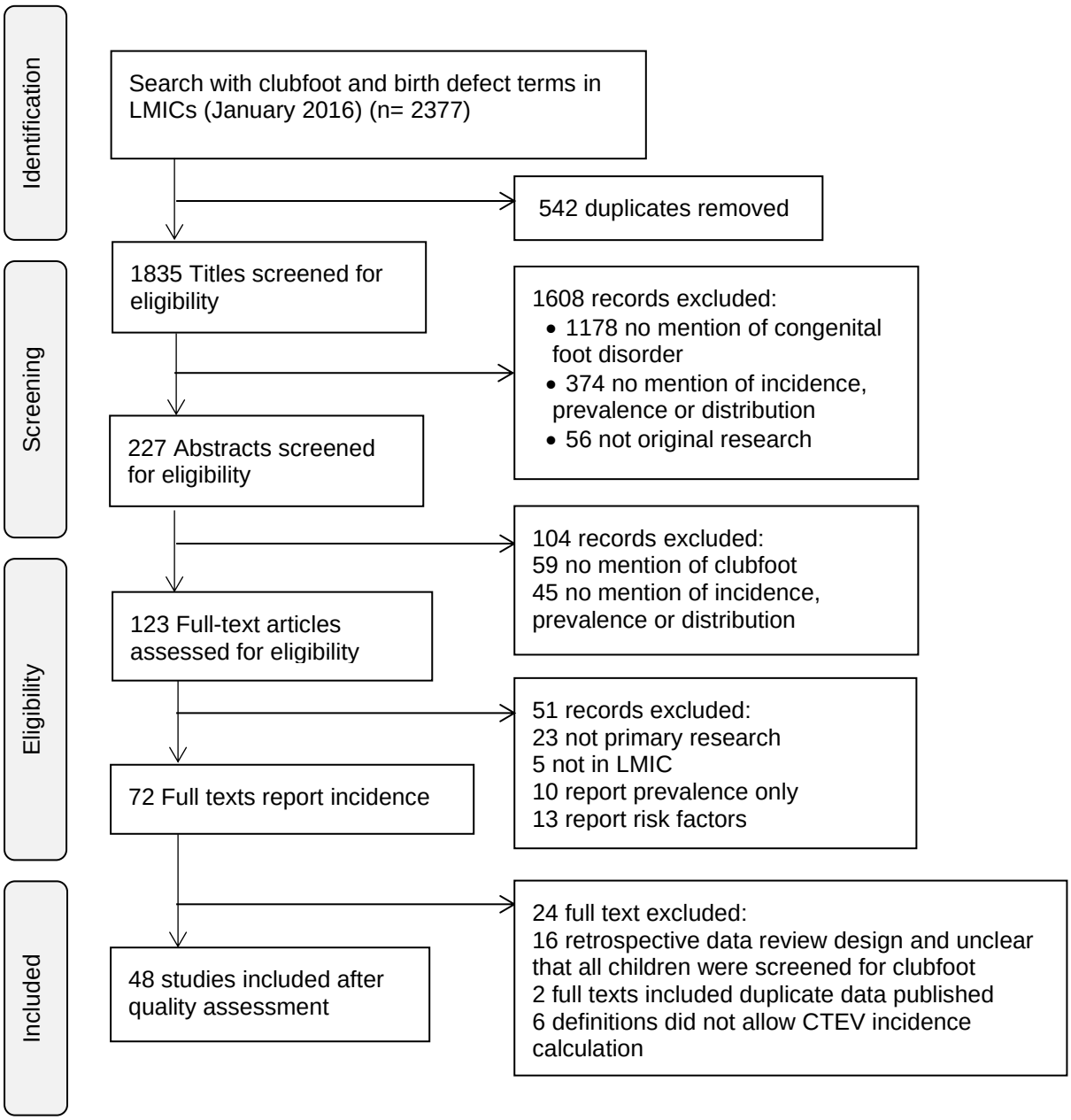

Figure 1 Search strategy with PRISM flow diagram

Study selection

Congenital talipes equinovarus was defined as a rigid deformity where the foot is fixed in a plantarflexed, supinated and adducted position. Studies were eligible if they met the following criteria: (1) original research that included congenital talipes equinovarus, (2) results reported, or allowed calculation of, birth prevalence of clubfoot, (3) all children were screened for clubfoot; and (3) undertaken in a LMIC as defined by the World Bank country classification 2015. Exclusion criteria comprised: (1) full text unavailable, (2) unclear that all children were screened for clubfoot (e.g. large reviews of medical records), (3) unclear source population that prevented clear definition of the population denominator, or (4) duplicate reports from the same study.

Data extraction and analysis

Data were extracted from articles that met inclusion criteria according to The Centre for Reviews and Dissemination (CRD) guidelines(21). The following data were extracted:

(1) General study information, including title, author and year of publication
(2) Study design
(3) Study setting and dates conducted
(4) Population characteristics
(5) Primary research outcome, including case definitions and results

All extracted values were examined by the second reviewer to ensure accuracy. Differences between the reviewers were discussed and a consensus was reached on all papers. One author was contacted for further information.

Data reporting per 1,000 births were assumed to be live births unless it was stated that stillbirths were included. Birth prevalence rates were calculated per 1,000 live births with 95% confidence intervals (Wilson score intervals), on the basis of the binomial distribution using Stata 14.0 (StataCorp LP, College Station, Texas), from the reported study population and the number of babies identified with clubfoot. It was decided *a priori* that the populations of China and India would be analysed independently of their WHO region due to their large population size. Tests for heterogeneity were performed. Weighted summary measures were estimated for the six WHO regions, India and China with a fixed effect model (22) in the meta-analysis. The relative weight that each study contributed was defined by the sample size of the study. The overall effect estimate is therefore a weighted combination of the studies that contribute to it. Summary measures were graphed with forest plots.

As the timeframe for the included studies is wide, an analysis was undertaken to identify if the birth prevalence of clubfoot was different in the oldest estimates. A two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare the birth prevalence in the time periods 1960 – 1985 and 1986 – 2015, consisting of twenty-five and thirty years respectively.

Cases born per million total population per year were estimated according to regional clubfoot birth prevalence and crude birth rate per 1,000 people. The Global Health Observatory data repository provided estimates of crude birth rate.

Results

1,835 studies were retrieved for assessment (Figure 1). Of these, 72 studies reported on birth prevalence of clubfoot and provided data from 25 countries (Web Appendix 3). 24 full texts were excluded, of which 15 papers were retrospective data collection and analysis and it was unclear if all children were screened (Web Appendix 4 contains details on the studies excluded). Therefore, forty-eight studies were selected for inclusion and provided data from 13,962,989 children in 20 countries.

Table 1 summarises the characteristics of the studies eligible for inclusion. All the studies drew cases from a hospital setting. Eight of 37 studies (21.6%) that used a prospective design with physical examination were undertaken in more than one hospital (23-30). Nine studies used a large database review in settings where there was systematic screening for clubfoot (31-39), one study analysed data from a single hospital defects monitoring system (40) and one study used a cluster sample survey (41). 13 papers (27%) were from the South East Asia region, with 11 papers in the region published from India. The West Pacific region consisted primarily of research undertaken in China and used large database reviews. Turkey was the only LMIC represented in Europe.

The pooled estimates for clubfoot birth prevalence for Africa (1.11 [0.96, 1.26]), South East Asia (1.21 [0.73, 1.68]), India (1.19 [0.96, 1.42]), and the Eastern Mediterranean Region (1.19 [0.98, 1.40]) are similar. The pooled estimate for clubfoot birth prevalence in LMICs within the Americas Region is 1.74 (1.69,1.80); in Turkey (Europe Region) 2.03 (1.54, 2.53) and in West Pacific (excluding China) 0.94 (0.64, 1.24). The birth prevalence is lowest in China at 0.51 (0.50, 0.53).

Analysis of the birth prevalence of clubfoot reported in two date ranges (1960 – 1985 and 1986 – 2015) demonstrated no evidence of a difference over time (p=0.56).

Table 1 Studies of CTEV Birth prevalence included in Systematic Review, 1960 – 2015*

Reference		Country	Study Time	Period of study	Population	Setting	Method of case ascertainment	Population N	Clubfoot N	Birth prevalence per 1000	Wilson (score)	Clubfoot definition
Primary Author	Year											
Africa												
Simpkiss (42)	1961	Uganda	1956 - 1957	10 months	live births	1 hospital	Clinical evaluation by medical student or midwife	1, 927	1	0.52	0.09 - 2.93	musculoskeletal system: talipes equinovarus
Lesi (43)	1969	Nigeria	1966 - 1967	1 year	Births	1 maternity hospital	Clinical evaluation within 12 hours of birth by primary author and assistant nurse	16, 720	19	1.14	0.73 - 1.77	congenital defects found according to system' bony: talipes
Pompe van Meerdervoort (44)	1976	South Africa	Not defined	about 3 years'	Live births	1 hospital	Physical examination day after delivery by paediatric/ orthopaedic registrar. Positive confirmation by clubfoot specialist.	10,000	35	3.50	2.52 - 4.86	Excluded spina bifida, arthrogryposis and CP. Noted CTEV: fixed deformity
Delport (45)	1995	South Africa	1986 - 1989	3 years	Live births	1 urban academic hospital	Clinical evaluation within 24 hours of birth by paediatrician or medical officer	17, 351	8	0.46	0.23 - 0.91	Talipes equinovarus ICD 9 code 75450
Venter (46)	1995	South Africa	1989 - 1992	3 years 6 months	Live births	1 rural hospital	Physical examination by trained nurse	7,617	19	2.49	1.60 - 3.89	musculoskeletal system: talipes equinovarus
Mkandawire (47)	2004	Malawi	2000-2002	22 months	Births	1 hospital	Physical examination of all neonates, when and by whom not outlined	16, 877	34	2.01	1.44 - 2.81	definition of idiopathic and secondary
Mathias (48)	2010	Uganda	2006 - 2007	20 months	Live Births	8 regional hospitals	Physical examination by delivery room staff and confirmation by clubfoot specialist	110,336	130	1.18	0.99 - 1.40	Clear definition of clubfoot: positional, idiopathic or syndromic
Orimolade (49)	2014	Nigeria	2014	6 months	Live births	1 tertiary hospital	Physical examination after delivery	1,551	5	3.22	1.38 - 7.52	Idiopathic clubfoot variety
Americas												
Monteleone-Neto and Castilla (30)	1994	Brazil	1982 - 1985	4 years	Live births	3 maternity hospitals in Cubatao	Physical examination, prospective collection	10,218	21	2.06	1.34 – 3.14	ECLAMC definition Limb deformity: "talipes"
Lopez – Camelo (37)	1996	Latin America	1967 - 1989	32 years	Births	Large database 24 geographic regions of Latin America	ECLAMC (Latin American Collaborative Study of Congenital Malformations)	2,159,065	3,769	1.75	1.69 – 1.80	pes equinus'

Guardiola (39)	2009	Brazil	2000 - 2005	5 years	Births	Large database	ECLAMC	26, 588	41	1.54	1.14 – 2.09	Clubfoot as defined by ECLAMC
Pachajoa (40)	2011	Columbia	2004 - 2008	4 years 7 months	Births	Review of data monitoring system in 1 tertiary care	hospital birth defects monitoring system	32, 995	58	1.76	1.36 -2.27	ICD-10 and ECLAMC version 2002
South East Asia												
Simatupang (50)	1977	Indonesia	1970 - 1975	5 years	live births	1 hospital [General RSUPP Medan]	Prospective, physical examination 'soon after birth'	17,241	19	1.10	0.71 - 1.72	talipes'
Kalra (51)	1984	India	not specified	14 months	births	1 obstetric department, [SN medical college, Agra]	physical examination within 28 hours of birth, no description of by whom	2, 720	4	1.47	0.57 - 3.78	"musculoskeletal system" talipes equinovarus'
Bahadur (52)	1986	India	1980 - 1984	5 years	live births	not stated	Examination of infants after birth	13, 321	21	1.58	1.03 - 2.41	congenital talipes equinovarus'
Chaturvdei (53)	1989	India	1986-1986	12 months	births	1 hospital	physical examination within 48hours of birth	3, 014	3	1.00	0.34 - 2.92	musculoskeletal talipes
Choudhury (54)	1989	India	1986 - 1987	12 months	Live births	1 hospital, West Bengal	Physical examination	10, 415	4	0.43	0.15 – 1.99	No numerator for clubfoot. Noted as talipes.
Agarwal (55)	1991	India	1981 - 1984	2 years 6 months	single births	1 hospital	Physical examination during the early neonatal period	9,405	30	3.19	2.24 - 4.55	Talipes equinovarus
Singh (56)	1991	India	1984 - 1987	4 years	live births	1 hospital, level II care to neonates	Physical examination by neonatal consultant	7, 015	32	4.56	3.23 - 6.43	CTEV
Taksande (57)	2010	India	2005 - 2007	2 years 7 months	live births	1 rural medical college hospital	Physical review by consultant at time of birth	9, 194	11	1.20	0.67 - 2.14	musculoskeletal system:'talipes'
Chotigavanichaya (58)	2012	Thailand	2009	4 months	births	1 hospital	Clinical examination within 24hours	3,396	8	2.36	1.19 – 4.73	idiopathic clubfoot used Dimeglio classification
Pujari (59)	2012	India	Not defined	1 year	live births	1 hospital	physical examination within 24-48hours of birth	4,280	6	1.40	0.64 – 3.06	CTEV
Agrawal (60)	2014	India	2010 - 2011	1 year	births >28 weeks	1 tertiary care hospital	Physical examination for musculoskeletal defects within 24hours of delivery	7, 268	15	2.06	1.25 - 3.40	talipes equinovarus' noted these were not positional
Sachdeva (61)	2014	India	2010	4 months	births	1 government hospital	Clinical evaluation by paediatrician soon after birth. Data collection by 30 trained residents	2, 862	8	2.80	1.42 - 5.51	talipes equinovarus

Baruah (62)	2015	India	2010 - 2013	2 years 9 months	live births	1 hospital	Physical examination within 24hours	17, 052	23	1.35	0.89 - 2.02	ICD-10 classification
Europe												
Say (63)	1973	Turkey	1969	10 months	live births >28 weeks	1 hospital	Physical examination within 48 hours by specialists	9,947	22	2.20	1.46 - 3.35	musculoskeletal system 'clubfoot'
Tuncbilek (26)	1999	Turkey	1993 - 1994	12 months	births >20 weeks	22 university hospitals	Physical examination by paediatrician	21, 907	43	1.96	1.46 - 2.64	ICD-10 was used 'pes equinus'
Eastern Mediterranean												
Akhtar (64)	1970	Pakistan	1965 – 1968	3 years	live births	Obstetric department in 1 hospital	Obstetric dept. reported data, reviewed by research team	3,570	3	0.84	0.29 - 2.47	specific report of CTEV in Pakistan
Khrouf (65)	1986	Tunisia	1983-1984	9 months	Births	1 teaching hospital	Clinical evaluation within 24hours of birth by paediatric staff	10, 000	26	2.6	1.77 - 3.81	musculoskeletal system, 'club foot' with additional deformities
Bittar (66)	1998	Lebanon	1991 – 1993	2 years 6 months	live births	1 hospital	Physical examination within 24 hours by senior resident and pre-discharge examination by paediatrician	3,865	7	1.81	0.88 - 3.73	musculoskeletal 'equinovarus'
Ali (67)	2008	Iran	2003 – 2006	2 years 8 months	live births	1 hospital	physical examination after birth by primary author	4,660	15	3.22	1.95 - 5.30	musculoskeletal 'clubfoot'
Karbasi (23)	2009	Iran	2003 – 2004	8 months	live births	All maternity hospitals in Yadz	Physical examination by Paediatrician	4, 800	19	3.96	2.54 - 6.17	ICD-10
Delshad (24)	2009	Iran	2005 – 2007	2 years	all births	Maternity wards in 6 government hospitals	Physical examination by paediatrician	61,112	62	1.01	0.79 - 1.30	ICD-10
Al-Ani (68)	2012	Iraq	2010 – 2011	1 year	births	1 tertiary hospital	Examined by neonatal specialists	5,864	8	1.36	0.69 - 2.69	specified difference idiopathic and secondary.
Golalipour (69)	2013	Iran	2007	1 year	live births	1 hospital	Physical examination by a paediatrician	6, 204	5	0.81	0.34 - 1.89	ICD-10 classification 'musculoskeletal system clubfoot'
El Koumi (70)	2013	Egypt	2011	1 year	live births	1 hospital	Physical examination within 24hours	2,517	6	2.38	1.09 - 5.19	ICD-10 'musculoskeletal minor talipes'
West Pacific												
Emanuel (25)	1972	China	1965 - 1968	3 years	Singleton live and stillborn >28weeks	6 hospitals in Taipei	Examination by 1 of 4 study physicians, 2 public health nurses follow up	25, 549	19	0.74	0.48 - 1.16	ICD 1965 version, "no reducible defect"

Boo (71)	1990	Malaysia	1988	4 months	births	1 maternity hospital,	Routine examination by Doctor, referred to research team	8, 369	4	0.48	0.19 - 1.23	calculated structural clubfoot
Thong (27)	2005	Malaysia	2002 - 2003	14 months	births	All health centres and hospitals in Kinta district	population-based birth defect register: physical examination by trained nurse	17, 720	23	1.30	0.87 - 1.95	ICD-10
Li (31)	2008	China	1997 - 2007	10 years	births	Guangdong Province, 21 cities	Hospital based surveillance program	150, 357	152	1.01	0.86 - 1.18	ICD-9 and ICD-10
Hoang (28)	2013	Viet Nam	2010	1 year	Live births	127 Commune Health Stations	Physical examination within 24hours of birth	13,954	17	1.22	0.76 – 1.95	ICD-10
Li (41)	2013	China	2008 - 2010	2 years	live births	4 counties in Hengyang province	Cluster sampling survey	52,307	50	0.96	0.73 - 1.26	clubfoot
Yi L (32)	2013	China	2001 - 2010	10 years	births	Large database review	Data from birth defects monitoring programme	8,273, 382	4233	0.51	0.49 – 0.53	ICD-10 Q66.0
Yi Q-Y (38)	2013	China	2008 - 2011	4 years	births	Birth defects monitoring programme in Dongguan	Prospective collection of birth defects on hospital cards	556 282	537	0.97	0.89 – 1.05	Congenital clubfoot
Wang (33)	2014	China	2006 - 2013	8 years	births	Database review in Haikou	Review birth defects registry forms and perinatal infants quarterly report	118, 199	62	0.52	0.41 - 0.67	talipes equinovarus'
Wei Hong (34)	2014	China	2011 - 2013	3 years	births	Hospital surveillance programme in Zuhai city	Data from monitoring institutions	87, 059	53	0.61	0.46 - 0.79	talipes equinovarus'
Yang (35)	2015	China	2003 - 2009	7 years	births	Database review 26 medical institutions [Longgang district]	review of birth defects surveillance network	191, 017	137	0.72	0.61 - 0.85	talipes equinovarus'
Xia (36)	2015	China	1997 - 2011	15 years	births	Large database 75 hospitals [Henan Province]	Population based congenital anomalies surveillance system	1,815, 920	757	0.42	0.39 - 0.45	ICD-10

*Studies are ordered by WHO region and year of publication

A meta-analysis by region was undertaken (Figures 2 – 9). The individual study results are displayed in the first column, identified under the title 'Study.' The summary birth prevalence is displayed in the final row with the test for heterogeneity denoted as I^2. (If $I^2 \leq 25\%$, studies are regarded as homogeneous). The second column visually displays the study results. The third column is the summary estimate of the birth prevalence of clubfoot, denoted by ES (95%CI) or effect size. This column gives the corresponding numerical results. The vertical line is the pooled estimate of birth prevalence and the x-axis is the value of clubfoot cases per 1,000 live births. The size of the box is directly related to the 'weighting' of the study in the meta-analysis and the weight in % in the final column indicates the influence of the study on the overall results. The horizontal lines through the boxes depict the length of the confidence intervals. The diamond in the last row of the graph illustrates the overall result of the meta-analysis. The middle of the diamond sits on the value of the summary birth prevalence and the width of the diamond depicts the width of the overall CI.

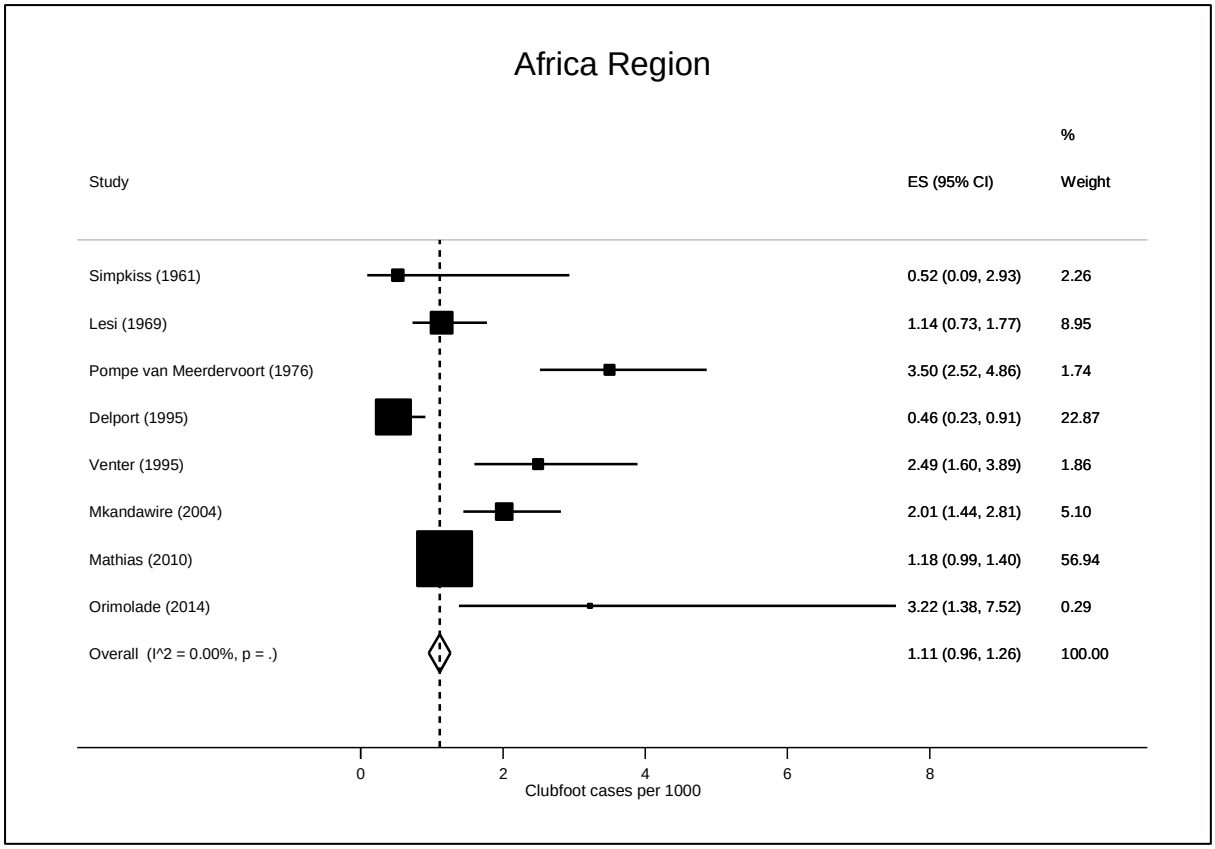

Figure 2 Birth prevalence of CTEV per 1,000 births (Africa Region)

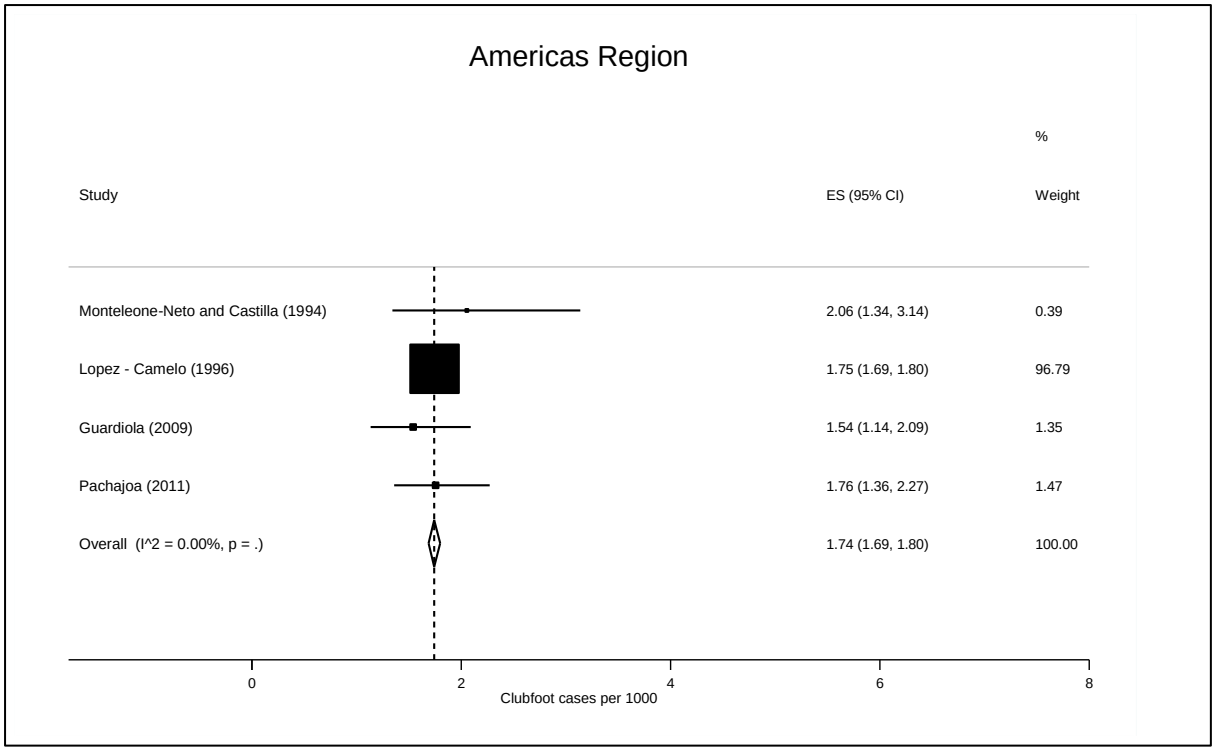

Figure 3 Birth prevalence of CTEV per 1,000 births (Region of the Americas)

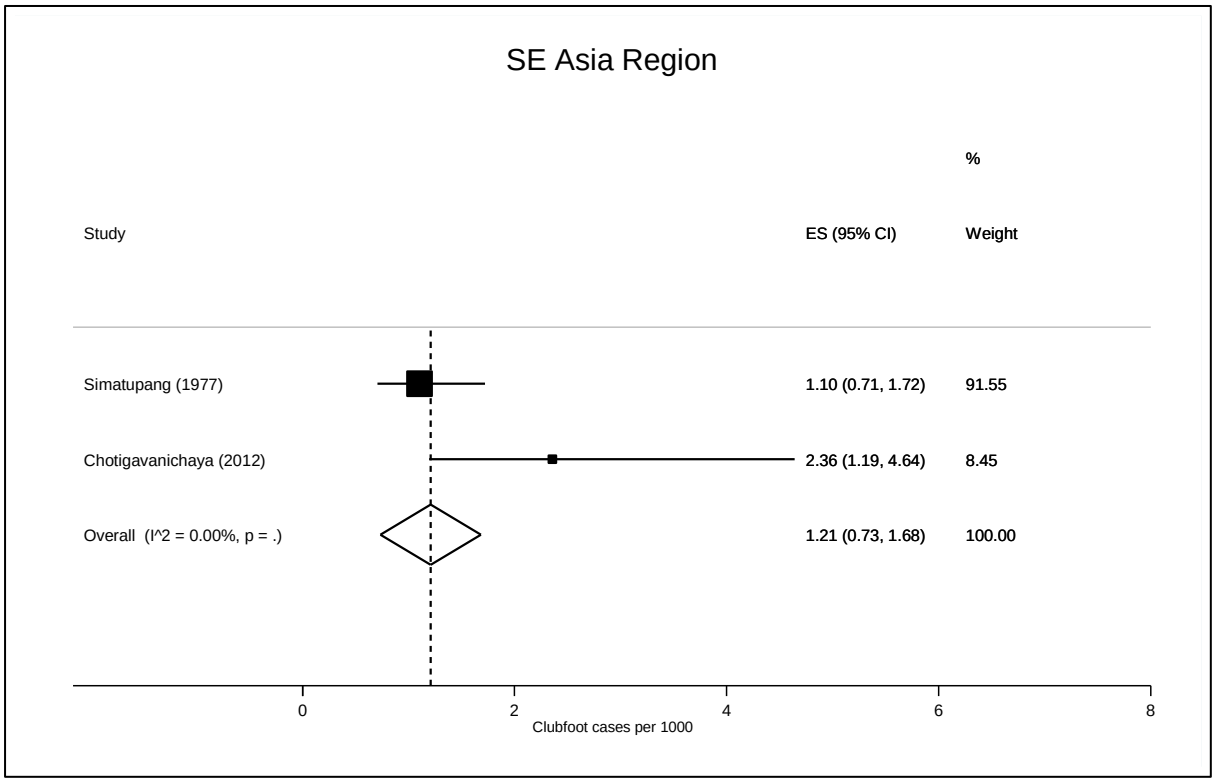

Figure 4 Birth prevalence of CTEV per 1,000 births (South East Asia Region excluding India)

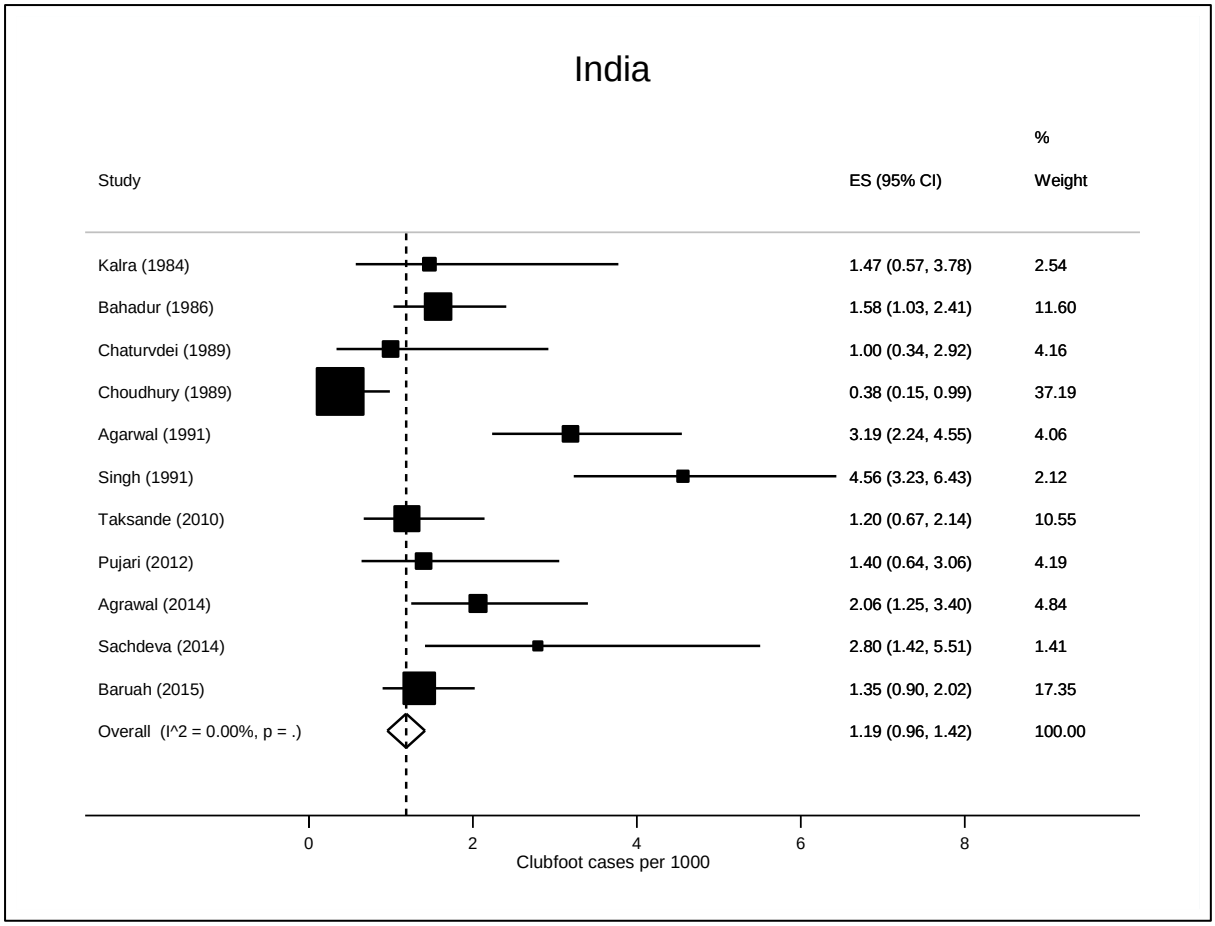

Figure 5 Birth prevalence of CTEV per 1,000 births (India)

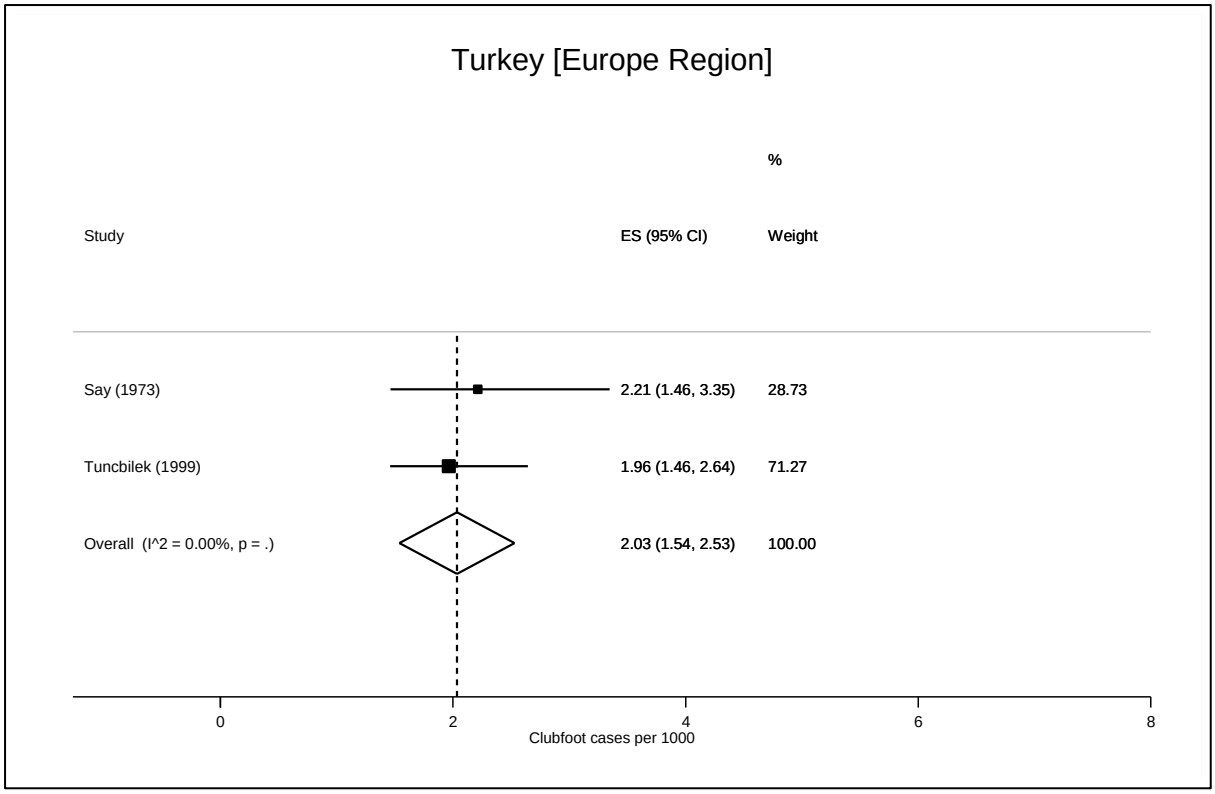

Figure 6 Birth prevalence of CTEV per 1,000 births (Europe Region)

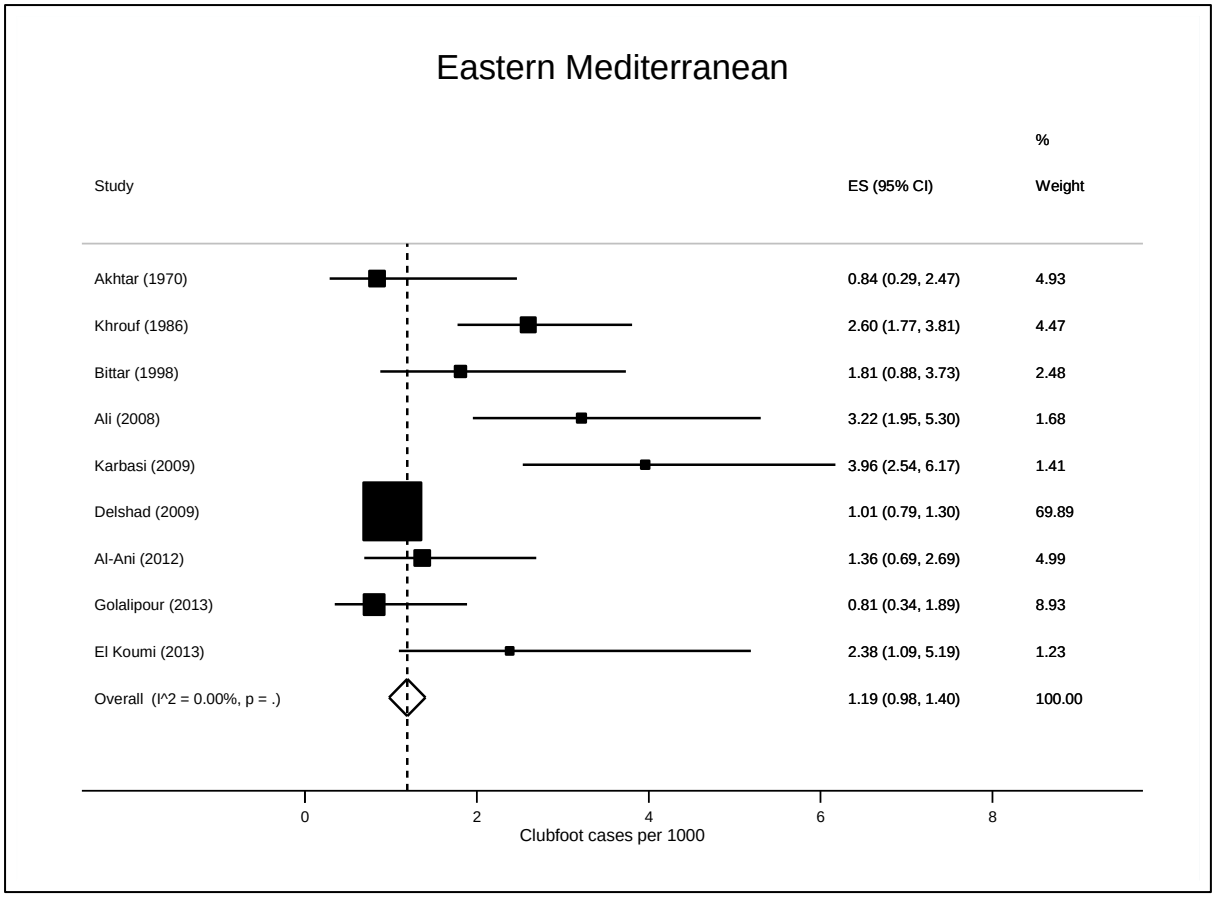

Figure 7 Birth prevalence of CTEV per 1,000 births (Eastern Mediterranean Region)

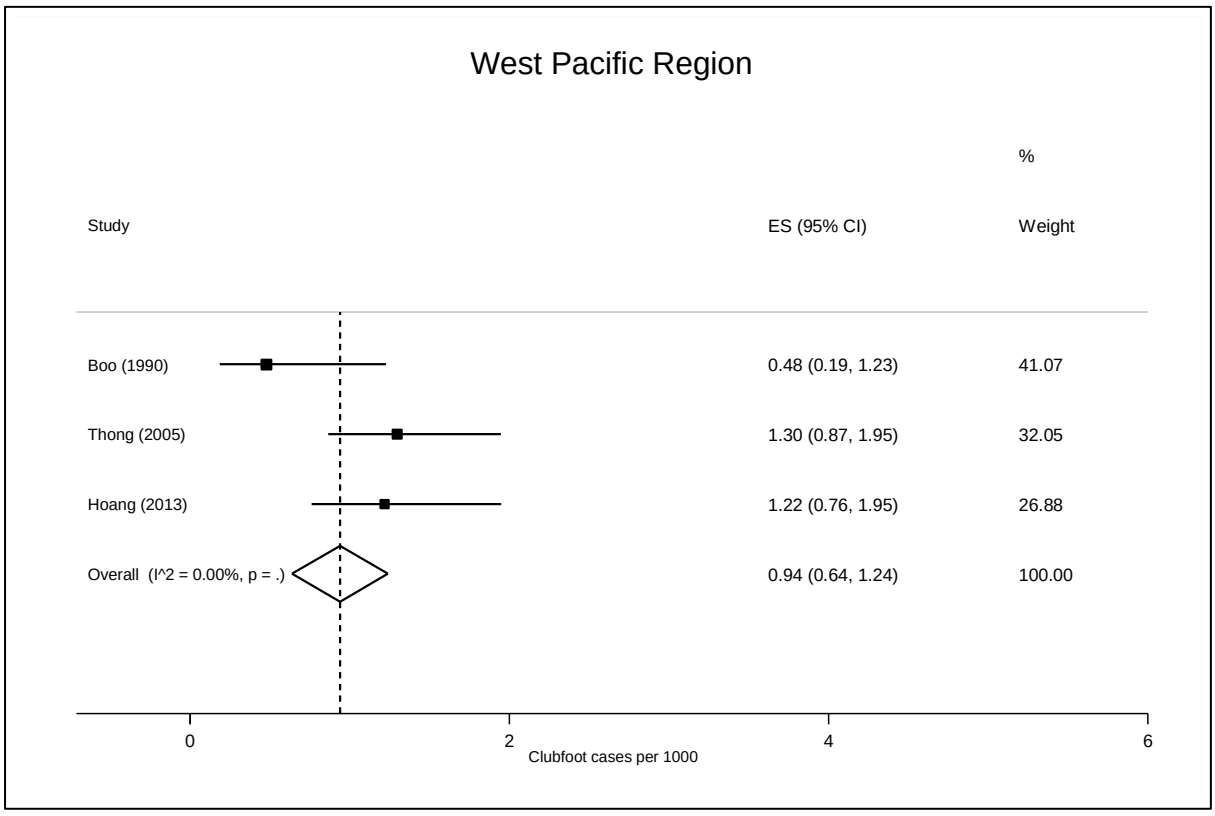

Figure 8 Birth prevalence of CTEV per 1,000 births (West Pacific Region excluding China)

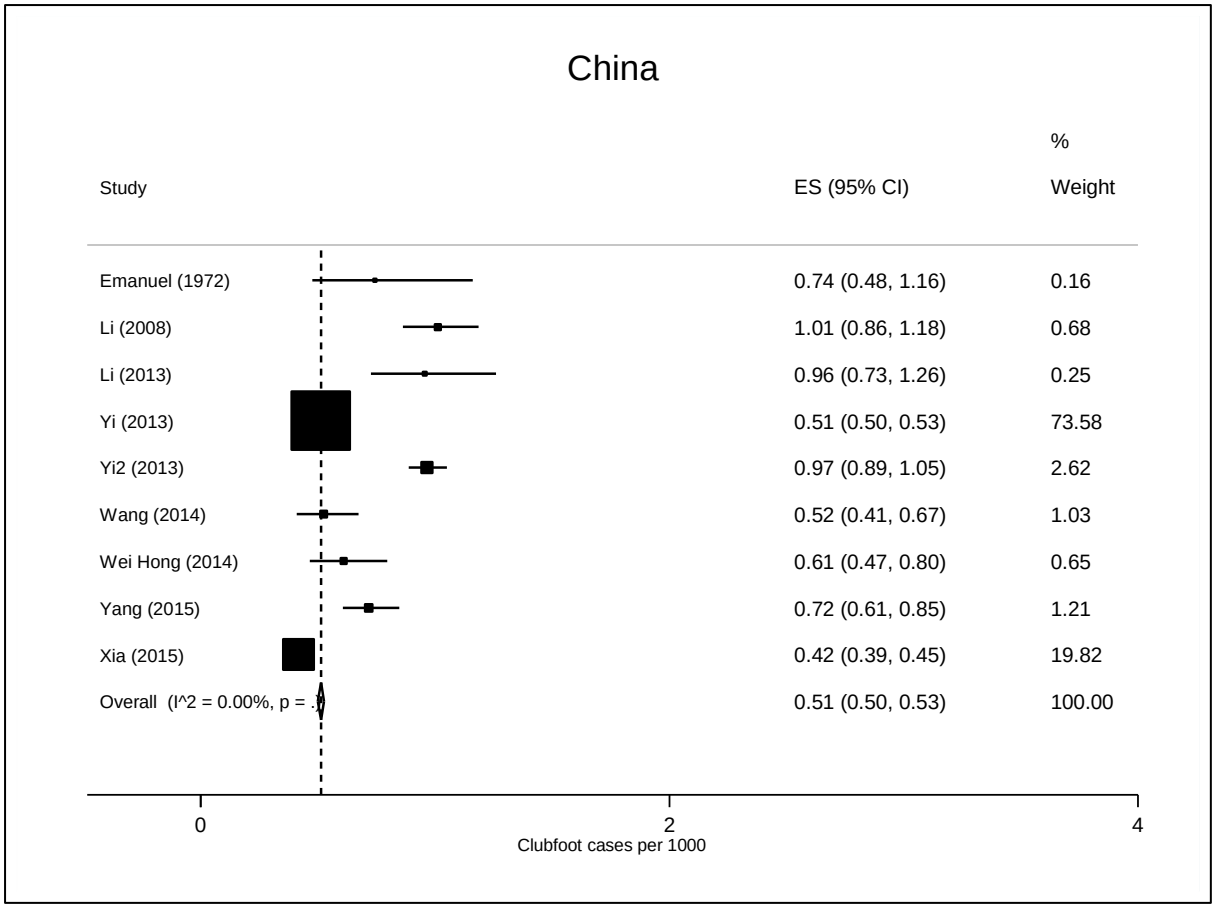

Figure 9 Birth prevalence of CTEV per 1,000 births (China)

Based on the evidence since 1960, figures to plan for clubfoot management can be calculated for the eight populations given the birth rate per million population (Table 2).

Table 2 Projected clubfoot cases born per million total population/year

Region	Birth prevalence	Crude Br/1000[$]	Clubfoot cases born per million total population/ year
Africa	1.11 (0.96, 1.26)	38.3	43 (37 – 48)
Americas	1.74 (1.69, 1.80)	17.0	30 (29 – 31)
SE Asia	1.02 (0.76, 1.27)	19.9	20 (15 – 25)
Turkey (Europe Region)	2.03 (1.54, 2.53)	17.0	35 (26 – 43)
Eastern Mediterranean	1.19 (0.98, 1.40)	26.2	31 (26 – 37)
India	1.19 (0.96, 1.42)	20.4	24 (20 – 20)
West Pacific	0.94 (0.64, 1.24)	14.7	14 (9 – 18)
China	0.51 (0.50, 0.53)	13.3	7

[$]Accessed WHO data, October 2016. http://apps.who.int/gho/data/view.main.CBDR2040

Population numbers are based on WHO region population birth rates. For planning purposes, regional estimates of birth prevalence should be applied to country specific birth rates.

Discussion

This review summarises 48 studies of clubfoot birth prevalence from LMIC settings with data from 13,962,989 children in 20 countries. To our knowledge, this is the first systematic review of birth prevalence of clubfoot. The results demonstrate a range in birth prevalence from 0.51 (0.50, 0.53) per 1,000 live births in China to 2.03 (1.54, 2.53) per 1,000 in Turkey. Pooled estimates of birth prevalence rates appear to be similar in Africa, South East Asia, Eastern Mediterranean regions and India. There was no evidence for a difference in clubfoot birth prevalence in LMICs between 1960 -1985 and 1986 – 2015.

The case numbers and denominator population size differ in the individual studies included in the meta-analyses. The birth prevalence of clubfoot in China is strongly influenced by two large outlier studies (32, 36) that decrease the pooled estimate. Both studies were database reviews of data from hospitals that monitored birth defects through physical examination and the data were collated on a congenital anomaly registration form. The authors note it is possible that cases were missed. Alternatively, the data may represent a unique feature of inheritance in the idiopathic clubfoot population of China. Only two papers contribute to the estimates of Turkey and the South East Asia region with combined screened populations of 31,854 and 20,637 children respectively.

Results compared to other studies

Many LMICs lack rigorous congenital anomaly surveillance programmes (72) which makes calculation of birth prevalence difficult. Current estimates range from 4 to 12 cases per 1,000 births (73) in LMIC settings. These are likely underestimated due to stigma and exclusion (74) and are also reliant on case definition and robust screening methods.

This analysis suggests some variation in the birth prevalence of clubfoot as previously indicated (75), however the range is not as large as reported by others (19). Except for China, there were similar estimates across the regions.

Current data heterogeneity suggests the resulting variation in clubfoot birth prevalence in LMICs is likely influenced by study design and data collection methods and possibly by region and therefore ethnicity as well. Case definition, the case mix between tertiary and secondary facilities and the training of observers may affect prospective reporting of

clubfoot. The true birth prevalence will be affected by risk factors, genetic and/or environmental, most of which are unknown.

Strengths and limitations

A strength of this study is the relatively large population denominator in several regions. It includes all categories of structural clubfoot (for example idiopathic or syndromic) as treatment is required in all cases although outcomes may differ. Data were excluded from clinics where it was not clear from the report how many babies were examined and did not have clubfoot, as birth prevalence cannot be calculated without a denominator. This has resulted in the exclusion of some studies (76, 77) that are regularly cited. This review is limited by the quality and representation of the available data from LMICs.

Implications

The estimated birth prevalence of clubfoot will be useful for the planning of services and to better estimate areas of need for country programmes. For instance, one equipped clinic in each district of 1 million people will be sufficient to handle clubfoot treatment if the new case load is up to 43 cases of clubfoot each year, as estimated by this review. Screening at birth for clubfoot is important, so that cases can be detected and treated early, when treatment is most effective. Scaling up appropriate services for screening and treatment remain a priority.

Future studies should ensure that a clear case definition and robust screening methods are undertaken to allow comparison of epidemiological data.

Conclusions

Clubfoot is relatively common and should be detected at birth. There is no evidence for a large variation in birth prevalence between regions or of the folklore about a large Polynesian birth prevalence. Comparison of prevalence figures for congenital malformations reported from different parts of the world requires clear case definition and comparable methods of data collection.

The published data over the last 55 years for clubfoot in LMIC suggests a birth prevalence in the range of 0.5 to 2.0 cases / 1,000 live births, which results in an estimated 7 to 43 cases of clubfoot / year / million population, dependent mainly on birth rate.

The regional figures, for example in sub-Saharan Africa of approximately 43 cases / year / million population provide useful information on planning treatment services for clubfoot in

LMIC. A standardised approach to the study of the epidemiology of clubfoot is required to better understand the variations of the birth prevalence of clubfoot and possible risk factors.

Funding

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Web Appendix 1 – MOOSE Checklist [for Meta-analysis Of Observational Studies in Epidemiology]

Background

Problem definition

The birth prevalence of clubfoot or congenital talipes equinovarus (CTEV) is reported to vary in the literature due to inconsistent case definition and population denominators.

Hypothesis statement

Studies of CTEV in low and middle income countries (LMICs) report different birth prevalence estimates. Studies will be homogenised and the differences in birth prevalence will be examined in terms of WHO country definition and changes in time.

Study outcomes

- Birth prevalence of CTEV: Number of cases of congenital talipes equinovarus per 1,000 live births
- Generate a homogenous dataset that will allow for comparisons between LMICs and between the date ranges of 1960 – 1985 and 1986 - 2015.

Type of exposure or intervention used

- Geography was assessed using LMICs (World Bank 2005) in the WHO regions: African region, Region of the Americas, South East Asia Region, European Region, Eastern Mediterranean Region and the Western Pacific Region. India and China were estimated individually due to large population size.
- Changes over time were assessed in two time periods: 1960 – 1985 and 1986 – 2015
- The Global Health Observatory data repository provided estimates of regional crude birth rate to allow estimation of cases born per million total population per year.

Type of study design used

- Observational studies of CTEV

Study population

- All children in the study population were screened for clubfoot

- Clear definition of study population with a reliable estimate of the denominator population.
- If the population was well defined and birth prevalence given without the number of cases outlined, cases were calculated with the given information.

Reporting of search strategy

Qualifications of searchers

- Tracey Smythe has trained in systematic methods of literature searching as part of her PhD studies at the London School of Hygiene and Tropical Medicine
- Prof Christopher Lavy, Prof Allen Foster and Dr Hannah Kuper have participated in many systematic reviews.

The researchers were guided by:

- Jane Falconer, librarian at LSHTM and Fellow of the Higher Education Academy
- David Macleod, Research Fellow, Department of Medical Statistics

Search strategy

- Six medical literature databases searched between January 1960 and January 2016
- The following search terms were used as keywords:

1	developing country
2	developing or less* developed or under developed or underdeveloped or middle income or low* income
3	underserved or under served or deprived or poor*) adj (economy or economies).ti,ab.
4	developing or less* developed or under developed or underdeveloped or middle income or low* income
5	underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
6	(low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
7	(low adj3 middle adj3 countr*).ti,ab.
8	(lmic or lmics or third world or lami countr*).ti,ab.
9	Name of Country according to World Bank 2015 classification
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	clubf??t
12	club-f??t
13	club ADJ1 f??t
14	talipes equinovarus
15	talipes ADJ2 equinovarus

16	talipes ADJ2 equino-varus
17	congenital talipes equinovarus
18	congenital ADJ2 talipes ADJ2 equinovarus
19	CTEV
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	birth defect or birth malformation or birth abnormality or congenital defect or congenital malformation or congenital abnormality
22	incidence or occurrence or frequency
23	21 and 22
24	20 or 23
25	10 and 25

Effort to include all available studies, including contact with authors

- The final list of included studies were discussed with experts in the field: Rosalind Owen, Executive Director of the Global Clubfoot Initiative and Nyengo Mkandawire, Professor of Orthopaedics, Malawi
- Studies of all languages were included and translated as required
- Primary authors were contacted for clarification of study period

Databases and registries searched

- EMBASE, Medline, Global Health, LLACS, Africa Wide Information and the Cumulative Index to Nursing, Allied Health Literature (CINAHL)

Use of hand searching

- The reference list of all included studies were examined for further relevant studies.

List of citations located and those excluded, including justification

- See web appendix 4 for full texts that were excluded
- Studies were first excluded by title and then by abstract
- The full text was obtained for any paper that was included at both title and abstract screening
- 72 full texts were read by 2 reviewers and included or excluded according to the criteria listed.

Inclusion Criteria	Exclusion criteria
(1) Original research that included congenital talipes equinovarus	(1) Full text unavailable
(2) Results reported, or allow calculation of, birth prevalence of clubfoot	(2) Unclear that all children were screened for clubfoot
(3) Undertaken in LMIC as defined by the World Bank country classification 2015	(3) Unclear source population that prevents clear definition of the population denominator
(4) All children were screened for clubfoot	(4)Duplicate reports from the same study

Method of addressing articles published in languages other than English

- Non-English articles were translated for each article obtained

Method of handling abstracts and unpublished studies

- Studies published only as abstracts where the case definition and denominator population were not defined were excluded, as were those that were unpublished.

Description of any contact with authors

- Four papers required additional information from authors to ascertain their precise study period. One author (Thong 2005) was contacted via the details provided in the published study. The study period was clarified as 7th January 2002 to 28th February 2003.

Reporting of methods

Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested

- All studies that provide observational epidemiological data on children born with confirmed CTEV
- Studies in LMICs in all WHO regions are included
- The studied period spans 55 years from 1960 to 2015

Rationale for selecting and coding of data

- Studies were included and excluded as per the criteria outlined above

- 10% of the abstracts were reviewed for agreement
- All full texts were reviewed independently by 2 reviewers (TS and either HK, CL or AF) and differences agreed by discussion
- Data were extracted according to The Centre for Reviews and Dissemination (CRD) guidelines
- Birth prevalence were recorded per 1,000 live births
- Wilson score confidence intervals were calculated

Documentation of how data were classified and coded

- Details are outlined within the methods section of the text

Assessment of confounding

- Not applicable with Wilcoxon rank-sum test due to small numbers of studies per region before 1985, two date ranges were assessed globally.

Assessment of study quality

- Inclusion/exclusion criteria were strict to ensure adequately defined study boundaries and case ascertainment

Assessment of heterogeneity

- Heterogeneity was assessed geographically, and statistically to identify differences between studies

Description of statistical methods

- Birth prevalence rates and Wilson score confidence intervals were calculated (using Stata 14.0) and plotted using forest plots
- The pooled estimate of birth prevalence was calculated per WHO region
- Wilcoxon rank sum test was used to examine change in birth prevalence between two time periods

Reporting of results

Graphic of individual summary estimates and pooled estimate

- Forest plots are drawn to demonstrate birth prevalence and confidence intervals

- A weighted pooled estimate of birth prevalence of clubfoot was calculated according to WHO region

Table giving descriptive information of all studies included and excluded

- Table of studies included is available within the body of text
- Web appendix 4 lists all excluded papers with reasons for exclusion

Indication of statistical uncertainty of findings

- 95% Wilson score confidence intervals for all calculated birth prevalence are given

Reporting of discussion

Quantification of bias

- Quantification of bias is not possible with this study design.

Justification of exclusion

- Papers were excluded based upon exclusion criteria and justification is outlined within text. Excluded papers and reasons for exclusion are listed in Web Appendix 4.

Assessment of quality of included studies

- The inclusion/exclusion criteria maximised the quality of included studies and the uncertainty is illustrated by 95% confidence

Reporting of conclusions

Consideration of alternative explanations for observed results

- Outlined in the discussion section of the main text

Generalisation of these conclusions

- Projected clubfoot cases per million population were estimated

Guidelines for further research

- Outlined in the discussion section of the main text

Disclosure of funding source

- Tracey Smythe received funding from the Beit Trust and Christian Blind Mission (CBM)

Web Appendix 2 Search terms for clubfoot and birth defects and LMICs

1	developing country
2	developing or less* developed or under developed or underdeveloped or middle income or low* income
3	underserved or under served or deprived or poor*) adj (economy or economies).ti,ab.
4	developing or less* developed or under developed or underdeveloped or middle income or low* income
5	underserved or under served or deprived or poor*) adj (countr* or nation? or population? or world)).ti,ab.
6	(low* adj (gdp or gnp or gross domestic or gross national)).ti,ab.
7	(low adj3 middle adj3 countr*).ti,ab.
8	(lmic or lmics or third world or lami countr*).ti,ab.
9	Name of Country according to World Bank 2015 classification
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11	clubf??t
12	club-f??t
13	club ADJ1 f??t
14	talipes equinovarus
15	talipes ADJ2 equinovarus
16	talipes ADJ2 equino-varus
17	congenital talipes equinovarus
18	congenital ADJ2 talipes ADJ2 equinovarus
19	CTEV
20	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	birth defect or birth malformation or birth abnormality or congenital defect or congenital malformation or congenital abnormality
22	incidence or occurrence or frequency
23	21 and 22
24	20 or 23
25	10 and 25

Web Appendix 3 Papers reporting CTEV birth prevalence published by year and WHO region prior to quality assessment

Years	Total number of Papers	African Region	Region of the Americas	South-East Asia Region	European Region	Eastern Mediterranean Region	Western Pacific Region
1960 - 1969	2	Uganda (1)[a], Nigeria (1)					
1970 - 1979	6	South Africa (1)		India (1), Indonesia (1), Pakistan (1)	Turkey (1)		Taiwan (1)
1980 - 1989	9	South Africa (1),		India (6), Thailand (1)		Tunisia (1)	
1990 - 1999	13	South Africa (2)	Brazil (1), Latin America (2)	India (3), Indonesia (1), Malaysia (1)	Turkey (1)	Lebanon (1), Pakistan (1)	
2000 - 2009	15	Malawi (2), Nigeria (2), Zimbabwe (1)	Brazil (1)	Malaysia (1)		Iran (4), Libya (1)	China (1), Philippines (1), Papua New Guinea (1)
2010 - 2015	26	Nigeria (3), Uganda (1)	Brazil (1), Columbia (2),	India (6), Thailand (1)		Egypt (1) , Iran (2), Iraq (1)	China (8), Viet Nam (1)

[a] Number of published papers

Web Appendix 4 Full text excluded studies

Primary Author and Reference	Year	Country	Study design	Data source	Time	Population	Population N	Clubfoot N	Birth prevalence /1000	Reason
Dash Sharma (78)	1970	India	Data review	Records of birth	3 years	live births	5,554	2	0.36	Retrospective data review, unclear if all children screened
Kromberg and Jenkins (76)	1982	South Africa	Data review	Data from register of births in the nursery ward, paediatric ward and mortuary records	2 years	births	29, 633	46	1.55	Retrospective data review, unclear if all children screened
Choudhury (79)	1984	India	Data review	Hospital records of birth registers	4 years	births	21, 016	6	0.29	Retrospective data review, unclear if all children screened
Limpaphayom (80)	1985	Thailand	Data review	Medical records	2 years	births	not specified	104	1.30	No specified population
Roychoudhury (81)	1988	India	Data review	Maternity records	not specified	births	72, 617	not specified	varied from 0.02 to 0.11	Retrospective data review, unclear if all children screened
Castilla (82)	1990	Latin America	large database review	ECLAMC (Latin American Collaborative Study of Congenital Malformations) data	4 years	births	Tropical: 287,165 Non tropical: 582, 585	tropical: 442 non: 615	tropical: 1.54 non: 1.06	ECLAMC data used in Lopez - Camelo paper
Masloman (83)	1991	Indonesia	Data review	Medical records of department of child health	5 years	births	13, 354	11	0.82	Retrospective data review, unclear if all children screened
Bhat (84)	1998	India	Prospective, physical examination	Physical examination within 24 hours	3 years 3 months	births	12, 797	40 (36 live, 4 still)	3.13	All foot deformities included
Najmi (85)	1998	Pakistan	Prospective, physical examination	Physical examination by Paediatrician	2 years 8 months	live births	11,148	2 TEV and 2 TE	0.18	Unclear definition
Singh (86)	2000	Libya	Data review	Maternal records, NICU registry and stillborn / death	1 year	Births	16, 186	2: clubfoot or 4 : talipes	0.37	Retrospective data review, unclear if all children screened

				certificates						
Madzivire (87)	2002	Zimbabwe	Data review	Children attending clubfoot clinic, with population under 4 years	3 years	Hospital catchment area	96,942	82	0.85	Retrospective data review, unclear if all children screened
Mkandawire (88)	2002	Malawi	Prospective physical examination	Research nurse identified and photographed	13 months	Live births	9,838	11	1.12	Data included in paper published in 2004
Padilla (89)	2003	Philippines	Large database	Birth defects registry	12 months	Births	191, 567	73	0.38	Includes all congenital deformities of the feet
Abdi-Rad (90)	2008	Iran	Data review	Chart review	4 years 6 months	Births	14, 121	27	1.90	Retrospective data review, unclear if all children screened
Ekanem (91)	2008	Nigeria	Data review	Data extracted from birth registries	23 years	Birth registry in 2 states of Nigeria	127, 929	31	0.24	Retrospective data review, unclear if all children screened
Culverwell (77)	2009	Papua New Guinea	Data review	Clubfoot clinic notes	2 years	Live births and children presenting to hospital	11, 215 (based on 2000 census data)	60	2.67	Retrospective data review, unclear if all children screened
Bakare (92)	2009	Nigeria	Prospective, physical examination	Physical examination	1 year	Live births	624	5	8.00	All foot deformities
Zarante (93)	2010	Columbia	Large database	ECLAMC	6 years 9 months	Births	52, 744	132	2.50	Foot deformities include calcaneovalgus
Ukoha (94)	2011	Nigeria	Data review	Hospital records	6 years	Children attending hospital between 1 day and 2 years	12,464	43	3.00	Data review for children attending hospital - not birth prevalence
Ekanem (95)	2011	Nigeria	Data review	Maternity records	13 years	Births	19,572	8	0.41	Retrospective data review, unclear if all

										children screened
Zhu (96)	2012	China	Data review	Data of neonates with congenital malformations was reviewed	1 year	Live births	6,725	2	0.30	Retrospective data review
Vakilian (97)	2013	Iran	Data review	Review of maternal files	7 years	Live births	20,751	not specified	2.98	Retrospective data review, unclear if all children screened
Nhoncanse (98)	2014	Brazil	Data review	Review of birth certificates	5 years	Live births	12,199	4	0.32	Retrospective data review, unclear if all children screened
Ghorpade (99)	2015	India	Data review	Medical chart review	10 years	Live births	10, 674	60	5.62	Retrospective data review, unclear if all children screened

[a] ordered by year

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