Systematic Review

Prevalence of Birth Defects in Iran: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Birth defects are a series of disorders that occur during embryonic life. In Iran, no national situation analysis is available to show the rate of congenital disorders. We aimed to estimate the prevalence of structural birth defects in Iran.

Methods: We searched for English studies on PubMed, Scopus and Google Scholar from January 1990 to July 2016. The search for Persian articles was performed in Scientific Information Database and Magiran. Two reviewers assessed the identified articles independently. The relevant studies were selected based on predefined criteria. Data were analyzed using the Comprehensive Meta-Analysis software. Random effect method was used for meta-analysis.

Results: In total, 42 studies were included. The prevalence of congenital anomalies was as follows: orofacial clefts, 1.4 per 1,000 births (95% confidence interval [CI]: 1.2–1.6); neural tube defects, 3.2 per 1,000 births (95% CI: 2.5–4.3); urogenital anomalies, 3.9 per 1,000 births (95% CI: 1.2–12.9); musculoskeletal malformations, 3.3 per 1,000 births (95% CI: 2.3–4.9); cardiovascular anomalies, 3.3 per 1,000 births (95% CI: 2.2–5.1); Down syndrome, 0.9 per 1,000 births (95% CI: 0.7–1.2); gastrointestinal disorders, 1.4 per 1,000 births (95% CI: 0.9–2.1).

Conclusion: Our results show that urogenital disorders are the most prevalent births defects in Iran, followed by musculoskeletal and cardiovascular malformations.

Keywords: Congenital anomalies, Iran, newborns, prevalence

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Introduction

Birth defects are defined as a series of abnormalities that occur during the pregnancy period. Congenital anomalies, congenital malformations, congenital disorders and congenital abnormalities, are synonyms for birth defects.[1] These disorders are classified as structural (e.g., orofacial clefts) or functional (e.g., metabolic disorders), and can result in seriously damaging effects on children's health and life. According to a report by the World Health Organization (WHO) in 2015, globally, congenital anomalies were identified as causes of death in about 276,000 newborns under 1 month of age every year.[2] In 2016, this rate reached 303,000 neonates.[3]

For about 50% of all births defects, no exact causes have been clarified[3]; however, genetic factors, environmental teratogens, socioeconomic status, micronutrient deficiencies and infections are discussed to be involved in the occurrence of congenital anomalies.[4,5] Therefore, investigating these causes and risk factors may help to prevent the anomalies. At present, vaccination, dietary intake of folate or iodine, and preconception healthcare are available options for prevention.[6,7]

The prevalence of birth defects can vary regionally. In the United States, it has been estimated that birth defects occur in 2.76% of newborns.[8] According to the European Surveillance of Congenital Anomalies (EUROCAT), the overall rate of birth defects in Europe was estimated to be 24.86 per 1,000 births during 2010–2014.[9] Also, a population-based registry study in Europe reported that the rate of multiple congenital anomalies was 1.58 per 1,000 births during 2004–2010.[10] Based on the WHO report in 2013, the rates of total structural and functional birth defects in the regions of Eastern Mediterranean and South-East Asia were 69 per 1,000 live births and 51 per 1,000 live births every year, respectively.[11]

The prevalence of congenital malformations in Iran has been reported in some studies. In Gorgan, northern Iran, a survey by Golalipour *et al*.[12] on 6,204 neonates revealed that the overall rate of structural birth defects was 17.7 per 1,000 live births. In another study, Mashhadi Abdolahi *et al*.[13] reported a rate of 11.29 per 1,000 births in Tabriz (2004–2012). In a study from Isfahan province, congenital disorders were responsible for more than 22% of newborn deaths.[14] Also, in a report by Forouzanfar *et al.,*[15] a rate of 22.4% was stated for birth defects as one of the principle causes of death in children under five years. Despite these data, there is no precise report on the prevalence of congenital anomalies in Iran, mainly due to lack of any published data from the National Birth Defect Registry. In the present national situation analysis, we aimed to estimate the prevalence rate of structural types of congenital anomalies in Iran.

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Materials and Methods

Information sources and search strategy

We searched studies from bibliographic databases, such as PubMed, Scopus and Google Scholar, using keywords, including "congenital abnormality" OR "congenital abnormalities" OR "congenital malformation" OR "congenital malformations" OR "congenital anomaly" OR "congenital anomalies" OR "birth defect" OR "birth defects" OR "congenital disorder" OR "congenital disorders" AND "Iran" OR "Iranian" OR "Iranians". The search was limited to "title/abstract" and articles published from January 1990 to July 2016. The Persian equivalents of these keywords were also used for searching in the Scientific Information Database (SID) and Magiran. We also manually explored the references of each included article to optimize our search strategy.

Inclusion and exclusion criteria

We included observational studies reporting the prevalence rate of the major structural congenital anomalies, including orofacial clefts (cleft lip and/or palate), neural tube defects (NTDs), Down syndrome, and urogenital, musculoskeletal, cardiovascular and gastrointestinal anomalies. The anomaly of a system should be considered in general, not as a specific organ. Reviews, case reports, editorials and letter to the editors were excluded. Lack of explicit methodology and results, duplicate publication and unavailability of full-text were other exclusion criteria. Papers which did not identify the birth defects exactly were also included to cover additional data.

Study selection and data extraction

Two authors independently investigated the titles and abstracts of the retrieved articles to select the relevant ones. Disagreements were discussed between the authors to reach consensus. The information, including first author, date of study, sample size, study population, location (city), and prevalence of congenital abnormalities was collected from each selected article.

Statistical analysis

Finally, data were analyzed using the Comprehensive Meta-Analysis software version 2.0 and we used random effect method for meta-analysis. Forest diagrams were plotted for the prevalence of all malformation types in Iranian newborns. Heterogeneity was checked using the I^2 index.

Results

After searching the above-mentioned databases and the reference lists, 1539 articles (after removing duplicates) identified. Of these, after reading the title and abstract, 60 articles were presented to two reviewers for possible inclusion. Eighteen articles were excluded based on the exclusion criteria. Finally, 42 articles, including 29 English and 13 Persian articles, were included for meta-analysis (Figure 1). The characteristics of the studies included in this

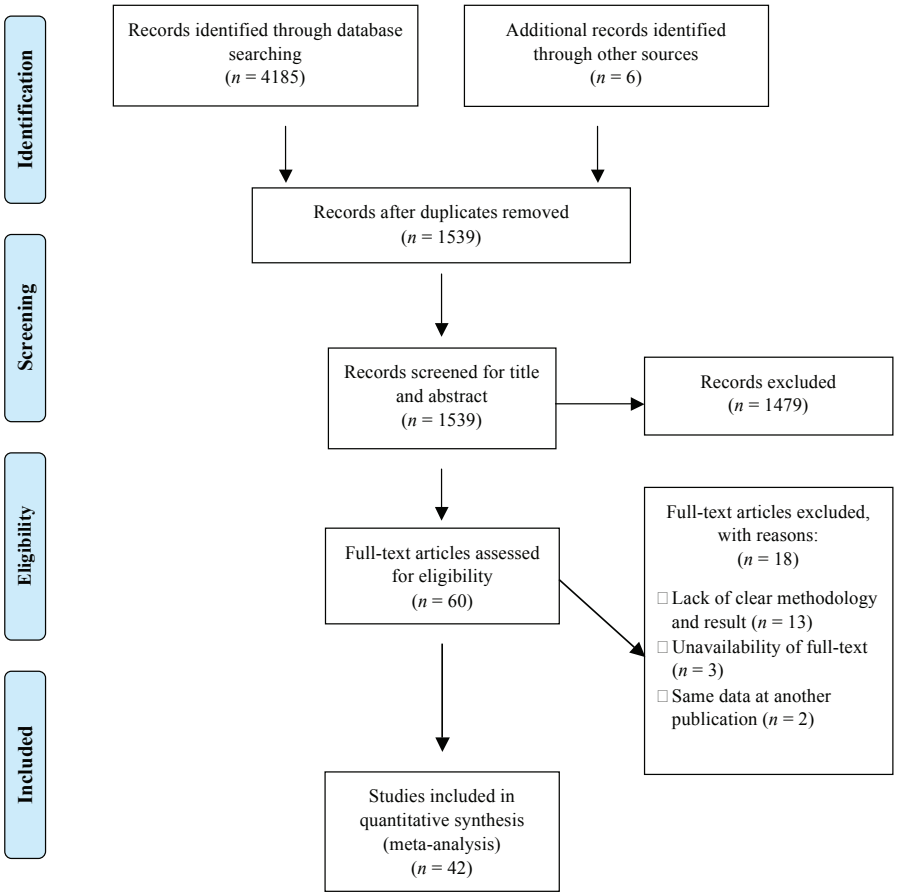

Figure 1. PRISMA flowchart.

Table 1. Summary of included studies regarding the prevalence of congenital anomalies in Iran.

Type of anomaly	Author	Ref.	Date of study	Sample	Population	Location	Region	Prevalence of anomaly (per 1,000)	Prevalence of anomaly in males (per 1,000)	Prevalence of anomaly in females (per 1,000)
Orofacial clefts	Kianifar	16	1981-2011	28519	Live births	Mashhad	9	1.9	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	1.02	-	-
	Mohajerani	17	1991-2000	87838	Live births	Tehran	10	1.49	-	-
	Tafazzoli	18	1997	6531	Live births	Qazvin	6	1.07	-	-
	Jamilian	19	1998-2005	11651	Live births	Tehran	10	2.14	-	-
	Jalili	20	2004-2008	57526	Live births	Tehran	10	1.79	-	-
	Golalipour	21	1998-2003	37951	Live births	Gorgan	1	0.97	1.08	0.86
	Golalipour	22	1998-1999	10,000	Live births	Gorgan	1	1.4	-	-
	Sadri	23	1994-2002	147500	Newborns	Tehran	10	1.3	-	-
	Abdi-Rad	24	2001-2005	14121	Births	Urmia	2	1.13	-	-
	Alijahan	25	2010-2011	6868	Live births	Ardabil	2	1.4		
	Zandi	26	1993-2008	143589	Live births	Hamedan	3	1.01	1.05	0.97
	Hosseini	27	2012	1800	Live births	Zabol	8	5	-	-
	Golalipour	28	1997-1999	10,000	Live births	Gorgan	1	1.4	-	-
	Yassaei	29	2003-2006	65236	Live births	Yazd	7	0.86	-	-
	Rajabian	30	1993-2003	147608	Live births	Shiraz	5	0.8	-	-
	Saki	31	2006-2007	4176	Live births	Ahwaz	4	3.8	-	-
	Mirfazeli	32	2004-2009	35009	Live births	Gorgan	1	1.05	1.2	0.87
	Golalipour	12	2007	6204	Live births	Gorgan	1	2.2	-	-
	Soltani	33	2010	26537	Live births	Kurdistan	3	1.09	-	-
Neural tube defects	Roozitalab	34	2000-2010	36755	Live births	Yasuj	5	2.12	-	-
	Golalipour	35	1998-2000	19545	Newborns	Gorgan	1	3.12	2.49	3.79
	Marzban	36	2002	2250	Live births	Zanjan	6	6.2	-	-
	Hosseini	27	2012	1800	Live births	Zabol	8	4.4	-	-
	Sereshti	37	2005-2006	2854	Births	Shahrekord	7	5	-	-
	Amini Nasab	38	2007-2012	22076	Births	Birjand	9	0.72	-	-
	Abdi-Rad	24	2001-2005	14121	Births	Urmia	2	9.84	-	-
	Afshar	39	1997-2001	16785	Births	Birjand	9	2.97	-	-
	Golalipour	40	1998-2005	30639	Live births	Gorgan	1	2.54	2.06	3.06
	Ahmadzadeh	41	2004-2006	4660	Live births	Ahwaz	4	2.4	-	-
	Alijahan	25	2010-2011	6868	Live births	Ardabil	2	1.9	-	-
	Behrooz	42	2002-2004	13262	Births	Ahwaz	4	4.2	-	-
	Ebrahimi	43	2005-2011	14034	Newborns	Yasuj	5	4.84	-	-
	Farhud	44	1991-1997	8585	Newborns	Hamadan	3	5.01	-	-
	Golalipour	45	1998-2005	49534	Births	Gorgan	1	2.8	-	-
	Talebian	46	2007-2012	38936	Neonates	Kashan	7	2.33	-	-
	Golalipour	47	1998-2001	26280	Births	Gorgan	1	3.08	0.278	3.38
Urogenital	Mosayebi	48	2001-2002	3529	Live births	Kashan	7	9.92	-	-
	Abdi-Rad	24	2001-2005	14121	Births	Urmia	2	1.27	-	-
	Ahmadzadeh	41	2004-2006	4660	Live births	Ahwaz	4	7.1	-	-
	Alijahan	25	2010-2011	6868	Live births	Ardabil	2	1.3	-	-

	Dastgiri	49	2000-2004	1574	Live births	Tabriz	2	3.96	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	0.26	-	-
	Golalipour	22	1998-1999	10,000	Live births	Gorgan	1	2.6	-	-
	Golalipour	40	1998-2005	30639	Live births	Gorgan	1	1.7	-	-
	Hosseini	27	2012	1800	Live births	Zabol	8	2.2	-	-
	Hesami	50	2011	885	Male neonates	Fasa	5	65.5	-	-
	Golalipour	12	2007	6204	Live births	Gorgan	1	1.7	-	-
	Safikhani	51	2005-2006	2423	Live births	Ahwaz	4	110.2	-	-
	Golalipour	28	1997-1999	10,000	Live births	Gorgan	1	2.5	-	-
Musculoskeletal	Mosayebi	48	2001-2002	3529	Live births	Kashan	7	6.8	-	-
	Sarrafan	52	2006-2007	5087	Live births	Ahwaz	4	5.89	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	1.06	-	-
	Hosseini	27	2012	1800	Live births	Zabol	8	3.9	-	-
	Amini Nasab	38	2007-2012	22076	Births	Birjand	9	0.86	-	-
	Abdi-Rad	24	2001-2005	14121	Births	Urmia	2	4.46	-	-
	Ahmadzadeh	41	2004-2006	4660	Live births	Ahwaz	4	7.9	-	-
	Alijahan	25	2010-2011	6868	Live births	Ardabil	2	2.9	-	-
	Dastgiri	49	2000-2004	1574	Live births	Tabriz	2	0.74	-	-
	Golalipour	22	1998-1999	10,000	Births	Gorgan	1	4.7	-	-
	Golalipour	12	2007	6204	Live births	Gorgan	1	3.7	-	-
	Golalipour	28	1997-1999	10,000	Live births	Gorgan	1	3.8	-	-
Cardiovascular	Nikyar	53	2007-2009	18162	Live births	Gorgan	1	7.6	8.2	7
	Ahmadzadeh	41	2004-2006	4660	Live births	Ahwaz	4	0.6	-	-
	Golalipour	40	1998-2005	30639	Live births	Gorgan	1	5.2	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	2.04	-	-
	Dastgiri	49	2000-2004	1574	Live births	Tabriz	2	1.36	-	-
	Dastgiri	54	2000-2009	185650	Births	Tabriz	2	2.42	-	-
	Amini Nasab	38	2007-2012	22076	Births	Birjand	9	1.54	-	-
	Nikyar	55	2007-2008	11739	Live births	Gorgan	1	8.6	9.96	7.34
	Golalipour	12	2007	6204	Live births	Gorgan	1	5.2	-	-
	Mosayebi	48	2001-2002	3529	Live births	Kashan	7	4.53	-	-
Down syndrome	Golalipour	12	2007	6204	Live births	Gorgan	1	1.45	-	-
	Hosseini	27	2012	1800	Live births	Zabol	8	1.6	-	-
	Golalipour	22	1998-1999	10,000	Live births	Gorgan	1	0.6	-	-
	Mosayebi	48	2001-2002	3529	Live births	Kashan	7	0.57	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	0.76	-	-
	Abdi-Rad	24	2001-2005	14121	Births	Urmia	2	0.92	-	-
	Ahmadzadeh	41	2004-2006	4660	Live births	Ahwaz	4	0.9	-	-
	Alijahan	25	2010-2011	6868	Live births	Ardabil	2	1	-	-
Gastrointestinal	Golalipour	12	2007	6204	Live births	Gorgan	1	2.2	-	-
	Amini Nasab	38	2007-2012	22076	Births	Birjand	9	0.77	-	-
	Mashhadi Abdolahi	13	2004-2012	22500	Live births	Tabriz	2	0.53	-	-
	Mosayebi	48	2001-2002	3529	Live births	Kashan	7	1.98	-	-
	Golalipour	22	1998-1999	10,000	Live births	Gorgan	1	1.7	-	-
	Golalipour	40	1998-2005	30639	Live births	Gorgan	1	2.2	-	-
	Golalipour	28	1997-1999	10,000	Live births	Gorgan	1	1.5	-	-

paper are presented in Table 1.[12,13,16–55] Unfortunately, most of the studies did not report the prevalence of birth defects for males and females separately.

Orofacial clefts

Twenty studies in 13 provinces of Iran showed that the prevalence of orofacial clefts was 1.4 per 1,000 births (95% confidence interval [CI]: 1.2–1.6).[12,13,16–33] Heterogeneity of the samples is shown in Figure 2. The largest sample size belonged to the studies by Rajabian *et al*.[30] and Sadri *et al*.[23] The highest prevalence was 5 per 1,000 live births[27] while the lowest was 0.8 per 1,000 live births.[30]

Neural Tube Defects

Analysis of 17 articles regarding NTDs indicated that prevalence of these disorders was 3.2 per 1,000 births (95% CI: 2.5–4.3) (Figure 3).[24,25,27,34–47] The largest sample size belonged to the study by Golalipour et al. on 49,534 births.[45] The highest prevalence of NTDs was 6.2 per 1,000 live births[36] while the lowest was 0.72 per 1,000 births.[38]

Urogenital anomalies

Searching the databases yielded 12 studies with 114,318 participants and 1 study that was performed only on male neonates.[12,13,22,24,25, 27, 28, 40, 41, 48–51] The results from the analysis of these studies revealed that the prevalence of urogenital anomalies in Iran is 3.9 per 1,000 births (95% CI: 1.2–12.9) (Figure 4). The highest and the lowest prevalence rates of these abnormalities were reported as 110.2 per 1,000 live births (among male neonates)[51] and 0.26 per 1,000 live births,[13] respectively.

Musculoskeletal anomalies

The analysis of 12 studies carried out in 8 provinces of Iran from 1997 to 2012 showed that the the prevalence of musculoskeletal disorders is 3.3 per 1,000 (95% CI: 2.3–4.9) as shown in Figure 4.[12,13,22,24,25,27,28,38,41,48,49,52] The highest and the lowest prevalence rates of these defects were 7.9 per 1,000 live births[41] and 0.74 per 1,000 live births,[49] respectively.

Other anomalies

Analysis of 10 studies addressing cardiovascular anomalies in Iran from 1998–2012 shows that the prevalence of these defects is 3.3 per 1,000 births (95% CI: 2.2–5.1) (Figure 6).[12,13,38,40,41,48,49,53–55] Furthermore, analysis of the data of 8 studies which assessed the prevalence of Down syndrome indicated a rate of 0.9 per 1,000 births (95% CI: 0.7–1.2) (Figure 7).[12,13,22,24,25,27,41,48] Among all studies included in this meta-analysis, 7 studies, involving 104,948 participants, reported the prevalence of gastrointestinal system defects. Based on analysis of these studies, the prevalence of these defects in Iran was 1.4 per 1,000 births (95% CI: 0.9–2.1) as presented in Figure 8.[12,13,22,28,38,40,48]

Discussion

In this meta-analysis, all national studies that investigated the prevalence of birth defects in Iran were evaluated. Urogenital defects were the most prevalent structural congenital malformations, followed by defects of musculoskeletal and cardiovascular systems and Down syndrome.

Orofacial clefts

After analyzing the results of national studies, the prevalence of orofacial defects was about 1.4 per 1,000 births, which is close to the prevalence rate (1.45 per 1,000 live births) reported from an American population in a study conducted during 2007–2011.[56] In addition, EUROCAT reported that the prevalence of orofacial between 2010 and 2014 was 1.37 per 1,000 births.[9] There was no comprehensive meta-analysis study on birth defects in Middle

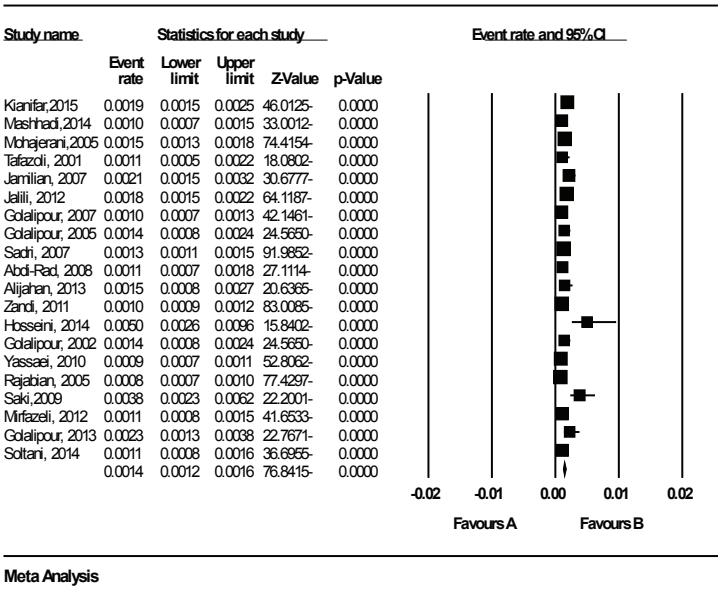

Figure 2. Prevalence of orofacial clefts in Iran.

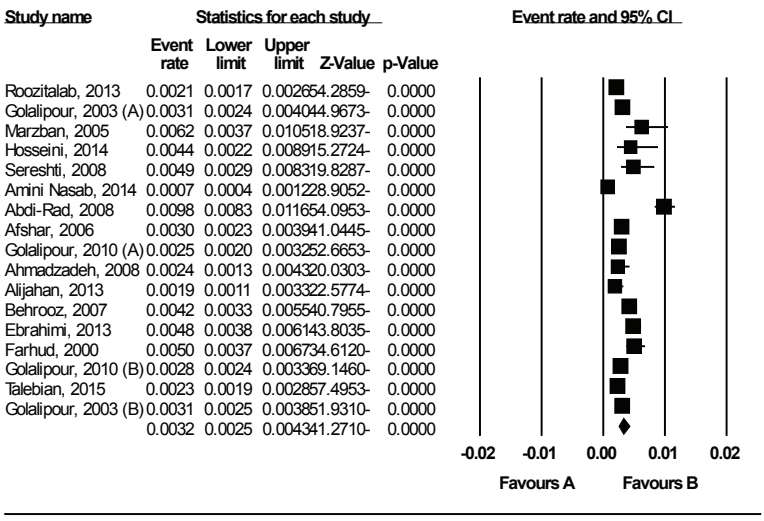

Figure 3. Prevalence of neural tube defects in Iran.

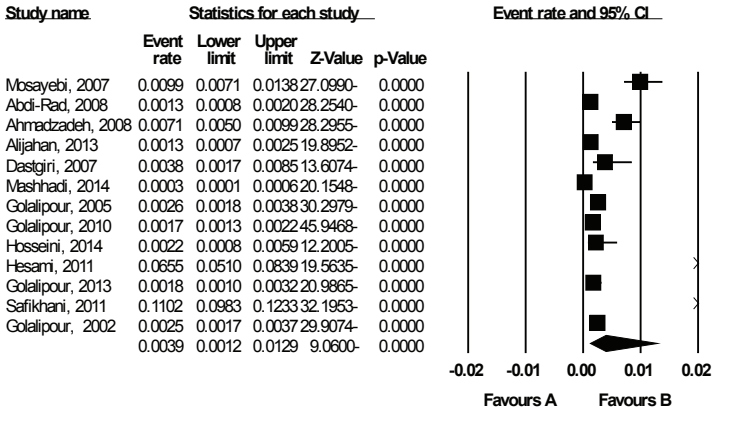

Figure 4. Prevalence of urogenital disorders in Iran.

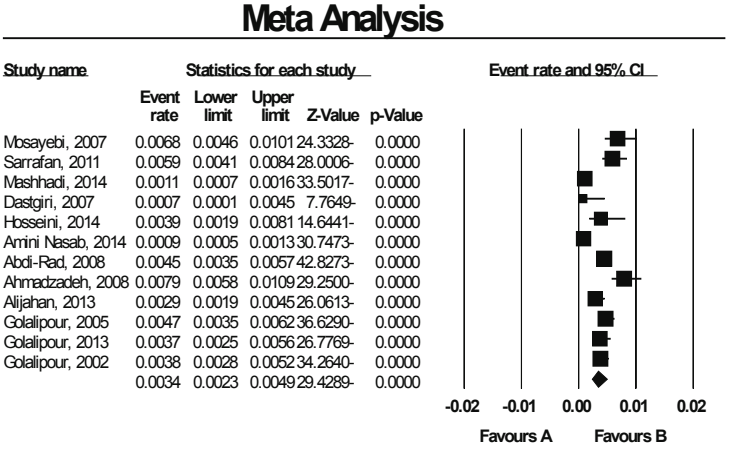

Figure 5. Prevalence of musculoskeletal anomalies in Iran.

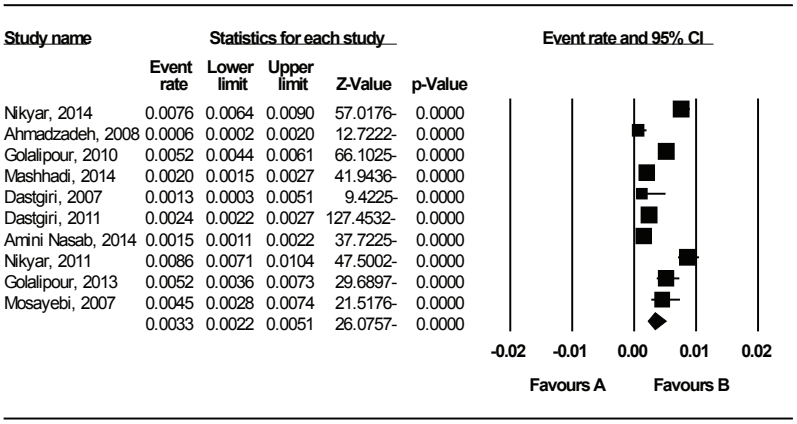

Figure 6. Prevalence of cardiovascular anomalies in Iran.

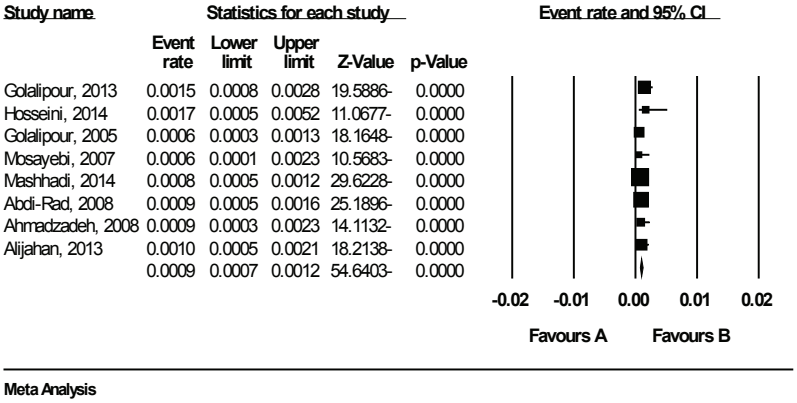

Figure 7. Prevalence of Down syndrome in Iran.

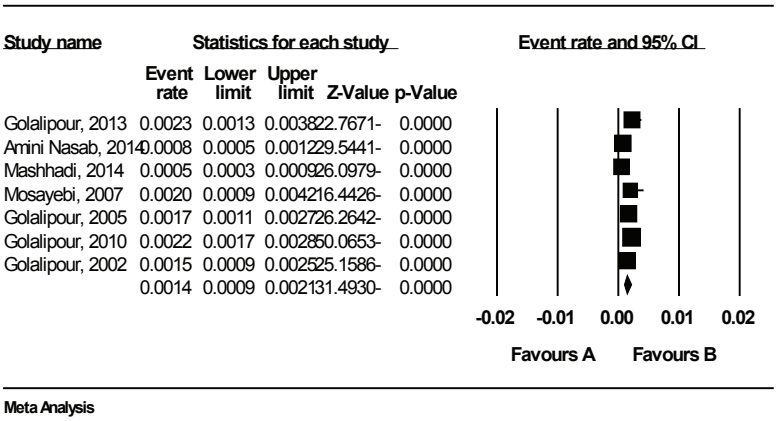

Figure 8. Prevalence of gastrointestinal abnormalities in Iran.

Eastern countries; however, in a systematic review by Sabbagh *et al.*, the mean prevalence of orofacial cleft in Saudi Arabia was about 1.25 per 1,000 live births.[57]

Neural tube defects

According to our findings, the prevalence of NTDs in Iran is about 3.2 per 1,000 births. This rate is slightly higher than that reported in countries from the Middle-East region. For example, a systematic review by Zaganjor *et al.*[58] (2016), which investigated the prevalence of NTDs worldwide, stated that the prevalence is about 0.21 per 1,000 births in the United Arab Emirates. On the other hand, the highest median prevalence of NTDs in the Middle

East pertained to Pakistan with a rate of 2.19 per 1,000 births.[58] According to the March of Dimes (MOD) report, this rate in South East Asia was evaluated as high as 4.7 per 10,000 live births in Bangladesh and Nepal and as low as 0.7 per 10,000 live births in Indonesia and Myanmar.[11,59] In Europe, EUROCAT reported a rate of 0.89 per 1,000 births.[9]

Urogenital disorders

The most prevalent congenital anomaly in our analysis pertained to the urogenital system with a rate of 3.9 per 1,000 births. This is higher than that mentioned in a study (2010–2013) from India, a third world country like Iran, which was 1.4 per 1,000 live births.[60] In European contries, it was determined that the rates of genital and urinary defects were 2.16 per 1,000 births and 3.3 per 1,000 births, respectively.[9] A higher rate was observed among Russian newborns for anomalies of the urogenital system (8.1 per 1,000 births).[5] In Korea, the prevalence of these abnormalities was estimated as high as 13 per 1,000 births.[4]

Musculoskeletal anomalies

Musculoskeletal anomalies are listed as common congenital anomalies worldwide. In our meta-analysis, the prevalence of these defects was about 3.3 per 1,000 births. This is lower than the pervalence estimated in Europe (4.2 per 1,000 births),[9] but higher than that reported in the United States (1.41 per 1,000 live births).[61] In Russia, the rate of musculoskeletal malformations and deformations were calculated as high as 12.7 per 1,000 births,[5] which is higher than that found in our study.

Other anomalies

Cardiovascular anomalies

In many countries, cardiovascular malformations are the most prevalent of congenital diseases. In Europe, the prevalence of cardiovascular malformations was reported about 8.09 per 1,000 births.[9] In contrast, this rate was estimated at 1 per 1,000 births among Palestinian infants.[62] Close to this result, in the United States, a rate of 1.47 per 1,000 live births was assessed.[61] In some South East Asian countries such as Indonesia, Maldives and Sri Lanka, the prevalence of cardiovascular malformations is approximately 7.9 per 1,000 live births.[11] The incidence of these defects was 3.3 per 1,000 births in our survey.

Gastrointestional anomalies

The present meta-analysis of all national studies from Iran showed that the incidence of gastrointestional anomalies is 1.4 per 1,000 births, which is near the rate seen among European newborns (1.69 per 1,000 births),[9] but higher than that reported among children born in the United States (0.68 per 1,000 live births).[61] Kumar and Singh reported a lower prevalence of gastrointestional disorders in English Caribbean countries (0.72 per 1,000 births) in comparison with our results.[63] Among Russian infants, these anomalies occur in 1.2 per 1,000 births.[5] Somewhat higher than this rate, a prevalence of 2.47 per 1,000 births was demonstrated in a survey from Korea.[4]

Down syndrome

This paper showed that the prevalence of Down syndrome in Iran is 0.9 per 1,000 births. In the United States, this rate was 1.44 per 100 live biths.[61] EUROCAT reported that the prevalence of this defect among European children was about 2.16 per 1,000 births.[9] A recent cross-sectional study in Tanzania recoreded a low rate of 0.11 per 1,000 live births.[64] The incidence of this syndrome in Korea was 0.47 per 1,000[4]. A recent report from southern Thailand showed a rate of 1.21 per 1,000 births.[65] The WHO reported a higher prevalence for Bhutan and Nepal (2.1 per 1,000 live births).[11] These data indicate a lower prevalence of Down syndrome in Iran compared with most of the aforementioned countries.

Causes and risk factors

Differences in the prevalence of congenital anomalies between areas and between countries can have several reasons. The literature disscusses low socioeconomic level as a potential important risk factor for congenital anomalies and mortality rates.[66,67] According to the MOD, about 94% of total birth defetcs occur in low- and middle-income countries.[68] Furthermore, an investigation in the United States showed differences in prevalence of birth defects between newborns of Hispanic mothers and those of non-Hispanic mothers.[69] In other words, the reports indicated that race and ethnicity may have a relationship with some congenital abnormaities and their survival.[70,71] There are also multiple risk factors, such as consanguinity of parents, alcoholic mother,[72] maternal obesity,[73] gestational diabetis,[74] maternal smoking,[75] environmental factors[76] and consuming drug during pregnancy,[77] which can potentially change the rates of congenital anomalies in different regions of countries.

Limitations

This study was limited by lack of comprehensive studies conducted in most reigons of Iran to estimate the prevalence of congenital anomalies in males and females separately. Also, this issue did not allow us to determine the rate of birth defects regionally. These limitations mainly stem from lack of a National Birth Defect Registry as mentioned above.

In conclusion, this study reported that urogenital anomalies are the most prevalent structural births defects in Iran, followed by musculoskeletal and cardiovascular disorders. Considering the high rate of congenital abnormalities in Iran, the recommendations for prevention and reduction in birth defects, based on the international plans, are as follows: increase in knowledge about birth defects and their etiology and diagnosis, planning for a national focal point and coordination mechansim for the prevention, formation of a national working group, and implemeting registration, surveillance and monitoring birth defects with high capacity.[78,79]

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