

Prevalence of Congenital Anomalies in Iran: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Congenital anomaly is a disturbance in fetal growth and development during pregnancy and is one of the main causes of morbidity and mortality in the first year of life. In addition, this anomaly causes a large waste of health care resources. We aimed to determine the prevalence and proportion rates of different congenital anomalies in Iran via a systematic review and meta-analysis.

Methods: The present study was performed to estimate the prevalence and proportion rates of different anomalies in Iran via a systematic review and meta-analysis. Therefore, all the studies performed in Iran between 2000 and 2016 were evaluated. For this purpose, Medlib, Scopus, Web of Science, PubMed, Cochrane Library, Science Direct, Google Scholar, Irandoc, Magiran, IranMedex, and SID databases were searched by two different expert individuals independently. For the qualification survey of the papers, the Strengthening the Reporting of Observational Studies in Epidemiology checklist was applied. Then, the extracted data were entered into STATA (ver.11.1) and analysed using statistical tests of stability and random effects models in meta-regression, a tool used in meta-analysis. The 95% confidence intervals were calculated by I-square models. Meta regression was introduced to explore the heterogeneities among studies.

Results: Overall, 36 papers with a total sample size of 909,961 neonates were analysed. The total prevalence rate for congenital anomalies was 18/1000 live births, 23.2/1000 and 18/1000 for boys and girls, respectively. Moreover, 55.8% of all congenital anomalies pertained to boys. The greatest prevalence and proportion rates of congenital anomalies belonged to musculoskeletal disorders followed by urogenital anomalies (9.3/1000 [34%] and 5.7/1000 [20%], respectively), and the lowest figures belonged to chromosomal and respiratory system anomalies (0.8/1000 [6%] and 0.3/1000 [2%], respectively).

Conclusion: According to the findings of this meta-analysis, the prevalence of congenital anomalies is notably high in Iran and annually imposes huge visible and non-visible expenses on individuals, societies, and health care systems. Therefore, preparation of tools and centres for the early diagnosis and prevention of birth defects and rehabilitation of those with congenital anomalies throughout Iran are essential.

Keywords: Congenital anomaly, Iran, Meta-analysis, Systematic review

Introduction

Congenital anomalies are fetal growth and developmental disturbances occurring during pregnancy that are of either structural or functional types (1). Anomalies visible at child birth are called apparent anomalies (2). Congenital anomalies are the main causes of morbidity and mortality among children

worldwide. They are considered the fifth cause of mortality and impose heavy costs on health care systems (3). Three million children with congenital anomalies are born annually, among whom 495,000 die in the first year of life (4, 5). Despite the great advancements in the aetiology and pathogenesis of congenital anomalies

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Please cite this paper as:

Daliri S, Sayehmiri K, Asadollahi Kh, Rezaei N, Saroukhani D, Karimi A. Prevalence of Congenital Anomalies in Iran: A Systematic Review and Meta-analysis. Iranian Journal of Neonatology. 2018 Jun; 9(2). DOI: [10.22038/ijn.2018.24791.1319](https://doi.org/10.22038/ijn.2018.24791.1319)

worldwide, still 22% of causes of death among neonates are these abnormalities (6).

There are many different risk factors for congenital anomalies, among which genetic, environmental, and teratogenic factors, such as chemical or radioactive substances, drugs, infections, malnutrition, chronic diseases, and consanguineous marriage, have been reported. However, the main cause of 66% of anomalies are remain unknown (7). Based on the results of previous studies, about 15% of congenital anomalies are due to genetic factors, 10% due to environmental factors, 20-25% due to mixed genetic and environmental factors, and biparous pregnancy accounts for 1-5% of congenital defects (3). About 10% of congenital anomalies are due to exposure to teratogenic, chemical, hormonal, or radioactive factors, smoking, drugs, infectious diseases caused by viruses such as *Cytomegalovirus*, and measles (8-10). Some maternal and fetal demographic factors during pregnancy such as maternal age, history of abortion, chronic diseases, pregnancy care, consanguineous marriage, prematurity, low-birth-weight, and neonatal gender have been also reported in relation to congenital anomalies (3, 11-13).

The prevalence rate of congenital anomalies at birth is 2-3% in the first year of life. Many anomalies of the internal organs such as the lungs, kidneys, and heart are not visible at birth, and they present by advancing age. Therefore, another 2-3% anomalies are detected up to the first five years of life, and totally, the prevalence rate of congenital anomalies at the end of the first five years of life is about 4-6% (8). The prevalence rate of congenital anomalies varies across different societies and countries due to differences in culture, heredity, as well as social and health conditions.

The prevalence rates of these anomalies in the developed countries such as the USA (2014) (14), UK (2014) (15), and in 22 European countries (2010) were reported 5.9, 27.6, and 23.9 (16) in 1000 live births, respectively. The prevalence rates of congenital anomalies in the developing countries such as Turkey (2009) (17), India (2013) (18), Nigeria (2008) (19), Brazil (2006) (20), Malaysia (2005) (21), UAE (2005) (22), Oman (2010) (23), and Kuwait (2005) were reported 29, 22.2, 35, 17, 14.3, 7.92, 24.6, and 12.5 (24) in 1000 live births, respectively. A descriptive study from Iraq reported a prevalence rate of 6.9/1000 births for congenital anomalies, among which 46.75% were boys. This

study also reported that 36.62% of anomalies were related to the central nervous system followed by 7.68% for cardiovascular, 6.19% for skeletal, 3.1% for urogenital system, and 17.68% of anomalies were associated with the ears, face, and skin (25).

There is not a precise figure as to the prevalence rate of congenital anomalies in Iran; however, different reports indicated an increasing trend of congenital anomalies in recent years. The prevalence rate of these anomalies in different provinces in Iran are diverse, so that the prevalence rates of congenital anomalies in Ahvaz (2013), Babol (2013), Tabriz (2013), Rafsanjan (2013), Zahedan (2013), Ardebil (2012), Kermanshah (2012), and Gorgan (2010) were reported 51, 19, 29.3, 10.6, 8.2, 17.9, 2.7, and 2.8 in 1000 live births, respectively (26-32). In a study performed in Ardabil Province in 2011, the prevalence and proportion rates of different anomalies were respectively as follow: the central nervous system 1.9/1000 births (22.8%), musculoskeletal system 2.9/1000 births (35.1%), gastrointestinal (GI) tract 1.4/1000 births (17.5%), urogenital system 1.3/1000 births (15.8%), and chromosomal disorders 0.7/1000 births (8.8%) (13).

In general, congenital anomalies widely occur in various countries and impose heavy direct and indirect costs on health care systems. Also, children born with these anomalies will face different educational, occupational, marital, and other social problems in future. Therefore, for diagnostic and preventive issues and providing rehabilitation tools and centres, the prevalence and severity rates of these anomalies should be estimated. Since there is a scarcity of studies showing the global aspect of congenital anomalies in Iran, the current study aimed at determining the prevalence and proportion rates of these anomalies and the different types of anomalies in Iran via a systematic review and meta-analysis.

Methods

Search strategy

The present study was performed to estimate the prevalence and proportion rates of different anomalies in Iran via a systematic review and meta-analysis. The review was conducted in accordance with PRISMA guidelines (33). Therefore, all the studies performed in Iran between January 1, 2000 and December 31, 2016 were evaluated. The articles were retrieved from different national and

international databases including Global Medical Article Limberly (Medlib), Scopus, Web of Science, PubMed, Cochrane Library, Science Direct, Google Scholar, Irandoc, Iranian Journal Database (Magiran), Iranian Biomedical Journal (IranMedex), and Scientific Information Databases (SID).

All the articles with medical subject headings (MeSH) keywords of "congenital anomalies" and "Iran" in the title, abstract, and text were investigated. Using the following keywords independently or in combined forms, the published papers were retrieved: "congenital anomalies", "the central nervous system anomalies", "musculoskeletal system anomalies", "gastrointestinal tract anomalies", "urogenital system anomalies", "cardiovascular system anomalies", "chromosomal anomalies", "neonatal anomalies" and "Iran" MeSh combined with the operator "OR" vs "AND".

Study selection

All the Persian- and English-language articles associated with congenital anomalies performed in Iran were evaluated, and after passing the qualification assessment, they were entered into analysis. The inclusion criteria for the qualification assessment were STORBE score greater than 20 and access to full text. The exclusion criteria included a score of less than 20, studies in special groups, limited sample size, missing the main data of anomalies such as the prevalence rate or type of anomalies, and interventional and case series studies. Meanwhile, if the prevalence rates were not mentioned in the article, but the relevant data for the estimation of prevalence rate were cited, the prevalence rates of different anomalies were estimated via associated statistical methods.

Quality assessment

For qualification survey of the papers, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was applied (34). This checklist contains 22 different parts and the score allocation for this checklist is based on the importance of each part, and the least score for article qualification is 15 out of 30. In this study, a score of 20 and above was acceptable.

Data extraction

Firstly, all the published papers were identified, and then a list of all the associated abstracts was collected. In the next step and

after masking the characteristics associated with papers such as authors and journals' names, the contents of the papers were investigated by two different expert individuals independently. In case of rejection of a paper by each investigator, the reason of rejection was required, and in case of any discrepancies between the two investigators, a third investigator was asked to evaluate the paper. The data were entered into a prepared checklist including the study sample size, study location, year of study, type of study, the prevalence rate of congenital anomalies, the proportion rate of congenital anomalies, type of anomaly, the involved organ, neonate's gender, and confidence intervals of 95%.

Totally, 283 papers associated with congenital anomalies were retrieved, among which 74 were duplicates, 112 were irrelevant, 49 lacked the relevant data, and 12 failed to achieve sufficient qualification based on the inclusion criteria. All these articles were discarded from the final analysis. Finally, 36 papers were confirmed to enter the analysis (Diagram 1).

All the identified papers were critically appraised by two reviewers independently.

Statistical analysis

The combination of heterogeneous and homogeneous studies was performed using the random effect and stable effect models in meta-analysis, respectively. I-squared model was used for combining results of studies in meta-analysis. Significance level was set at <0.1 , and I-squared statistic was used for estimation of inconsistency within the meta-analyses (35). Univariate and multivariate regression analyses were run to explore the possible sources of heterogeneity among the studies. We analyzed sources of heterogeneity by subgroup and meta-regression analysis using dichotomous and continuous variables. Egger's test was conducted to examine potential publication bias. Egger's test can reveal or asymmetric funnel plot. The latter indicates the existence of a significant publication bias or a systematic heterogeneity between studies. Data manipulation and statistical analyses were performed using STATA software, version 11.1. *P*-values less than 0.05 were considered statistically significant. The study was approved by the Ethics Committee of Ilam University of Medical Sciences, Iran. In addition, an epidemiologist and a statistician were participated to revise the study.

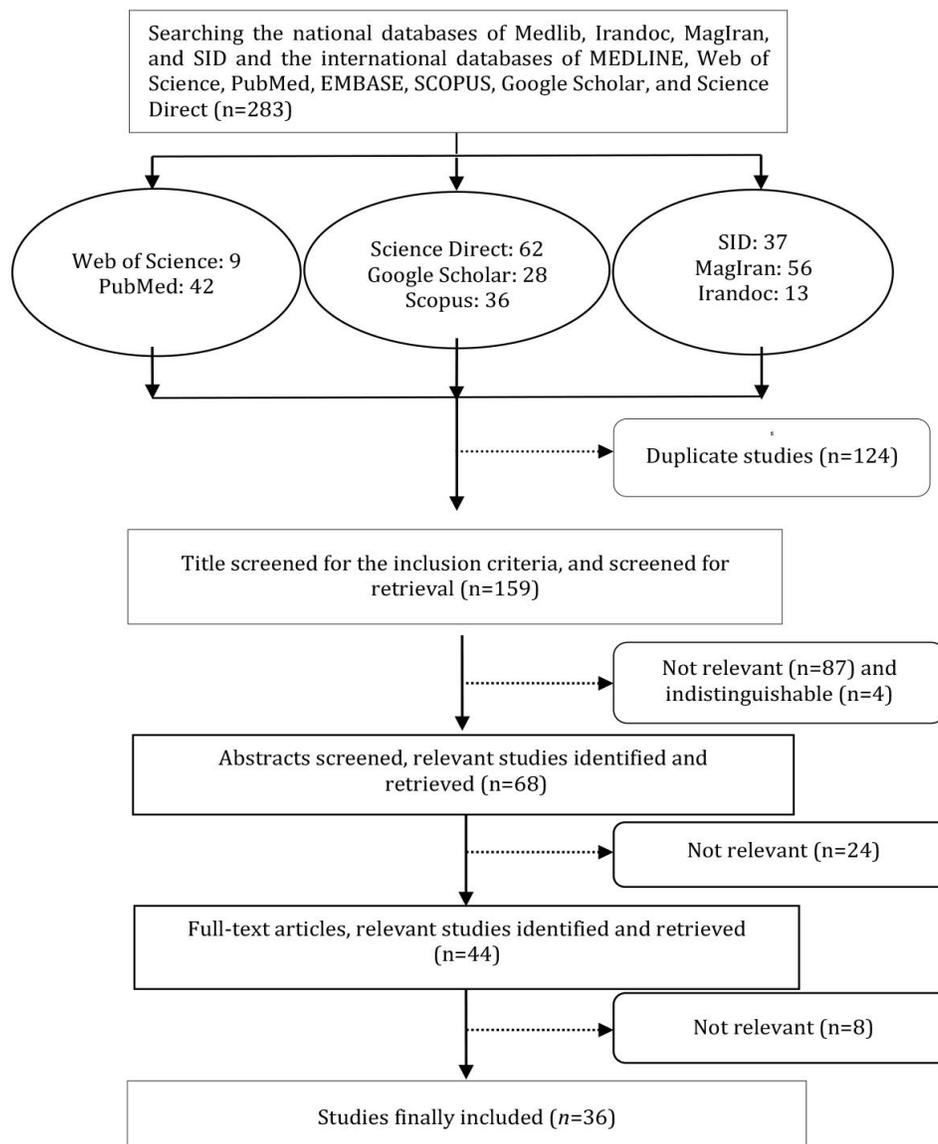


Diagram 1. Results of PRISMA flow of the systematic literature search

Results

Overall, 36 papers with a total sample size of 909,961 people including 12 case-control studies, 5 cohort studies, and 19 descriptive-analytical studies performed in Iran between 2000 and 2016 were entered into the analysis (Table 1). The total prevalence rate for congenital anomalies was 18/1000 live births (15.6-20.5; 95% CI), including 23.2/1000 and 18/1000 for boys and girls, respectively. Further, 55.8% of all the congenital anomalies belonged to boys and 43.1% pertained to girls, and 1.1% was unknown for sex (Figure 1, Table 2).

The findings of 26 studies on musculoskeletal anomalies with a sample size of 210,417 participants showed a prevalence rate of 9.3/1000 live births for this anomaly, and its proportion rate was 34%. The highest prevalence and proportion rates among all the congenital anomalies belonged to musculoskeletal anomalies. Among all the studies associated with musculoskeletal anomalies, the least prevalence rate pertained to Amininasab study (2011) from Birjand with 0.9/1000 live births, and the highest prevalence rate belonged to Vakilian study (2007)

Table 1. General characteristics of the studied articles eligible for the meta-analysis

Author	Study location	Year of study	Number of samples	Study type
Hoseini S (3)	Sistan and Baloochestan	2013	1800	Case-control
Khoshhal-Rahdar F (26)	Dezful	2013	4235	Descriptive-analytical
Taheri M (36)	Yazd	2012	21867	Case-control
Mashhadi Abdolahi H (37)	Tabriz	2012	22500	Descriptive-analytical
AmininasabZ (11)	Birjand	2011	22076	Case-control
Mohsenzadeh A(38)	Khoramabad	2011	43195	Descriptive-analytical
Aleeejahan R (13)	Ardebil	2011	6868	Case-control
Jalali SZ (39)	Rasht	2011	1824	Descriptive-analytical
Dastgiri S (40)	Tabriz	2011	224753	Descriptive-analytical
Kavianyn N(41)	Golestan	2010	92420	Descriptive-analytical
Nikyar B (42)	Gorgan	2009	18162	Prospective
Mohamadzadeh I(43)	North Iran	2009	1686	Descriptive-analytical
Dastgiri S (44)	Tabriz	2009	185650	Descriptive-analytical
Shekoochi M (45)	Hamedan	2008	4252	Descriptive-analytical
GolalipourMG (46)	Gorgan	2008	10000	Case-control
Masoodpoor N (31)	Rafsanjan	2008	6089	Descriptive-analytical
Vakilian K(47)	Shahrood	2007	20751	Descriptive-analytical
Nazemi Gheshmi AM (48)	Hormozgan	2007	7007	Descriptive-analytical
Sarafan N (49)	Ahvaz	2007	5087	Prospective
Golalipour M (50)	Gorgan	2007	6024	Descriptive-analytical
Sereshti M (51)	Shahrekord	2006	2854	Descriptive-analytical
Ahmadzadeh A (52)	Ahwaz	2006	4660	Prospective
Akbarzadeh R (53)	Sabzevar	2006	7786	Descriptive-analytical
Abdi-Rad I (2)	Urmia	2005	14121	Descriptive-analytical
Khatami F (54)	Mashhad	2005	9200	Prospective
Akhavan Karbasi S (7)	Yazd	2004	4800	Case-control
Dastgiri S (55)	North West Iran	2004	95105	Case-control
Pouladfar GH (56)	Boushehr	2004	14300	Case-control
Hematyar M (57)	Tehran	2003	1000	Descriptive-analytical
Ghahremani M (58)	Gonabad	2001	12513	Case-control
Marzban A (59)	Zanjan	2000	2345	Case-control
Khosravi SH (60)	Arak	2000	2069	Case-control
Ghorbani M (9)	Golestan	2000	12853	Case-control
Tootoonchi P (61)	Tehran	2000	2291	Descriptive-analytical
Zamani A (62)	Tehran	2000	14073	Prospective

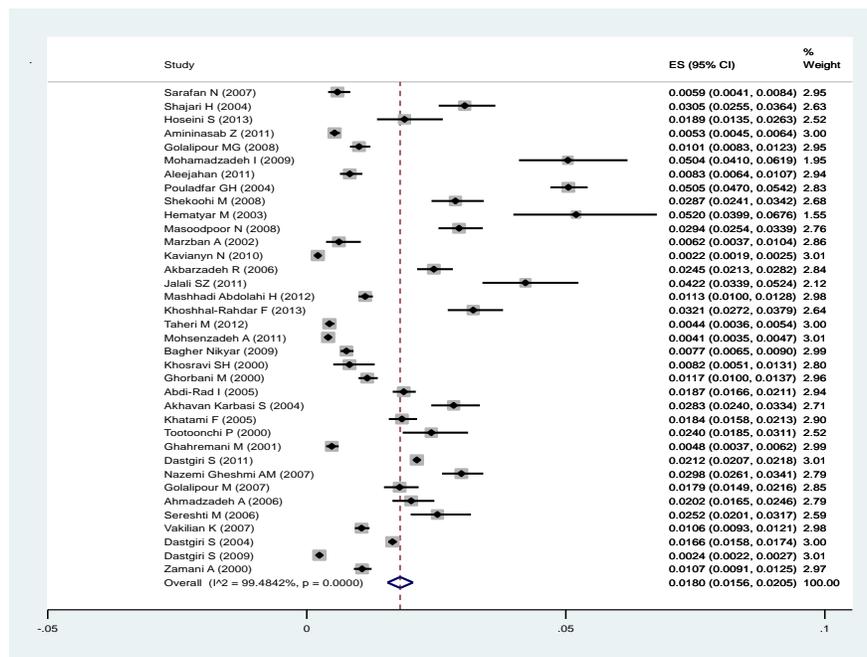


Figure 1. Forest plots of the prevalence of congenital anomalies and 95% confidence interval based on a random effect model in meta-analysis. The midpoint of each segment, the segment estimating the prevalence rate, and 95% confidence interval in each study are shown. Diamond mark overall prevalence rate based on the results of the meta-analysis is presented.

Table 2. The prevalence and proportion rates of congenital malformations in Iran between 2000 and 2016 based on systematically review and meta-analysis

Variable	N*	n**	Prevalence per 1000 (95%CI)	Proportion% (95%CI)	
Musculoskeletal anomalies	26	210417	9.3 (7.4 – 1.13)	34 (29 – 39)	
Genitourinary anomalies	25	408007	5.7 (4.6 – 6.9)	20 (16 – 25)	
Face Ears, eye, skin, and nose anomalies	18	129676	3.3 (2.4 – 4.2)	12 (9 – 15)	
Cleft palate anomalies	5	45615	1.9 (1.1 – 2.8)		
Central nervous anomalies	25	193280	3.1 (2.4 – 3.8)	12 (8 – 17)	
Cardiovascular anomalies	18	361732	2.2 (1.6 – 2.9)	8 (5 – 11)	
Digestive system anomalies	21	382087	1.7 (0.9 – 2.4)	5 (3 – 7)	
Chromosomal anomalies	13	122435	0.8 (0.5 – 1.1)	3 (1 – 4)	
Respiratory anomalies	7	67351	0.3 (0.2 – 0.5)	2 (2 – 3)	
Other anomalies	12	113480	0.9 (0.5 – 1.2)	4 (1 – 6)	
Total congenital anomalies	36	909961	18 (15.6 – 20.5)	-	
Total anomalies based gender	Boy	26	164617	22.3 (18.9 – 25.6)	55.8 (52.1 – 58.3)
	Girl	26	160894	18.2 (15 – 21.4)	43.1(41.4 – 46.9)

* number of study
 ** number of sampel

from Shahrood with a prevalence rate of 30/1000 live births. Also, the greatest proportion rate of musculoskeletal anomalies was associated with Ghahremani study (2001, 55%) from Gonabad, and the least proportion rate belonged to Abdollahi study (2012, 16%) from Mashhad. In this evaluation, the I^2 index was 98% showing a wide discrepancy among studies (figures 2 and 3).

The findings of seven studies associated with anomalies of the respiratory system with a sample size of 67,351 participants showed that among all

the congenital malformations, this anomaly had the lowest prevalence and proportion rates (0.3/1000 live births [2%], respectively).

Among all the studies associated with respiratory system anomalies, the highest prevalence rate belonged to Totonchi study (2000) from Tehran with 1.7/1000 live births, and the least prevalence rate belonged to Ahmadzadeh study (2006) from Ahvaz and Abdollahi study (2012) from Mashhad, both with a prevalence rate of 0.2/1000 live births. Also,

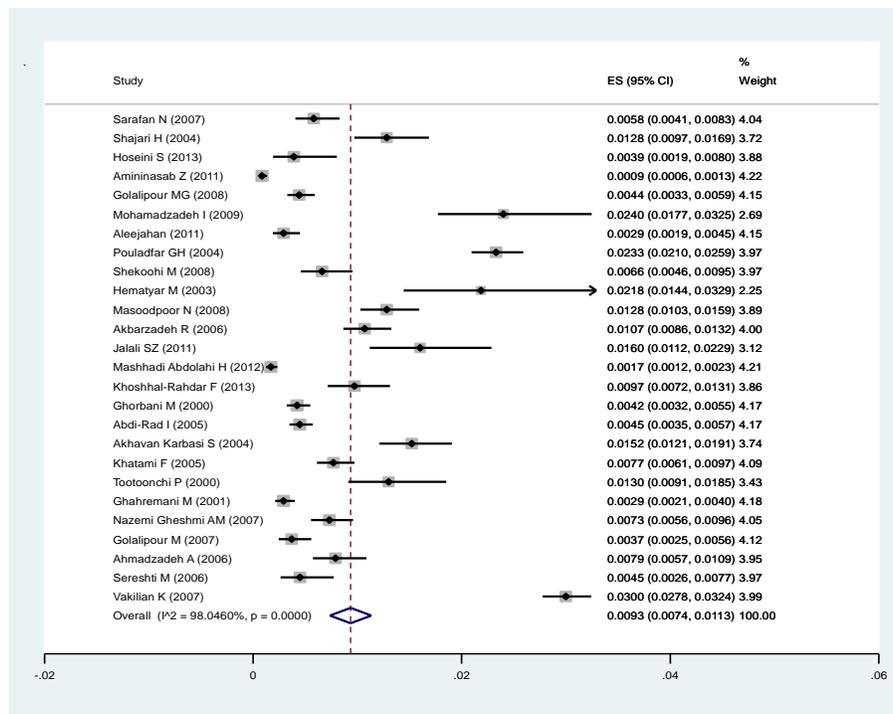


Figure 2. Forest plots of prevalence of musculoskeletal anomalies and 95% confidence intervals based on a random effect model in meta-analysis; the midpoint of each segment, the segment estimating the prevalence rate, and 95% confidence interval in each study are demonstrated. Diamond mark prevalence of musculoskeletal anomalies based on the results of the meta-analysis is exhibited.

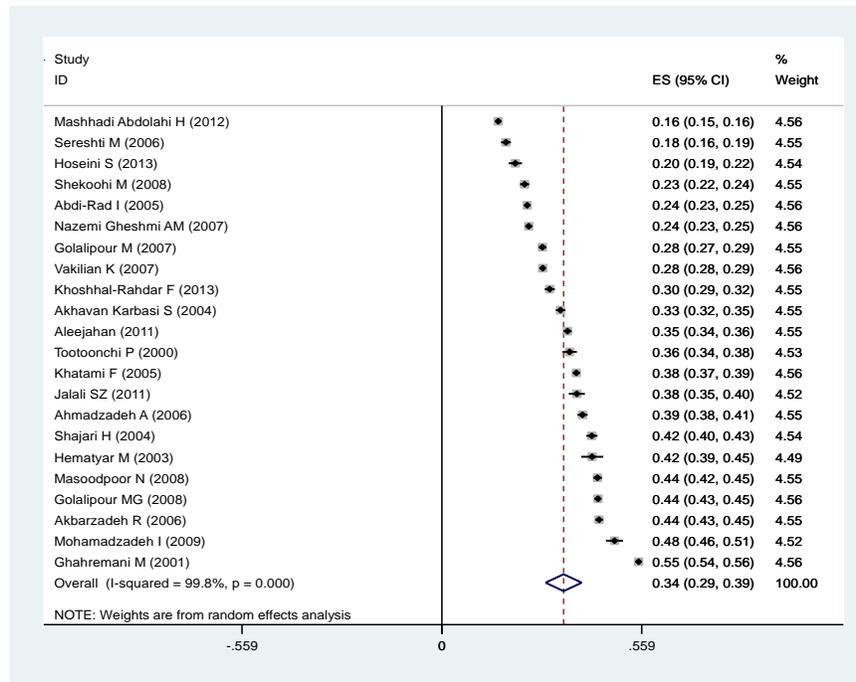


Figure 3. Forest plots of the proportion of musculoskeletal anomalies and 95% confidence intervals based on a random effects model meta-analysis. The midpoint of each segment and the segment estimate of 95% confidence interval in each study are shown. Diamond mark of musculoskeletal anomalies based on the results of the meta-analysis is presented.

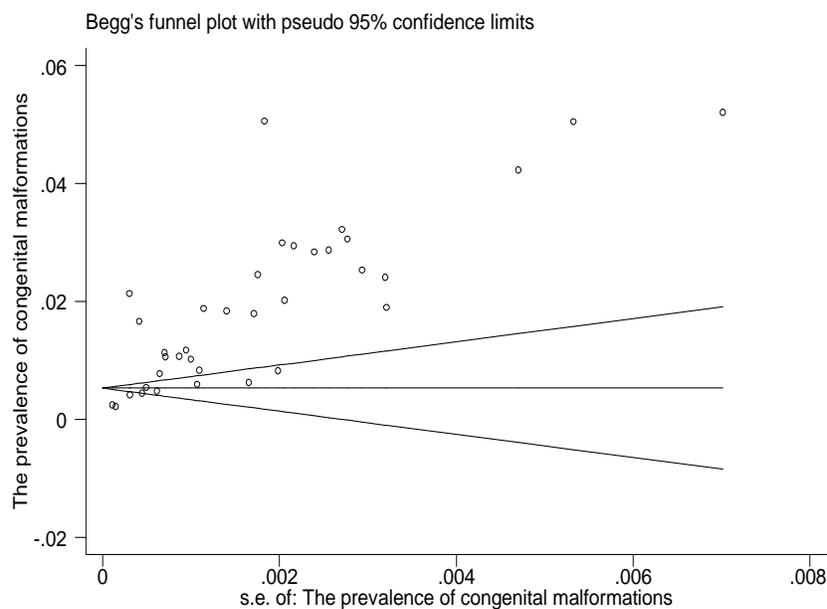


Figure 4. Funnel chart of the prevalence rate of congenital anomalies among the evaluated studies

the greatest proportion rate of respiratory system anomalies belonged Totonchi study (2000) from Tehran (5%), and the least proportion rate pertained to Ahmadzadeh study (2006) from Ahvaz (1%; Table 2).

For the assessment of publication bias, funnel

chart, and Egger test were applied. Based on symmetrical aspect of funnel chart, it could be concluded that publication bias has not occurred. In addition, the *P*-value of Egger test was 0.36 showing an insignificant result (Figure 4). The relationship between year of publication and the

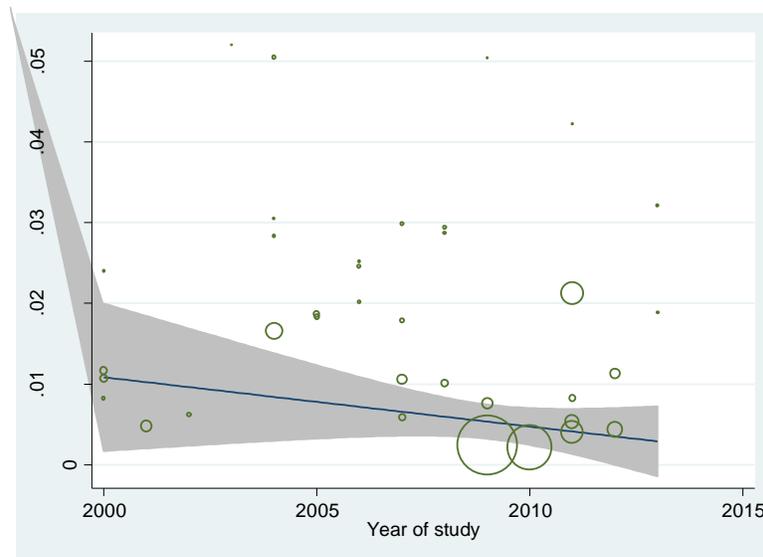


Figure 5. Meta-regression chart of the prevalence rate of congenital anomalies based on the year of study

prevalence rate of congenital anomalies was evaluated via a meta-regression analysis, and the results showed that by increasing the year of study, the prevalence rate of congenital anomalies decreased, but this decline was not statistically significant ($P=0.72$; Figure 5).

Discussion

The current study was carried out as a systematic review and met-analysis to reveal the prevalence and proportion rates of different congenital anomalies in Iran during 2000-2016. Based on the results of this study, total prevalence rate of congenital anomalies in Iran was 18/1000 live births. Both prevalence and proportion rates of congenital anomalies were higher among boys than girls. According to the World Health Organization in 2016, 303,000 newborns were born with congenital anomalies. With an estimated 99 million births a year worldwide, the global prevalence of congenital anomalies is 3 per 1000 live births. The results showed that the prevalence of congenital anomalies in Iran is far higher than the global average (63).

A study from Pakistan by Shabbir Hussain et al. in 2014 reported a prevalence rate of 70.4/1000 live births, including 80.99/1000 among boys and 59.81/1000 among girls. Furthermore, the proportion rate of anomalies among boys was 57.52% and 42.47% among girls (64). Another study from Barbados by Keerti Singh et al. (2014) reported a prevalence rate of 6.2/1000 live births for congenital anomalies (14). A study by Dolk et al. across 22 European

countries (2010) reported a prevalence rate of 23.9/1000 live births for congenital anomalies (16). Rachel Sokal et al. in the UK reported a prevalence rate of 30.7/1000 live births for boys (proportion rate: 51.4%) and 24.3/1000 live births for girls (proportion rate: 48.6%) in 2014, and the ratio of boys/girls in this study was 1.26 (15). The prevalence rate of congenital anomalies in Nigeria (2014) was 20.73/1000 live births (65), and in India (2016), it was 23/1000 live births (66). According to the findings of these studies, almost all countries, either developed or developing, are involved with congenital anomalies and there are no countries without congenital anomalies. In addition, the prevalence rate of congenital anomalies in some countries, similar to Iran, was higher among boys than girls and the odds of showing anomalies among boys was higher.

The current meta-analysis also revealed that the highest prevalence rate belonged to musculoskeletal anomalies with 9.3/1000 live births followed by urogenital anomalies (5.7/1000 live births), ear, eye, and face together (3.3/1000 live births), central nervous system (3.1/1000 live births), cardiovascular system (2.2/1000 live births), GI tract (1.7/1000 live births), chromosomal disorders (0.8/1000 live births), respiratory system (0.3/1000 live births), and all other anomalies (0.9/1000 live births).

The prevalence rates of different anomalies reported by Shabbir Hussain from Pakistan (2014) were as followed respectively: central nervous system anomalies (14.33/1000 live

births [20.3%]), musculoskeletal anomalies (13.08/1000 live births [18.58%]), urogenital anomalies (10.59/1000 live births [15.04%]), cardiovascular system (9.35/1000 live births [13.27%]), ear, eye, neck, and face together (8.4/1000 live births [11.94%]), and GI tract (8.4/1000 live births [8.4%]) (64). The prevalence and proportion rates of different anomalies reported from Barbados (2014) were as followed respectively: musculoskeletal anomalies (0.9/1000 live births [15.5%]), GI tract (0.8/1000 live births [13.2%]), central nervous system anomalies (0.7/1000 live births [11.1%]), chromosomal disorders (0.5/1000 live births [8.7%]), cleft palate (0.4/1000 live births [6.5%]), urogenital anomalies (0.4/1000 live births [6.2%]), respiratory system (0.2/1000 live births [2.7%]), and all other anomalies (0.9/1000 live births [15.1%]) (14).

The prevalence rates of different anomalies reported from 22 European countries (2010) were as followed respectively: cardiovascular system (6.5/1000 live births), chromosomal disorders (3.6/1000 live births), urogenital anomalies (3.1/1000 live births), central nervous system anomalies (2.3/1000 live births), and cleft palate (2.3/1000 live births) (16). Based on the type of anomaly, the prevalence rates reported from Nigeria by Mkpe Abbey were 5.61/1000, 3.1/1000, 2.22/1000, 1.3/1000, 1.69/1000, 1.17/1000, 0.52/1000, and 0.39/1000 live births for the following organs respectively: the central nervous system, face, neck, and skin together, cardiovascular system, GI tract, musculoskeletal system, urinary system, genital system, and anomalies of all other organs (65). In addition, the prevalence rates of congenital anomalies reported by Prajka Bhide from India were as follows respectively: cardiovascular system (6.6/1000 live births), musculoskeletal system (4.9/1000 live births), urinary system (3.8/1000 live births), central nervous system (2.7/1000 live births), GI tract (2.2/1000 live births), genital system (1.6/1000 live births), respiratory system (1.09/1000 live births), and all other anomalies (2.2/1000 live births) (66). Based on our study and other reports from different countries, anomalies associated with the musculoskeletal, cardiovascular, central nervous, and urogenital systems were more prevalent than other congenital anomalies. Although all congenital anomalies are important for early diagnosis and prevention, the above-mentioned anomalies should be considered more due to their higher

prevalence in different societies.

Generally, congenital anomalies widely occur in different countries, and there is no society in the world without congenital anomalies. In other words, neonates in all countries, either developed or developing, are at some risk of anomalies. Iran is among the countries with high prevalence of congenital anomalies, such that based on the results of the current study 18 out of 1000 live births are involved with congenital anomalies. The annual birth rate in Iran is high and it could be concluded that the number of neonates with anomalies is high and increasing. These neonates will face different educational, occupational, marital, and other social problems, and even most of them may die in the first five years of life. Therefore, by improving diagnosis and prevention of these defects and provision of rehabilitation tools and centres, the prevalence rate of these anomalies may decline.

Conclusion

According to the findings of this meta-analysis, the prevalence of congenital anomalies is notably high in Iran, which annually imposes huge visible and non-visible costs on individuals, societies, and health care systems. Therefore, the preparation of tools and centres for the early diagnosis and prevention of birth defects, as well as rehabilitation of these individuals would be essential.

Limitations of the study

This study had some limitations including lack of homogeneity in reporting anomalies by different studies, overlap of some anomalies and lack of differentiation, lack of homogenous coefficients for the estimation of prevalence rate in different studies, low quality of some studies that resulted in their elimination, and existence of heterogeneity among studies.

Acknowledgments

We wish to thank all the researchers whose studies were used in this meta-analysis. We also thank the Deputy of Research and Technical information of Ilam University of Medical Sciences for their financial support.

Conflicts of interests

None declared.

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