

## Congenital clubfoot in Europe: a population-based study

Hao Wang, University of Groningen, The Netherlands ([hao.wang@rug.nl](mailto:hao.wang@rug.nl))  
Ingeborg Barisic, Children's Hospital Zagreb, Medical School University of Zagreb, Croatia ([ingeborg.barisic@kdb.hr](mailto:ingeborg.barisic@kdb.hr))  
Maria Loane, Institute of Nursing & Health Research, Ulster University, Northern Ireland, UK ([ma.loane@ulster.ac.uk](mailto:ma.loane@ulster.ac.uk))  
Marie-Claude Addor, Department of Woman-Mother-Child, University Hospital Center CHUV, Lausanne, Switzerland ([marieclaude.addor@chuv.ch](mailto:marieclaude.addor@chuv.ch))  
Linda M Bailey, Congenital Anomaly Register and Information Service for Wales, Public Health Wales NHS Trust ([CARIS@wales.nhs.uk](mailto:CARIS@wales.nhs.uk))  
Miriam Gatt, Directorate for Health Information and Research, Malta ([miriam.gatt@gov.mt](mailto:miriam.gatt@gov.mt))  
Kari Klungsoyr, Division of Mental and Physical Health, Norwegian Institute of Public Health and Department of Global Public Health and Primary Care, University of Bergen, Norway ([kari.klungsoyr@uib.no](mailto:kari.klungsoyr@uib.no))  
Olatz Mokoroa, Public Health Division of Gipuzkoa and Biodonostia Research Institute, San Sebastian, Spain ([o-mokoroa@euskadi.eus](mailto:o-mokoroa@euskadi.eus))  
Vera Nelen, Provinciaal Instituut voor Hygiene, Belgium ([vera.nelen@provincieantwerpen.be](mailto:vera.nelen@provincieantwerpen.be))  
Amanda J Neville, IMER Registry, Center for Clinical and Epidemiological Research, University of Ferrara and Azienda Ospedaliero Universitario di Ferrara, Italy ([nvm@unife.it](mailto:nvm@unife.it))  
Mary O'Mahony, Health Service Executive, Ireland ([maryt.omahony@hse.ie](mailto:maryt.omahony@hse.ie))  
Anna Pierini, Tuscany Registry of Congenital Defects, Institute of Clinical Physiology - National Research Council/Fondazione Toscana "Gabriele Monasterio", Pisa, Italy ([apier@ifc.cnr.it](mailto:apier@ifc.cnr.it))  
Anke Rissmann, Malformation Monitoring Centre Saxony-Anhalt, Medical Faculty, Otto-von-Guericke University Magdeburg, Germany, ([anke.rissmann@med.ovgu.de](mailto:anke.rissmann@med.ovgu.de))  
Christine Verellen-Dumoulin, Center for Human Genetics, Institut de Pathologie et de Génétique, Charleroi, Belgium ([christine.verellen.dumoulin@ipg.be](mailto:christine.verellen.dumoulin@ipg.be))  
Hermien EK de Walle, University of Groningen, University Medical Centre Groningen, Department of Genetics, Groningen, The Netherlands ([h.e.k.de.walle@umcg.nl](mailto:h.e.k.de.walle@umcg.nl))  
Awi Wiesel, University Medical Center of Mainz, Dept. of Pediatrics, Birth Registry Mainz Model, Germany ([awi.wiesel@unimedizin-mainz.de](mailto:awi.wiesel@unimedizin-mainz.de))  
Katarzyna Wisniewska, Department of Preventive Medicine, Epidemiology Unit, Poznan University of Medical Sciences, Poland ([kwisniewska@ump.edu.pl](mailto:kwisniewska@ump.edu.pl))  
Lolkje TW de Jong-van den Berg, University of Groningen, The Netherlands ([paulenlokkje@gmail.com](mailto:paulenlokkje@gmail.com))  
Helen Dolk, Institute of Nursing & Health Research, Ulster University, Northern Ireland, UK ([h.dolk@ulster.ac.uk](mailto:h.dolk@ulster.ac.uk))  
Babak Khoshnood, INSERM UMR 1153, Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Center of Research in Epidemiology and Statistics Sorbonne Paris Cité (CRESS), DHU Risks in Pregnancy, Paris Descartes University, Paris, France, [babak.khoshnood@inserm.fr](mailto:babak.khoshnood@inserm.fr)  
Ester Garne, Paediatric Department, Hospital Lillebaelt Kolding, Denmark ([ester.garne@rsyd.dk](mailto:ester.garne@rsyd.dk))

Corresponding author:

Ester Garne, Paediatric Department, Hospital Lillebaelt, Kolding, Denmark ([ester.garne@rsyd.dk](mailto:ester.garne@rsyd.dk))

## **Abstract**

We aimed to assess prevalence, birth outcome, associated anomalies and prenatal diagnosis of congenital clubfoot in Europe using data from the EUROCAT network, and to validate the recording of congenital clubfoot as a major congenital anomaly by EUROCAT registries. Cases of congenital clubfoot were included from 18 EUROCAT registries covering more than 4.8 million births in 1995-2011. Cases without chromosomal anomalies born during 2005-2009, were randomly selected for validation using a questionnaire on diagnostic details and treatment. There was 5,458 congenital clubfoot cases of which 5056 (93%) were liveborn infants. Total prevalence of congenital clubfoot was 1.13 per 1000 births (95% CI 1.10-1.16). Prevalence of congenital clubfoot without chromosomal anomaly was 1.08 per 1000 births (95% CI 1.05-1.11) and prevalence of isolated congenital clubfoot was 0.92 per 1000 births (95% CI 0.90–0.95), both with decreasing trends over time and large variations in prevalence by registry . The majority of cases were isolated congenital clubfoot (82%) and 11% had associated major congenital anomalies. Prenatal detection rate of isolated congenital clubfoot was 22% and increased over time. Among 301 validated congenital clubfoot cases, diagnosis was confirmed for 286 (95%). In conclusion, this large population-based study found a decreasing trend of congenital clubfoot in Europe after 1999-2002, an increasing prenatal detection rate, and a high standard of coding of congenital clubfoot in EUROCAT.

## **Key words.**

Congenital clubfoot, prevalence, trend, prenatal diagnosis, associated anomalies

## Introduction

Congenital clubfoot, congenital talipes equinovarus, is one of the more common major congenital anomalies with a prevalence of around 1 per 1000 livebirths [Parker et al, 2009]. Clubfoot is a congenital anomaly of several tissues of the foot and ankle, with one or both feet turning inward and downward. Congenital clubfoot is clinically differentiated from postural clubfoot, a postnatally reduced positional defect. In congenital clubfoot, the foot cannot be moved into a normal position by hand. Treatment of congenital clubfoot includes the Ponseti method with multiple casting or splinting, and/or surgery (Dobbs et al, 2000, Ganesan et al, 2017). The prevalence of congenital clubfoot has been reported as higher in males compared to females (2.0-2.5 times) [Kancherla et al, 2010; Moorthi et al, 2005]. In about half of the patients, the anomaly is bilateral, and for unilateral clubfoot, the right side is affected slightly more frequently than the left side [Cardy et al, 2011]. Congenital clubfoot develops early in pregnancy and it can be detected by ultrasound from 12 weeks of gestation [Keret et al, 2002]. The overall rate of prenatal detection of congenital clubfoot was reported to be around 60% in three states of the USA in 2006-2011 [Mahan et al, 2014]. The prenatal detection rate was higher in cases associated with other anomalies [Mahan et al, 2014; Offerdal et al, 2007; Seravalli et al, 2015].

The etiology of congenital clubfoot is thought to be a combination of genetic and environmental factors. It has higher recurrence within families, however a twin study suggested that environmental factors also play a significant role in the etiology of congenital clubfoot [Engell et al, 2014]. Several environmental risk factors, in particular maternal smoking, have been related to the risk of congenital clubfoot [Pavone et al, 2018, Werler et al, 2015]. Some maternal medical conditions and medication use could increase the risk of congenital clubfoot, such as obesity (Werler et al, 2013) and use of selective serotonin reuptake inhibitors (SSRI) [Yazdy et al, 2014; Wemakor et al, 2015]. In a EUROCAT study investigating lamotrigine exposure associated with an increased risk for orofacial

clefts, there was an unexplained excess risk of congenital clubfoot among lamotrigine-exposed pregnancies [Dolk et al, 2008].

The aim of the current study was to estimate the prevalence, trend over time, prenatal diagnosis and associated anomalies of congenital clubfoot in Europe using data from a population-based surveillance program of congenital anomalies (EUROCAT), 1995-2011. In addition, this study aims to validate the registration of congenital clubfoot as a major congenital anomaly by EUROCAT registries.

## **Methods**

The EUROCAT registries are population-based congenital anomaly registries in Europe, covering about 30% of the European birth population. Details of the EUROCAT database and the methods of case ascertainment have been described previously [Dolk et al, 2008]. In brief, congenital anomalies in livebirths, fetal deaths including stillbirths and spontaneous abortions from gestational age (GA) 20 weeks, and terminations of pregnancy following prenatal diagnosis at any GA (TOPFA) were recorded in the EUROCAT database, according to the EUROCAT Guides [EUROCAT website]. The inclusion criteria for the EUROCAT database is a code within the congenital anomaly chapter in ICD9 (740-759) or in ICD10 (Q-chapter). One syndrome and up to eight congenital anomalies per baby/fetus can be registered in the EUROCAT database with ICD9 or ICD10 codes with the British Paediatric Association extensions. Additional information can be added in a text variable. Anomalies on the EUROCAT list of minor anomalies are not included if isolated. Clubfoot of postural origin is on the list of minors for exclusion (Q668). Information on anomalies was obtained from multiple sources, including hospital records, birth and death certificates and post-mortem examinations [Greenlees et al, 2011]. The follow-up period for inclusion of congenital anomalies in the EUROCAT varies among registries: the diagnosis of a congenital anomaly is up to one year of age in most registries. The current study included data from 18 registries, covering a total of 4,840,588 births in the period of 1995-2011.

All cases of the EUROCAT subgroup “clubfoot”, based on the ICD 9 code 75450 or ICD 10 code Q660, were extracted from the central EUROCAT database (n=5,810). A total of 352 cases were excluded as the clubfoot was secondary to another primary anomaly: neural tube defect (NTD), bilateral renal agenesis, Potter sequence or arthrogryposis multiplex congenital [Garne et al, 2011], since these would be etiologically different. There was large variation in the proportion of cases with secondary clubfoot excluded by registry (Data in Appendix).

A computer algorithm was used to classify the remaining infants and fetuses with congenital clubfoot into isolated, potential multiple congenital anomaly, genetic syndrome, teratogenic syndrome and chromosomal anomaly [Garne et al, 2011]. All potential multiple congenital anomaly cases were manually reviewed by a paediatrician (EG) and checked by a geneticist (IB). The potential multiple cases were re-classified as true multiple congenital anomaly or re-classified to another group.

The trend analysis and the validation study included all infants and fetuses that did not have a chromosomal anomaly (non-chromosomal).

#### Validation study of clubfoot records in EUROCAT

Twenty infants with congenital clubfoot or all infants if less than 20 in the period from 2005 up to 2009, were randomly selected from 16 registries participating in the validation study. Registries in Hainaut and Strasbourg did not participate in this part of the study. A questionnaire on diagnostic details, treatment type and family history of each infant was completed by the local registry based on medical records.

#### Data analysis

Total prevalence of congenital clubfoot was calculated by the total number of infants and fetuses with clubfoot divided by total births (live and stillbirths). Analysis of annual trends in the prevalence of clubfoot (non-chromosomal and isolated) was conducted using random-effects Poisson regression models to take into account the heterogeneity across registries. The number of births was used as

the “exposure” variable in the Poisson regression model. Year of birth was categorised into the following time periods: 1995-1998, 1999-2002, 2003-2005, 2006-2008, 2009-2011. The Poisson model presented prevalence rate ratio (PRR) estimates and 95% confidence intervals (CI) relative to the 1995-1998 time period. All analyses were performed using STATA, version 13.0 (StataCorp LP, College Station, Texas).

## Results

During 1995–2011, a total of 5,458 infants and fetuses with congenital clubfoot were reported from 18 EUROCAT registries giving a total European prevalence of congenital clubfoot of 1.13 per 1000 births (95% CI 1.10-1.16). There were 5,056 (93%) livebirths, 106 (2%) fetal deaths from 20 weeks and 296 (5%) TOPFA. Among livebirths 3,262 were males (65%) and 1,788 were females (35%), giving a male: female ratio of 1.8:1.

After case review/classification there were 4,468 (82%) infants and fetuses with isolated clubfoot , 591 (11%) with clubfoot as part of multiple congenital anomalies, 144 (3%) was diagnosed with a genetic syndrome, only nine (0.2%) infants and fetuses were reported as associated with teratogenic syndromes and 246 (5%) had a chromosomal anomaly. Of the 591 infants and fetuses with congenital clubfoot and associated major anomalies, congenital heart defects were most frequently associated with congenital clubfoot (n=187, 32%), including 80 with ventricular septal defect (VSD), followed by anomalies of the nervous system (n=110, 19%), and urinary anomalies (107, 18%). The most common chromosomal anomaly was trisomy 18 (n=111, 2%) (Table 1).

The overall prevalence of congenital clubfoot without an associated chromosomal anomaly was 1.08 per 1000 births (95% CI 1.05–1.11) with large regional differences, ranging from 0.44 per 1000 births in Tuscany and 0.45 per 1000 births in Basque Country to 1.68 per 1000 births in Wales (Table 2). The

large regional differences were also seen in the prevalence of isolated congenital clubfoot. The trend analysis showed a statistically significant decreasing trend for both groups after 1999-2002 (Figure 1)

In 22 % (921/4165) of infants and fetuses with congenital clubfoot as the only anomaly and with time of diagnosis known, the clubfoot was diagnosed prenatally, with considerable variation between registries. The prenatal detection rates ranged from less than 10% in Antwerp, Cork & Kerry, Mainz, Wielkopolska, Zagreb, Norway and Malta to higher than 50% in Paris (57%) and Vaud (51%). The prenatal diagnosis increased significantly from 20% in 1999-2002 to 29% in 2009-2011 ( $P < 0.01$ ).

#### Validation of clubfoot records in EUROCAT

A total of 308 infants and fetuses with congenital clubfoot were sampled for validation. Of these, a questionnaire was completed for 301 infants and fetuses by 16 registries. Of the 301 whose questionnaires were completed, medical records were obtained for 184 (61.1%). The verification of the diagnosis by medical records varied by registry. All sampled clubfoot cases from Denmark, Mainz and Malta were verified by medical records. The sampled clubfoot cases from Emilia Romagna and Paris could only be verified by registry data and not by original medical records.

The diagnosis congenital clubfoot was confirmed for 286 out of the 301 infants and fetuses (95%), of which 176 were validated by medical records, whereas 110 were based on registry information. Two infants had questionable congenital clubfoot and 13 infants did not have congenital clubfoot (four from Emilia Romagna, three from Mainz, two from Norway; one infant in four registries). Of the 13 who did not have the major anomaly congenital clubfoot, nine infants were confirmed to have other anomalies of the feet: one case with talipes calcaneovarus (Q661), one case with talipes varus (Q662), two cases with talipes calcaneovalgus (Q664), three cases with talipes valgus (Q666) and two cases with postural talipes (Q668). Of the 13 infants who did not have congenital clubfoot, eight

were verified by medical records (i.e. 4.3% of those verified by medical records). Twelve of the 13 cases who did not have congenital clubfoot were livebirths and one was a TOPFA.

Epidemiology data of the validation study are presented in Table 3. No statistically significant differences were identified between males and females in terms of laterality, family history of congenital clubfoot, proportion isolated, or birth type. Of infants with known clubfoot treatment, the majority (94%) were treated with splint/casts/surgery.

## **Discussion**

This European congenital clubfoot study based on data from 18 EUROCAT registries (1995-2011), covering almost 5 million births, found a total of 5,458 infants and fetuses with congenital clubfoot and a total prevalence of 1.13 per 1000 births, 1.08 per 1000 for congenital clubfoot without chromosomal anomaly and 0.92 per 1000 births for congenital clubfoot as the only major congenital anomaly. We found decreasing trends in the prevalence over the 17 years included in the study. Our study showed that 95 % of the infants and fetuses from a validation study of congenital clubfoot records in EUROCAT were confirmed as true congenital clubfoot. This is particular importance since the reporting of congenital clubfoot can be affected by miscoding of the more common postural clubfoot as true congenital clubfoot.

The prevalence of congenital clubfoot in our study was comparable with those observed in other European population-based studies: 1.03 per 1000 livebirths in Sicily [Pavone et al, 2012] and 1.1 per 1000 livebirths in Norway [Dodwell et al, 2015]. However, the recorded prevalence of congenital clubfoot in our study was lower compared to 1.4 per 1000 livebirths for isolated congenital clubfoot found in a study in Sweden [Wallander et al, 2006], 1.8 per 1000 livebirths for all congenital clubfoot cases and 1.1 per 1000 births for isolated congenital clubfoot in a study in Southern Australia [Byron-Scott et al, 2005], 1.14 per 1000 livebirths for isolated congenital clubfoot in Iowa [Kancherla et al, 2010] and 1.29 per 1000 livebirths pooling 10 birth defects surveillance programs in the US [Parker et



al, 2009]. The lower prevalence of congenital clubfoot in our study might be partly due to the exclusion of secondary clubfoot associated with NTD or bilateral renal agenesis, postural clubfoot and other subtypes of foot anomalies in our data.

The overall prevalence of congenital clubfoot varied more than threefold among registries in our study. The large regional differences were also found in isolated congenital clubfoot. There may be differences in case ascertainment and also underreporting among registries with the lowest prevalence, which may account for the varied prevalence. However, the regional differences in prevalence of congenital clubfoot might also reflect a true difference. Other studies have observed differences in prevalence of congenital clubfoot based on ethnic groups and region of residence [Parker et al, 2009; Moorthi et al, 2005; Wallander et al, 2006].

The observed decrease in the prevalence of congenital clubfoot may be a true decrease, but may also be explained by changes in the EUROCAT coding guidelines in 2002 with more focus on excluding postural clubfoot as a minor anomaly. The validation study from the more recent period of the study (2005-2009) showed that 95% of our cases from these years were true congenital clubfoot.

Our study supported previously reported findings that males were more commonly affected by congenital clubfoot. EUROCAT data lacked complete information on laterality, but the profile from the random sample in the validation study was in agreement with other descriptive studies: approximately half of confirmed congenital clubfoot cases were bilateral and a right-sided was predominant among unilateral clubfoot [Kancherla et al, 2010; Roye et al, 2004]. Congenital clubfoot is known to recur in some families [Cardy et al, 2007; Cardy et al 2011]. In the random sample, nine percent of the infants and fetuses with congenital clubfoot had a family history, mainly with a first-degree relative affected, and this can be considered a minimum estimate. This corresponds with

previous studies showing 7-21% of patients with congenital clubfoot having an affected relative and is in line with the multifactorial type of inheritance (Alvarado et al, 2016).

Several theories on the causes of congenital clubfoot have been proposed, although the exact etiology has not been established: restriction of the uterus in early pregnancy, disturbance of endochondral ossification of the foot, occurrence secondarily to neurological abnormalities or a connective tissue disorder, and vascular disruption [Miedzybrodzka, 2003]. Studies have consistently shown an association between maternal smoking and increased risk of congenital clubfoot [Kancherla et al, 2010; Werler et al, 2015]. A number of other environmental risk factors and medical conditions have been related to the risk of congenital clubfoot in some studies, but not in others, including maternal age, parity, education level [Parker et al, 2009; Hollier et al, 2000], solvent exposure (including paint-thinner, paint-lacquer-glue remover, and others, e.g., turpentine, toluene, carbon tetrachloride) [Dodwell et al, 2015], high levels of alcohol and coffee intake [Miedzybrodzka et al, 2003] and maternal obesity [Werler et al, 2013]. Recently, several studies have investigated the association between medication use in pregnancy and risk of congenital clubfoot. In a population-based case-control study conducted in the USA, the risk of congenital clubfoot was associated with the use of antiviral drugs (odds ratio (OR) 4.2, 95% CI 1.5-11.7) [Werler et al, 2013] and the use of SSRI (OR 1.8, 95% CI 1.1-2.8) [Yazdy et al, 2014]. A significant increased risk of congenital clubfoot among SSRI-exposed women was not found in a Danish study (OR 1.3, 95% CI 0.9-2.0) [Henriksen et al, 2015]. A case malformed-control study using the EUROCAT database showed that the use of SSRI was related to the risk of congenital clubfoot (OR=2.4, 95% CI 1.6-3.7) [Wemakor et al, 2015]. Dolk et al. showed an excess risk of congenital clubfoot in relation to lamotrigine exposure using EUROCAT database (including the same 18 registries as our current study) [Dolk et al, 2008] although the excess risk was not statistically significant in the independent updated dataset from the EUROCAT database [Dolk et al, 2016].

Congenital clubfoot has been diagnosed prenatally as early as GA 12 weeks by ultrasound [Keret et al, 2002] and therefore detectable by the malformation screening scans usually carried out at GA 18-22 weeks in most European countries. In our study, the prenatal detection rate of isolated congenital clubfoot improved during the study period. The increase in prenatal diagnosis of congenital clubfoot was also observed in Norway during 1987- 2004 [Offerdal et al, 2007] and in Tuscany in the period of 1991-2011 [Seravalli et al, 2015]. In Wales, routine fetal anomaly scans are part of the antenatal screening program, but these no longer include antenatal detection of specifically clubfoot. The variance of antenatal detection rates between registries might be due to the different policies regarding purpose and timing of the antenatal routine ultrasound screening in each country.

Most epidemiological studies are based on isolated congenital clubfoot. Our study found that more than 80% were classified as isolated congenital clubfoot, which was higher than 59.5% in the South Australia study [Byron-Scott et al, 2005]. The difference may be mainly due to the exclusion of secondary clubfoot associated with renal agenesis, neural tube defects and arthrogryposis multiplex congenita in our study. Among infants and fetuses with congenital clubfoot and associated major anomalies, the most common associated anomalies were congenital heart defects with ventricular septal defects being most frequent. Comparable with the study in South Australia, trisomy 18 was the most common chromosomal anomaly associated with congenital clubfoot.

A strength of the current study is the use of the EUROCAT database, which is a population-based European surveillance of congenital anomalies with inclusion of all types of births and all major congenital anomalies without bias for inclusion of congenital clubfoot. The EUROCAT database covers a large geographically defined study population, and the well-validated and standardized diagnostic information on all types of congenital anomalies. Multiple sources of ascertainment of cases are used to avoid ascertainment-bias from specialized centers. Our study had a large sample

size of almost 5500 cases over a long time period from a total of 4.8 million births. Another strength of our study is the exclusion of other subtypes of foot anomalies or postural clubfoot, which avoids the potential misclassification of the cases when examining the risk factors of congenital clubfoot.

We recommend that etiological studies should report their prevalence rate of congenital clubfoot so that extent of bias due to potential misclassification of postural clubfoot can be estimated.

The limitation of our study is the combination of data from different registries with different data-coding practices and variable case ascertainment. We took some of these heterogeneities across registries by using random-effects models that at least to some extent take differences across registries into account. We were not able to examine some potential risk factors of congenital clubfoot, such as smoking, which are not included in the routine EUROCAT data collection.

In conclusion, we have established a well validated prevalence rate of congenital clubfoot in Europe at close to one per 1,000 births, a prevalence of a similar order to some of the other more common congenital anomalies such as orofacial clefts and neural tube defects. This can be used as a baseline expected prevalence for studies of the effect of medication during pregnancy and other risk factors on outcome, but geographical variation in prevalence also needs to be taken into account. During the study period, the minority of cases were diagnosed prenatally. While the observed decrease in prevalence of congenital clubfoot is reassuring, further monitoring is required, as well as further research to understand the etiology of congenital clubfoot so that true prevention can be achieved.

**Acknowledgement:** We thank the previous registry leaders for contributing data from the Strasbourg registry to this paper, before closure of the registry.

**Funding:** Partial financial support for this study was provided by the European Union under the Seventh Framework Programme (grant agreement HEALTH-F5-2011-260598) and by Glaxo Smith Kline funding for a study of lamotrigine safety in pregnancy (University of Groningen and University of Ulster 2007-2011). Neither funder had any involvement in the study.

**Conflicts of interest:** all authors declare no conflicts of interest

**Figure 1**

Prevalence of congenital clubfoot per 1000 births in 18 EUROCAT registries 1995-2011

## References

Alvarado DM, McCall K, Hecht JT, Dobbs MB, Gurnett CA. (2016). Deletion of 5' HOXC genes are associated with lower extremity malformations including clubfoot and vertical tarus. *J Med Genet*, 53, 250-55

Byron-Scott R, Sharpe P, Hasler C, Cundy P, Hirte C, Chan A, Scott H, Baghurst P, Haan E. (2005). A south Australian population-based study of congenital talipes equinovarus. *Paediatr Perinat Epidemiol*, 19(3), 227-237.

Cardy AH, Barker S, Chesney D, Sharp L, Maffulli N, Miedzybrodzka Z.(2007). Pedigree analysis and epidemiological features of idiopathic congenital talipes equinovarus in the united kingdom: A case-control study. *BMC Musculoskelet Disord*, 8, 62.

Cardy AH, Sharp L, Torrance N, Hennekam RC, Miedzybrodzka Z. (2011). Is there evidence for aetiologically distinct subgroups of idiopathic congenital talipes equinovarus? A case-only study and pedigree analysis. *PLoS One*, 6(4), e17895.

Dobbs MB, Morcuende JA, Gurnett CA, Ponseti IV (2000). Treatment of idiopathic clubfoot: a historical review. *Iowa Orthop J*. 2000;20:59-64.

Dodwell E, Risoe P, Wright J. (2015). Factors associated with increased risk of clubfoot: A norwegian national cohort analysis. *J Pediatr Orthop*, 35(8), e104-9.

Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg LT, EUROCAT Antiepileptic Drug Working Group.(2008). Does lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations? *Neurology*, 71(10), 714-722.

Dolk H, Wang H, Loane M, Morris J, Garne E, Addor MC, Arriola L, Bakker M, Barisic I, Doray B, Gatt M, Kallen K, Khoshnood B, Klungsoyr K, Lahesmaa-Korpinen AM, Latos-Bielenska A, Mejnartowicz JP,

Nelen V, Neville A, O'Mahony M, Pierini A, Rißmann A, Tucker D, Wellesley D, Wiesel A, de Jong-van den Berg LT. (2016). Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. *Neurology*, 86(18), 1716-1725.

Engell V, Nielsen J, Damborg F, Kyvik KO, Thomsen K, Pedersen NW, Andersen M, Overgaard S. (2014). Heritability of clubfoot: A twin study. *J Child Orthop*, 8(1), 37-41.

EUROCAT. EUROCAT Guide 1.3 and reference documents, instructions for the registration and surveillance of congenital anomalies, September 2005, <http://www.eurocat.ulster.ac.uk/pdf/EUROCAT-Guide-1.3.pdf>. Accessed 06/10, 2015.

Ganesan B, Luximon A, Al-Jumaily A, Balasankar SK, Naik GR (2017). [Ponseti method in the management of clubfoot under 2 years of age: A systematic review](#). *PLoS One* 12(6):e0178299

Garne E, Dolk H, Loane M, Wellesley D, Barisic I, Calzolari E, Densem J (2011). Paper 5: Surveillance of multiple congenital anomalies: Implementation of a computer algorithm in european registers for classification of cases. *Birth Defects Res A Clin Mol Teratol*, 91 Suppl 1, S44-50.

Greenlees R, Neville A, Addor MC, Amar E, Arriola L, Bakker M, Barisic I, Boyd PA, Calzolari E, Doray B, Draper E, Vollset SE, Garne E, Gatt M, Haeusler M, Kallen K, Khoshnood B, Latos-Bielenska A, Martinez-Frias ML, Materna-Kirylyuk A, Dias CM, McDonnell B, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoélina H, Rankin J, Rissmann A, Ritvanen A, Salvador J, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D, Wertelecki W. (2011). Paper 6: EUROCAT member registries: Organization and activities. *Birth Defects Res A Clin Mol Teratol*, 91 Suppl 1, S51-S100

Henriksen DP, Pottegard A, Jimenez-Solem E, Damkier P (2015). In utero SSRI exposure and risk of clubfoot. *Epidemiology*, 26(3), e34-5.

- Hollier LM, Leveno KJ, Kelly MA, McIntire DD, Cunningham FG. (2000). Maternal age and malformations in singleton births. *Obstet Gynecol*, 96(5 Pt 1), 701-706.
- Kancherla V, Romitti PA, Caspers KM, Puzhankara S, Morcuende JA. (2010). Epidemiology of congenital idiopathic talipes equinovarus in iowa, 1997-2005. *Am J Med Genet A*, 152A(7), 1695-1700
- Keret D, Ezra E, Lokiec F, Hayek S, Segev E, Wientroub S. (2002). Efficacy of prenatal ultrasonography in confirmed club foot. *J Bone Joint Surg Br*, 84(7), 1015-1019.
- Mahan ST, Yazdy MM, Kasser JR, Werler MM. (2014). Prenatal screening for clubfoot: What factors predict prenatal detection? *Prenat Diagn*, 34(4), 389-393.
- Miedzybrodzka Z. (2003). Congenital talipes equinovarus (clubfoot): A disorder of the foot but not the hand. *J Anat*, 202(1), 37-42.
- Moorthi RN, Hashmi SS, Langois P, Canfield M, Waller DK, Hecht JT. (2005). Idiopathic talipes equinovarus (ITEV) (clubfeet) in Texas. *Am J Med Genet A*, 132A(4), 376-380.
- Offerdal K, Jebens N, Blaas HG, Eik-Nes SH (2007). Prenatal ultrasound detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway. *Ultrasound Obstet Gynecol*, 30(6), 838-844.
- Parker SE, Mai CT, Strickland MJ, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A; National Birth Defects Prevention Network. (2009). Multistate study of the epidemiology of clubfoot. *Birth Defects Res A Clin Mol Teratol*, 85(11), 897-904.
- Pavone V, Bianca S, Grosso G, Pavone P, Mistretta A, Longo MR, Marino S, Sessa G. (2012). Congenital talipes equinovarus: An epidemiological study in sicily. *Acta Orthop*, 83(3), 294-298.



Pavone V, Chisari E, Vescio A, Lucenti L, Sessa G, Testa G (2018) .The etiology of idiopathic congenital talipes equinovarus: a systematic review. *J Orthop Surg Res*; 13:206

Roye BD, Hyman J, Roye DP,Jr.(2004) Congenital idiopathic talipes equinovarus. *Pediatr Rev*, 25(4), 124-130.

Seravalli V, Pierini A, Bianchi F, Giglio S, Vellucci FL, Cariati E (2015). Prevalence and prenatal ultrasound detection of clubfoot in a non-selected population: An analysis of 549, 931 births in Tuscany. *J Matern Fetal Neonatal Med*, 28(17), 2066-2069.

Wallander H, Hovellius L, Michaelsson K (2006). Incidence of congenital clubfoot in Sweden. *Acta Orthop*, 77(6), 847-852.

Wemakor A, Casson K, Garne E, Bakker M, Addor MC, Arriola L, Gatt M, Khoshnood B, Klungsoyr K, Nelen V, O'Mahoney M, Pierini A, Rissmann A, Tucker D, Boyle B, de Jong-van den Berg L, Dolk H. (2015). Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: A European register-based study. *Eur J Epidemiol*, 30(11), 1187-1198.

Werler MM, Yazdy MM, Mitchell AA, Meyer RE, Druschel CM, Anderka M, Kasser JR, Mahan ST (2013). Descriptive epidemiology of idiopathic clubfoot. *Am J Med Genet A*, 161A(7), 1569-1578.

Werler MM, Yazdy MM, Kasser JR, Kasser JR, Mahan ST, Meyer RE, Anderka M, Druschel CM, Mitchell AA. (2015). Maternal cigarette, alcohol, and coffee consumption in relation to risk of clubfoot. *Paediatr Perinat Epidemiol*, 29(1), 3-10.

Yazdy MM, Mitchell AA, Louik C, Werler MM (2014). Use of selective serotonin-reuptake inhibitors during pregnancy and the risk of clubfoot. *Epidemiology*, 25(6), 859-865.

**Table 1.** Classification of cases with congenital clubfoot and associated major congenital anomalies, 18 EUROCAT registries, 1995-2011

Classification	Most common associated anomalies	
Multiple congenital anomaly <sup>1</sup>	Total	N=591
	Congenital heart defects	187
	Ventricular septal defect	80
	Nervous system	110
	Hydrocephalus	39
	Urinary	107
	Congenital hydronephrosis	31
	Oral clefts	75
Genetic syndromes	Total	N=144
	22q11.2 microdeletion	14
	Pena-Shokeir syndrome type I	13
Teratogenic syndromes	Total	N=9
Chromosomal	Total	N=246
	Edwards syndrome /trisomy 18	101
	Down syndrome/trisomy 21	48

<sup>1</sup>A case may have more than one associated congenital anomaly (example: clubfoot with VSD and hydronephrosis)

**Table 2** Prevalence per 1000 births of congenital clubfoot cases without chromosomal anomaly and congenital clubfoot cases without associated anomalies (isolated cases) in 18 EUROCAT registries, 1995-2011

Registry	Time period	Total births	Total cases	Total cases without chromosomal anomaly		Isolated congenital clubfoot cases		
				No	Prevalence (95% CI) per 1,000 birth	No	Prevalence (95% CI) per 1,000 birth	% of total cases
Belgium, Antwerp	1997 – 2011	286,751	296	283	0.99 (0.88–1.10)	243	0.85 (0.75–0.96)	82
Belgium, Hainaut	1997 – 2005	110,557	64	63	0.57 (0.45–0.73)	58	0.53 (0.41–0.68)	91
Croatia, Zagreb	1995 – 2010	105,353	80	77	0.73 (0.59–0.91)	67	0.64 (0.50–0.81)	84
Denmark, Odense	1995 – 2011	92,211	122	120	1.30 (1.09–1.56)	109	1.18 (0.98–1.43)	89
France, Paris	1997 – 2011	508,721	572	545	1.07 (0.99–1.17)	450	0.89 (0.81–0.97)	79
France, Strasbourg	1997 – 2004	102,495	139	131	1.28 (1.08–1.52)	113	1.10 (0.92–1.33)	81
Germany, Mainz	1996 – 2011	52,190	72	70	1.34 (1.06–1.70)	61	1.17 (0.91–1.50)	85
Germany, Saxony Anhalt	1996 – 2011	250,210	413	388	1.55 (1.40–1.71)	324	1.30 (1.16–1.44)	79
Ireland, Cork & Kerry	1996 – 2010	131,119	158	143	1.09 (0.93–1.29)	110	0.84 (0.70–1.01)	70
Italy, Emilia Romagna	2000 – 2011	426,650	425	409	0.96 (0.87–1.06)	352	0.83 (0.74–0.92)	83
Italy, Tuscany	2002 – 2011	296,483	135	131	0.44 (0.37–0.52)	119	0.40 (0.34–0.48)	88
Malta	1996 – 2010	63,051	58	56	0.89 (0.68–1.15)	45	0.71 (0.53–0.96)	78

Netherlands, Northern	1995 – 2011	323,72 8	324	310	0.96 (0.86– 1.07)	259	0.80 (0.71– 0.90)	80
Norway	1999 – 2011	774,98 5	111 1	1087	1.40 (1.32– 1.49)	100 5	1.30 (1.22– 1.38)	91
Poland, Wielkopolska	1999 – 2010	440,09 6	396	387	0.88 (0.80– 0.97)	346	0.79 (0.71– 0.87)	87
Spain, Basque Country	1995 – 2010	297,53 1	148	134	0.45 (0.38– 0.53)	105	0.35 (0.29– 0.43)	71
Switzerland, Vaud	1997 – 2011	112,15 6	105	95	0.85 (0.69– 1.04)	79	0.70 (0.57– 0.88)	75
UK, Wales	1998 – 2011	466,30 1	840	783	1.68 (1.57– 1.80)	623	1.34 (1.24– 1.45)	74
Total	1995 – 2011	484058 8	545 8	5212	1.08 (1.05– 1.11)	4,4 68	0.92 (0.90– 0.95)	82

**Table 3.** Characteristics of congenital clubfoot cases confirmed in the validation study. Data from 16 EUROCAT registries<sup>1</sup>

	Total		Male		Female	
	N	%	N	%	N	%
Confirmed clubfoot						
Total	286		186	65%	96	34%
Birth type						
Livebirth	269	94%	180	97%	89	93%
Stillbirth	5	2%	2	1%	3	3%
TOPFA	12	4%	4	2%	4	4%
Malformations						
Isolated clubfoot	210	75%	141	76%	68	73%
Associated with other anomalies	72	25%	44	24%	25	27%
Unknown due to termination	4		0		3	
Laterality						
Bilateral	158	57%	105	58%	50	56%
Unilateral	117	43%	76	42%	40	44%
left	45	16%	30	16%	14	15%
right	65	24%	41	22%	24	25%
unilateral, side unknown	7	3%	5	3%	2	2%
Unknown	11		5		6	
Surgery/Spint <sup>2</sup>						
Yes	168	94%	123	98%	45	87%
No	10	6%	3	2%	7	14%
Unknown	91		54		37	
Family history of clubfoot						
Yes	22	9%	14	9%	8	11%
No	216	91%	148	91%	68	89%
Unknown	48		24		20	

<sup>1</sup> registries in Hainault and Strasbourg not included

<sup>2</sup>Among livebirth

