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Systematic review (Pages: 16082-16100)

Epidemiology of Pediatric Acute Poisoning in Iran: A Systematic Review and Meta-Analysis

Samira Alinejad [1, 4], Tayyebeh Chahkandi [2], Omid Mehrpour [3, 4], Jeffrey Brent [5], *Seyed Mohammad Riahi [6]

1 Pediatric Resident, Department of Pediatrics, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran.
2 Birjand Atherosclerosis and Coronary Artery Research Center, Department of Pediatric, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.
3 Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA.
4 Medical Toxicology and Drug Abuse Research Center (MTDRC), Birjand University of Medical Sciences (BUMS), Birjand, Iran.
5 School of Medicine, University of Colorado, Aurora, CO, USA.
6 Cardiovascular Diseases Research Center, Department of Epidemiology and Biostatistics, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran.

Abstract

Background: The epidemiology of pediatric poisoning differs from one country to another. Due to the scarcity of reviews on this issue in Iran, we performed a systematic review and meta-analysis of studies providing data on Iranian pediatric poisoning epidemiology.

Methods: PubMed, Web of Sciences, Science direct, Embase, Scopus and the Persian databases Magiran, Scientific Information Database (SID), and Iranmedex were searched. Twenty-seven studies published between 2002 and 2019 were included, based on the inclusion and exclusion criteria.

Results: 54.7% of the participants in the reviewed studies were male, and 88.1% of them were unintentional. Most of the children were in the age range of 3-5 years. Non-pharmaceutical agents were the most common causes of poisonings (n=7175, 59.2%) and among them, illicit drugs (19.3%) followed by hydrocarbons (16.4%) constituted the most common non-pharmaceutical poisonings. Illicit drugs, especially opioids, showed an upward trend from 2002 to 2019. Among pharmaceuticals, central nervous system (CNS) drugs (50.4%), especially benzodiazepines (BZDs) (25.8%) and analgesics (14.5%), were the most frequent agents implicated. CNS complaints (51.8%), followed by gastrointestinal complaints (27.6%), were the most common symptoms. Ingestion was the most common route of poisoning (22.1%). Most of the poisoning cases occurred in summer (28.2%). 21.7% of the cases were hospitalized and the mortality rate was 0.8%. A remarkable downward trend in both hospitalization and death rates occurred over time.

Conclusion: Overall, non-pharmaceutical toxicity was found to be the most common cause of poisoning. However, considering the agents separately, pharmaceuticals, illicit drugs, and hydrocarbons were the most common causes of poisoning, respectively. In contrast to the decreasing trend in hydrocarbons, pesticides, and pharmaceutical poisonings, we found an increase in opioid poisoning during our study period.

Key Words: Children, Intoxication, Iran, Prevalence.

* Please cite this article as: Alinejad S, Chahkandi T, Mehrpour O, Brent J, Riahi SM. Epidemiology of Pediatric Acute Poisoning in Iran: A Systematic Review and Meta-Analysis. Int J Pediatr 2022; 10 (5):16082-16100. DOI: **10.22038/ijp.2021.55738.4416**

****Corresponding Author:***

Seyed Mohammad Riahi, Cardiovascular Diseases Research Center, Department of Epidemiology and Biostatistics, School of Medicine, Birjand University of Medical Sciences, Birjand, Iran. Email: Riahim61@gmail.com

Received date: Mar.04,2021; Accepted date:Apr.11,2021

1- INTRODUCTION

Acute poisoning is an essential pediatric health issue (1-3), and is the third most common injury in children under the age of 16 admitted to emergency departments in Iran. In the U.S. More than 1 million cases of acute pediatric poisonings are reported annually to the American Association of Poisoning Control Centers with a mortality rate of 0.5 in 100000 people (4). In contrast, the mortality rate in Iran is even more than the rate in the U.S. (5). According to the World Health Organization (WHO), more than 3 million acute toxicity cases occur in developing countries, due to poor hygiene, limited access to healthcare resources, and inadequate knowledge about poisonings (3, 6). Patterns of poisoning vary by region, time period, and accessibility to poisonous substances. They also depend on demographic characteristics, social beliefs and customs, literacy status, economic status, neighboring countries, and ease of access to opium and drugs. In developed countries, most pediatric poisonings are due to drugs, cosmetics, cleaning products, alcohol, and stimulants. In contrast, in developing countries, the most common causes of poisoning are hydrocarbons, pesticides, traditional medicines, plants, and opium compounds (1, 7-12).

Pediatric poisonings are different from those of the adults in terms of intention and outcomes (3, 13, 14). Although it can be lethal, more than 85% of cases require no medical intervention because the ingested substance has a low order of toxicity, or the amount ingested is not clinically significant. Thus, with early diagnosis and treatment, most of the poisonings have an excellent prognosis in this population (2).

The epidemiologic characteristics of pediatric poisoning differ from country to country. Thus, knowledge of regional poisoning patterns can play an essential role in planning for the prevention, care, and treatment of patients. Due to the insufficiency of epidemiologic data in Iran, we sought to conduct this systematic review and meta-analysis to better understand pediatric poisoning status in our region and to decide on further strategies to improve poisoning management in this population.

2- MATERIALS AND METHODS

This systematic review and meta-analysis is extracted from a pediatric resident thesis and was performed according to the Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines (supplementary 1) (15). The registration number is I.R.BUMS.REC.1398.210, and it was approved on October 18, 2019.

2-1. Data Sources and Search Strategy

To find relevant studies published before September 2019, two independent reviewers, concurrently, searched the English databases (i.e., PubMed, Web of Sciences, Science direct, Embase, and Scopus) and Persian databases (i.e., Magiran, SID, and IranMedex). Medical subject headings and Embase Subject Headings were used to develop the search strategy, and for each database, the strategy was revised. The search was conducted using the following keywords or their Persian equivalents, with the Boolean operators (AND, OR): (“prevalence” OR “epidemiology” OR “rate” OR “pattern” OR “incidence”) AND (“intoxication” OR “poisoning” OR “poison” OR “toxin” OR “scorpion sting” OR “snakebite” OR “envenomation” OR “bites and stings” OR “bites” OR “stings”) AND (Iran) (Supplementary 2).

2-2. Inclusion and Exclusion Criteria

Our inclusion criteria encompassed all Persian and English studies resulting from our search strategies and reporting the epidemiology of poisoning in the Iranian

population under 18 years of age. The exclusion criteria were: 1) studies with unknown sample sizes; 2) studies whose full text was unavailable; 3) studies published as theses or conferences; 4) studies carried out on non-Iranian populations; 5) studies about the epidemiology of a specific agent's poisoning; and 6) studies conducted on the population aged above 18 years old.

2-3. Outcome Measurement

The outcomes of interest were (1) the demographic features of patients; (2) the most common agents responsible for pediatric poisoning; (3) the trends of pediatric poisoning during the years 2002-2019; (4) determining the effects of climate on poisoning; (5) the hospitalization and mortality rates of pediatric poisoning across the country.

2-4. Study Selection

The retrieved articles were imported into EndNote X8.2. After removing duplicates, two reviewers independently screened the titles and abstracts of all articles to identify studies meeting our predetermined inclusion criteria. The inter-rater agreement was 0.98. The 27 articles meeting our inclusion criteria and incorporated into our meta-analysis are shown in **Table 1**. The records' flow is presented in the PRISMA diagram (**Fig. 1**).

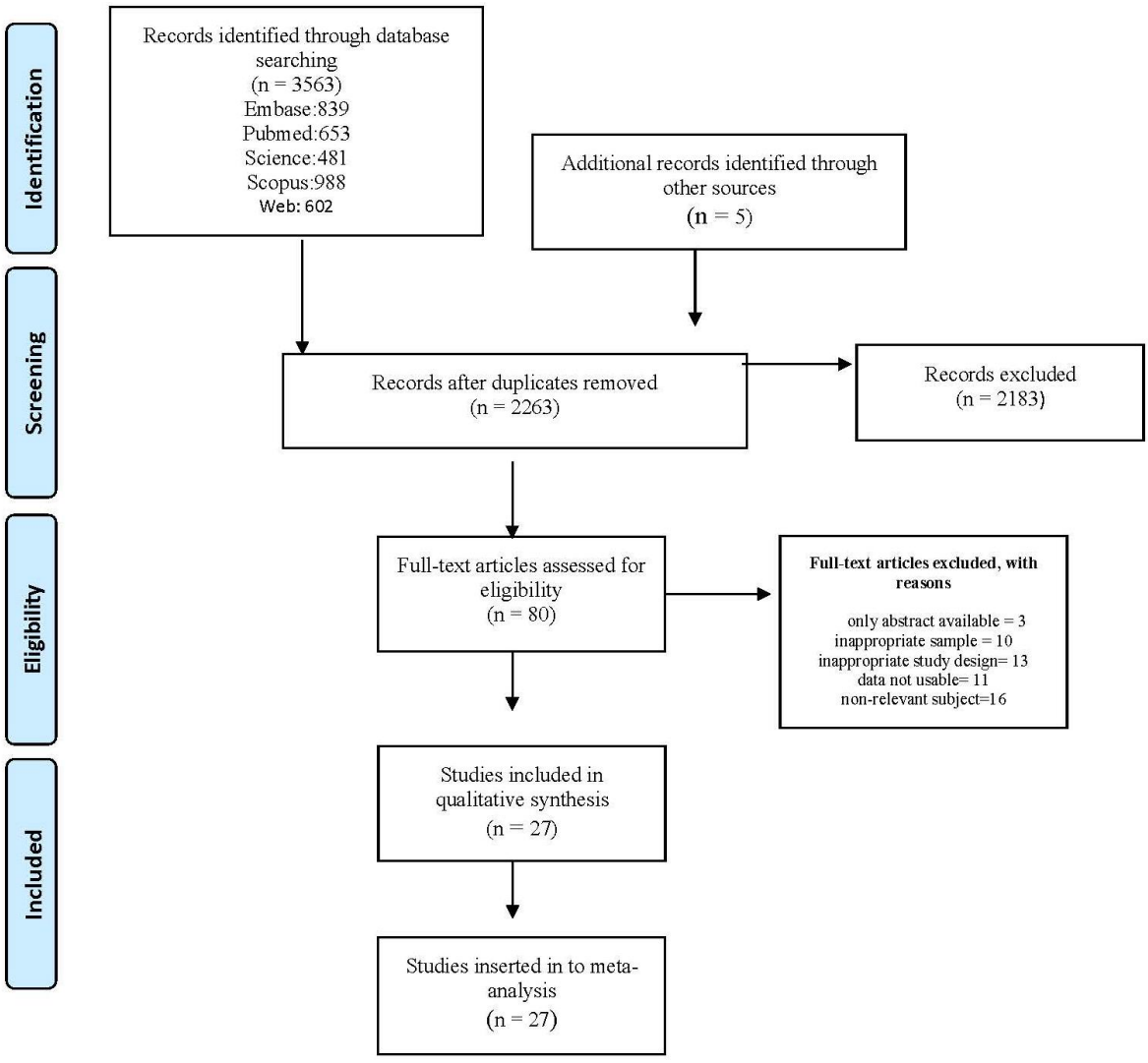

Fig. 1: Flow diagram of study selection process in meta-analysis

Table-1: Characteristics of the Studies included in the meta-analysis

Author	Publication	Language	Start-end	Sample size	Mean age	Age range	male	Location (urban %)	Province (City)	Climate	Poisoning agents	Score
Gheshlaghi, F (1)	2013	En	2008-2001	344	3.07 1.43	0-10	50%	-	Isfahan (Isfahan)	Hot and dry	P.H., H, P, Pnt BS, D, U, O	8
Haghighat, M (2)	2013	En	2009-2020	773	3.86 1.5	0-18	33%	-	Fars (Shiraz)	Hot and dry	P.H., H, I, P, Pnt, D, U	8
Mehrpour, O (3)	2015	En	2006-2020	246	3.1 2.7	0-13	58%	56.91%	South Khorasan (Birjand)	Hot and dry	PH, H, Co, I P, BS, D, U, O	8
Moghadamnia, A (63)	2004	En	1995-2001	98		0-13	58%	-	Mazandaran (Babol)	Moderate	PH, H, I, D, P	8
Pirzadeh, Z (24)	2016	En	2009-2012	434	3.4 3.9	0-13	63%	-	Ghazvin (Ghazvin)	Cold and dry	PH, H, CO, I, P, Pnt, BS, D	8
Feiz Disfani, H (5)	2019	En	2018	243		0-15	48%	69%	Khorasan Razavi (Mashhad)	Moderate	PH , CO , D , O	8
Alizade, A (33)	2017	En	2011-2013	1701	5 0.16	0-14	45%	-	Khorasan Razavi (Mashhad)	Moderate	P.H., I, P, Pnt BS, O	8
Khajeh, A (27)	2012	En	2008-2009	147	2.93 3.05	0-14	56%	-	Sistan and Baluchestan (Zahedan)	Hot and dry	P.H., H, CO, I P, U, O	8
Mojtabayi, H (54)	2012	Far	2010	141		0-12		-	Gilan (Rasht)	Moderate	P.H., H, I, BS, D, R, O	8
Arjmand, A (12)	2014	En	2008-2012	224	3.54 2.99	0-17	55%	71%	Markazi (Arak)	Cold and dry	PH, H, I, P, Pnt, D, R, U, O	8
Talebian, A (13)	2007	Far	1998-2003	119	5.5 3.3		66%	68.9%	Isfahan (Kashan)	Hot and dry	P.H., H, CO, Pnt, D, O	8
Farzaneh, E (37)	2014	Far	2007-2011	336	4.1	0-13	58%	77.7%	Ardabil (Ardabil)	Moderate	PH, H, CO, I, P, Pnt, D, R	8
Rafiei, M (28)	2003	Far	1994-1996	502		0-12	56%	-	East Azerbaijan (Tabriz)	Cold and dry	P.H., H, I, P, Pnt BS, D, U, O	8
Ghorashi, Z (64)	2003	Far	2000-2003	306			53%	63%	East Azerbaijan (Tabriz)	Cold and dry	P.H., H, CO, I P, R, O	8
Zare Fazl Elahi, Z (29)	2009	Far	2002-2006	729		0-16	50%	-	West Azerbaijan (Urmia)	Moderate	P.H., H, I, P, BS, D, O	8

Author	Publication	Language	Start-end	Sample size	Mean age	Age range	male	Location (urban %)	Province (City)	Climate	Poisoning agents	Score
Motlagh, M (9)	2002	Far	2001	110		0-7	58%	-	Khuzestan (Ahvaz)	Hot and dry	P.H., H, I, P, Pnt, R	8
Assar, SH (25)	2009	En	2001-2004	143		0-4	58%	-	Khuzestan (Ahvaz)	Hot and dry	PH, H, I, D U, O	8
Mahmoudi, GH (14)	2013	En	2011	230	3.1 2.4	0-11	50%	-	Lorestan (Khoram Abad)	Moderate	P.H., H, CO, P, Pnt, O	8
Kashef, S (38)	2002	Far	1997-1998	690		0-15	60%	-	Fars (Shiraz)	Hot and dry	P.H., I, P, Pnt BS, U, O	8
Haghighat, M (34)	2009	En	2007	463			51%	-	Fars (Shiraz)	Hot and dry	PH, O	7
Sadeghi Bojd, S (50)	2014	En	1998-2008	317			51%	-	Sistan and Baluchestan (Zahedan)	Hot and dry	P.H., H, I, P, U,Pnt, O	8
Koushanfar, A (42)	2003	Far	1998	3199		0-12	60%	-	Tehran (Tehran)	Moderate	PH, H, I, Pnt BS, D, O	8
Manouchehrifar, M (53)	2015	En	2014	414	4.2 3.43	0-14	57%	-	Tehran (Tehran)	Moderate		7
Vazirian, SH (35)	2005	En	2002-2003	172			61%	74.4%	Kermanshah (Kermanshah)	Moderate	P.H.	7
Haratipour, H (36)	2016	Far	2011-2012	201		0-12	54%	73.6%	Golestan (Gorgan)	Moderate	PH, I, O	8
Haresabadi, M (51)	2013	Far	2011-2012	211		0-12	58%	43.1%	North Khorasan (Bojnourd)	Moderate	PH, H, CO, I P D, U, O	8
Nikvarz, M (10)	2017	Far	2015	121	3 2	0-13	53%	45.5%	Kerman (Jiroft)	Hot and dry	P.H., H, CO, I P, Pnt, R, O	8

P.H.: Pharmaceutical; H: Hydrocarbon; I, Illicit; P, Pesticide; Pnt, Plant; B.S., Bites and Stings; D: Detergents; Co: Carbon Monoxide; R: Raticide; U: Unknown; O: Other.

2-5. Data Extraction

Two authors (SA and SMR) extracted the following data from each article: the authors' names, year of publication, start and end dates of each study, language, sample size, province, location, climate, age (mean, S.D., range), gender, types of poisonings (pharmaceutical and non-pharmaceutical), implicated substance, outcome, intention, signs, symptoms, and route of exposure. The extracted information was entered into Excel spreadsheets.

2-6. Risk of Bias Assessment

After the relevant studies were selected, their quality was assessed by two authors (SA, SAM) independently using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data (16).

2-7. Data synthesis and statistical analysis

Random effect models were used to estimate pooled prevalence and 95% confidence intervals (CIs). Pooled prevalence and CIs were calculated using a Freeman Tukey double arcsine transformation to provide an estimate of the standard error (S.E.) of prevalence and CIs. Heterogeneity among the studies was assessed with I^2 statistics (17, 18). These statistics range from 0 -100%, and values of 70% or more were considered to represent substantial heterogeneity (19, 20). Subgroup analyses and meta-regression were performed to determine the sources of heterogeneity among studies (21). Since the purpose of the prevalence studies is not to examine the relationship between exposure and outcome, no assessment of publication bias was deemed necessary (22). The significance level (S.L.) in all analyses was considered at P-value < 0.05. However, the S.L. in analyses done with less than five studies was considered to be P = 0.1. All statistical analyses were done using Stata version 13.0 (Stata Corp, College Station, TX, USA).

3-SEARCH RESULTS

3-1. Study Characteristics

All selected studies had a cross-sectional design. Twenty-seven articles, with a total of 12,473 participants, were included in the meta-analysis. All the studies were published from 2002 to 2019. The studies' sample sizes ranged from 98 to 3,199 cases. The most common age range of children was 3-5 years. The main characteristics of the included studies are shown in **Table 1**. From the total sample of 12,473 patients, 6,747 (54.7%) were male (**Fig. 2**), and 19 articles showed the predominance of unintentional poisoning. Females were more responsible for intentional poisonings (71.2%) (**Table 2**).

3-2. Meta-analysis Results

3-2-1. Poisoning agents

Non-pharmaceutical agents were the most common causes of poisonings (n=7175, 59.2%) (95% CI: 54.5-63.8, I^2 = 96.1%). Pharmaceuticals (n=5023, 40.7%) (95%, CI: 36.1 to 45.5, I^2=96.1), illicit drug toxicity (19.3%) (95% CI: 9.9 to 30.8, I^2 =99.5%) and hydrocarbons (16.4 %) (95% CI: 13.1 to 20, I^2 = 94%) were the most common causes of non-pharmaceutical poisoning. However, there was a substantial heterogeneity between studies. Opioids were the most common agents responsible for illicit poisoning (18%) (95% CI: 9.1 to 29.1, I^2 = 99.4%). Plant poisoning, constituting 2.9% of cases, were the least common cause among non-pharmaceutical agents (**Table 2**).

Among pharmaceuticals, Central Nervous System (CNS) drugs, responsible for 50.4 % (95% CI: 40.9 to 59.8, I^2 =97%) of cases were the most common of the pharmaceuticals. Benzodiazepines, with the pooled proportion of 25.8% (95% CI: 18.3 to 34, I^2 =96%), were the most commonly implicated CNS drugs.

Analgesics were responsible for 14.5% of drug poisonings. Acetaminophen, with the frequency rate of 11.9% (95% CI: 5.6 to 20.1, I^2 = 90.4 %), was the most common analgesic. Finally, antibiotics were the least common cause of poisoning among pharmaceutical agents, making up 1.9% of cases (**Table 3**).

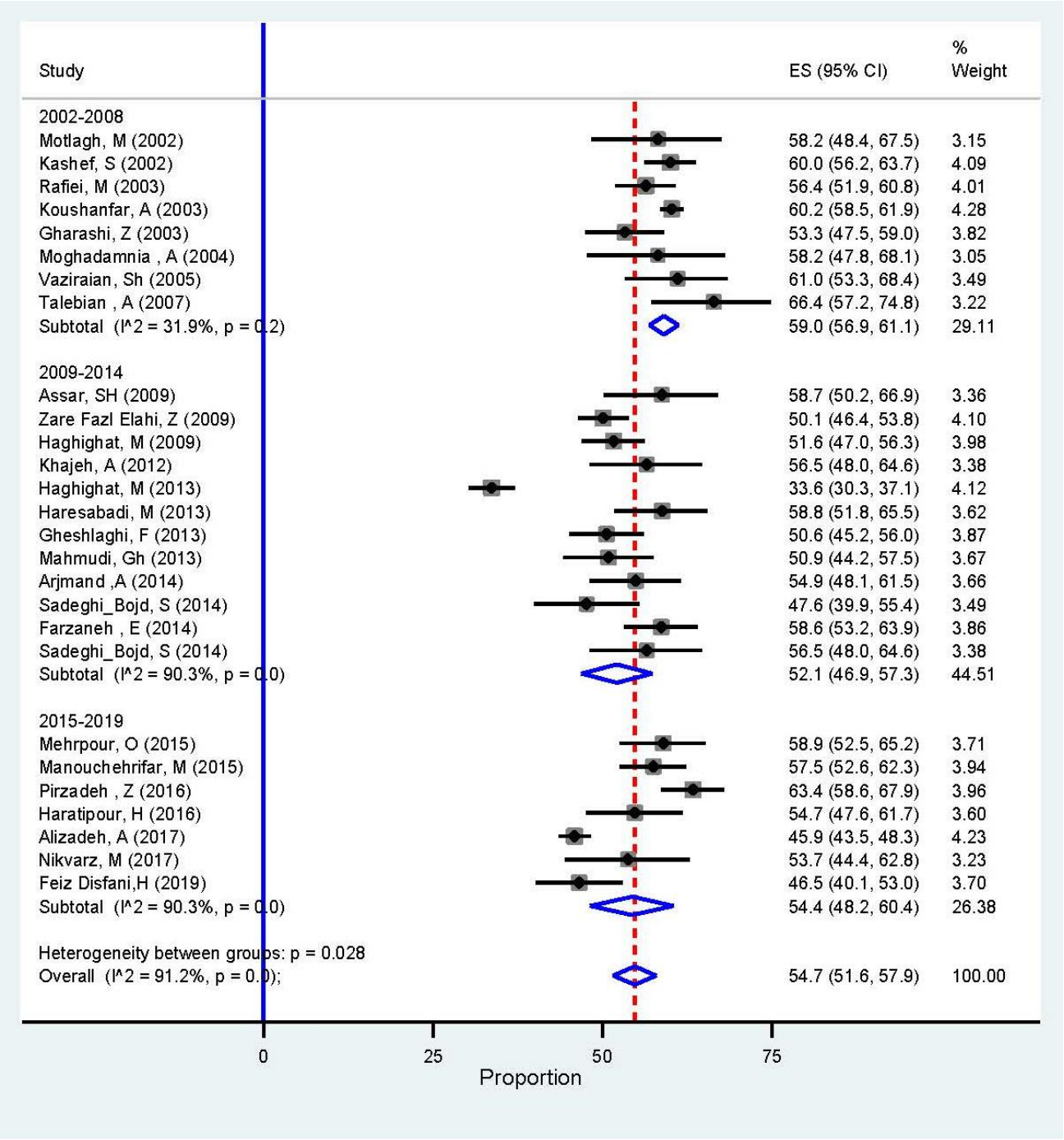

Fig. 2: Forest plot of male gender poisoning proportion

Table-2: Trends of poisoning agents, outcomes and other factors from 2002-2019

Variable		N	n/N	Pooled proportion (95% CI)	I^2
Poisoning Agents					
Pharmaceutical	2002-2008	8	2186/5196	39.1(34.5-43.8)	86.4
	2009-2014	13	1941/4058	45 (37.8-52.2)	95.2
	2015-2019	6	896/2946	34.2 (24.2-45)	96.3
	Overall	27	5023/12200	40.7 (36.1-45.5)	96.1
Hydrocarbon	2002-2008	6	3011/5196	29.2(22.7-36.1)	91.6
	2009-2014	12	2116/4058	12.5 (9.4-16)	88
	2015-2019	3	2048/2946	10.1 (8.3-12.2)	0
	Overall	21	7175/12200	16.4 (13.1-20)	94
CO	2002-2008	2	946/4334	2.1 (0.8-3.7)	97.9
	2009-2014	4	426/3595	1.4 (0.6-2.4)	16.2
	2015-2019	4	94/923	4.2(1-9.2)	90.2
	Overall	10	1466/8852	2.5 (1.2-4.2)	81.2
Illicit	2002-2008	6	9/425	8 (3.9-13.3)	95.7
	2009-2014	11	14/924	16.2 (7.8-26.9)	98.2
	2015-2019	5	50/1044	44.9 (23.4-67.4)	99
	Overall	22	73/2393	19.3 (9.9-30.8)	99.5
Opioid	2002-2008	5	260/4905	9.6 (4.3-16.8)	96.3
	2009-2014	11	614/3365	12.9 (5.5-22.7)	98.2
	2015-2019	5	1522/2703	42.7 (22.7-64)	98.9
	Overall	21	2396/10973	18 (9.1-29.1)	99.4
Alcohol	2002-2008	1	248/4403	2.4 (1.2-4.1)	-
	2009-2014	4	553/3365	2.3 (1-3.9)	63.7
	2015-2019	3	1430/2703	1.6 (0.8-2.6)	0
	Overall	8	2211/10471	2.1 (1.4-2.9)	39.1
Pesticide	2002-2008	5	12/502	6.5 (4.4-8.9)	67.1
	2009-2014	10	43/1486	6 (3.8-8.7)	87.6
	2015-2019	4	13/801	3.4 (0.9-7.4)	92.2
	Overall	19	68/2789	5.4 (3.7-7.5)	91.8
Plants	2002-2008	5	125/1706	3.8 (0.3-10.7)	98
	2009-2014	6	198/3311	2.7 (2-3.4)	0
	2015-2019	3	52/2502	1.8 (1.1-2.6)	18.4
	Overall	14	375/7519	2.9 (1.5-4.7)	94.2
Bites and stings	2002-2008	3	11/4620	3.8 (0.5-9.9)	97.7
	2009-2014	3	57/2077	3.6 (1.2-7.2)	84.1
	2015-2019	3	42/2256	7.2 (2.6-16.4)	97.1
	Overall	9	210/8953	4.7 (2.6-7.4)	95.4
Detergent	2002-2008	4	174/4391	4.5 (1.1-10)	94.4
	2009-2014	8	61/1214	5 (3-7.5)	85.9
	2015-2019	3	107/2381	6.9 (1.3-16.3)	95
	Overall	15	342/7986	5.2 (3.5-7.2)	90.7
Rodenticide	2002-2008	2	260/3918	3.3 (1.7-5.3)	68.9
	2009-2014	3	156/2901	3.4 (2-5.1)	16.3
	2015-2019	1	71/923	5 (1.8-10.5)	-

Variable		N	n/N	Pooled proportion (95% CI)	I^2
	Overall	6	487/7742	3.5 (2.5-4.7)	0
Unknown	2002-2008	2	14/416	12 (10.2-13.9)	99.4
	2009-2014	8	25/701	3.6 (2.3-5.2)	62.8
	2015-2019	1	6/121	1.2 (0.3-3.5)	-
	Overall	11	45/1238	4.6 (2.1-8.1)	94.2
Other	2002-2008	5	152/1192	13.2 (6.9-21)	97.1
	2009-2014	9	71/2159	10.3 (4.4-18.4)	96.7
	2015-2019	5	3/246	6.4 (1.6-14.1)	96.3
	Overall Outcomes	19	226/3597	9.9 (5.9-14.9)	98
Death	2002-2008	7	23/5077	0.9 (0.2-2)	83.2
	2009-2014	13	52/4058	0.9 (0.4-1.6)	69.1
	2015-2019	7	19/3360	0.6 (0-1.7)	83.5
	over all	27	94/1249	0.8 (0.4-1.3)	81.1
Death reason	Drug	4	12/882	1.3 (0.6-2.2)	0
	Hydrocarbons	7	14/348	3.7 (1.3-7)	32.2
	Pesticide	4	5/124	3.2 (0.3-7.8)	0
	Bites and stings	2	6/125	3.9 (1-8.3)	0
Hospitalization					
PICU	2002-2008	1	50/164	30.5 (23.5-38.1)	-
	2009-2014	4	55/318	16.4 (12.3-20.9)	0
	2015-2019	2	63/452	12.4 (9.4-15.8)	19.8
	Overall	7	168/934	28.1 (14.3-42.2)	94.7
Other Factors Unintentional	2002-2008	5	1603/1768	90.1 (77.4-98)	98
	2009-2014	10	2431/3349	83.4 (71.5-92.6)	98.5
	2015-2019	4	1233/1259	95.4 (89.9-98.8)	93.1
	Overall	19	5267/6412	88.1 (80.3-94.2)	98.7
Intentional	Female	4	816/1145	71.2 (66.8-75.4)	15.5
	Male	4	329/1145	25.6 (20.2-31.4)	46
	Male 2002-2008	8	3091/5196	59 (56.9-61.1)	31.9
	2009-2014	12	1930/39/17	52.1 (46.9-57.3)	90.3
	2015-2019	7	1726/3360	54.4 (48.2-60.4)	90.3
	Overall	27	6747/12473	54.7 (51.6-57.9)	91.2

CO, Carbon Monoxide; PICU, Pediatric Intensive Care Unit; N, number of studies; n/N, subgroup poisoning cases/total poisonings

3-2-2. Time Trends of poisonings during 2002-2019

The rate of pharmaceutical poisoning decreased from 45% (n=1941) (95% CI: 37.8 to 52.2, I^2 =95.2) in 2014 to 34.2% (n=896) (95% CI: 24.2 to 45, I^2 =96.3) in 2019. In contrast, there was a significant increase in illicit poisonings from 8% (n=260) (95% CI: 3.9 to 13.3, I^2 =95.7) in 2002 to 44.9% (n=1522) (95% CI: 23.4 to 67.4, I^2 =99), in 2019. Opioids showed a marked increase in the number of cases over the course of the time period of our study. In contrast, a marked decrease in the frequency of cases of alcohol poisoning occurred, from 2.4% (n=12) in 2002 to 1.6% (n=13) in 2019. Although

hydrocarbon toxicity was the second most common cause of poisoning among non-pharmaceutical agents, there was a substantial decrease from 29.2% (n=946) (95% CI: 22.7 to 36.1, I^2 =91.65) in 2002 to 10.1% (n=94) (95% CI: 8.3 to 12.2, I^2 =0) in 2019.

Pesticide poisoning cases decreased during the years of our study. There was a remarkable reduction in the rate of hospitalization, as well as pediatric intensive care unit (PICU) admissions, from 40.3% (n=50) (95% CI: 15.2 to 68.6, I^2 =99.4%) in 2002 to 5.3% (n=63) (95% CI: 3.6 to 7.6, I^2 =98.3%) in 2019. The pediatric poisoning mortality rate decreased from 0.9% (95% CI: 0.2 to 2, I^2 =83.2%) in 2002 to 0.6% (n=19) (95% CI: 0.1 to 7, I^2 =83.5%) in 2019 (**Fig. 3**). Envenomation (3.9%) followed by hydrocarbons (3.7%) were responsible for the highest proportion of deaths. More detailed information is presented in **Table 2**.

Table-3: Pharmaceutical subgroup proportions from 2002-2019

Variable	N	Pooled proportion (95% CI)	I^2
Multidrug	5	10.2 (8-12.5)	0
Analgesic	13	14.5 (8.8-21.2)	95.6
NSAID	6	9.3 (5.9-13.4)	73.8
Acetaminophen	5	11.9 (5.6-20.1)	90.4
Other analgesic	3	5.9 (0-27.8)	97.3
CNS drug	19	50.4 (40.9-59.8)	97
Antidepressants	3	19.5 (2.2-47)	97.7
Anticonvulsant	8	6.2 (4.2-8.6)	66.9
Benzodiazepines	17	25.8 (18.3-34)	96
TCA	11	14.8 (10.7-19.4)	84.5
Antipsychotic	3	13.8 (11.2-16.6)	0
Other	7	4.5 (2.2-7.5)	83
Cardiovascular	9	6 (3.1-9.8)	85.1
AB	7	1.9 (0.7-3.4)	61
Iron	4	3.1 (1.4-5.4)	26.4
Antihistamine	9	4.9 (2.4-8)	81.9
GI	9	7.2 (3.4-12.1)	86.6
Respiratory	1	3.7(1.5-7.6)	0
Unknown	8	16 (4.6-32.2)	97.2
Other	14	20.2 (6.3-39.2)	99.1

NSAID: Nonsteroidal anti-inflammatory drugs CNS: Central nervous system
TCA: Tricyclic antidepressants AB: Antibiotics
G.I.: Gastrointestinal

3-2-3. Signs, symptoms, and routes of poisoning

Most cases (51.8%) showed CNS signs (95% CI: 44.5 to 59, I^2 =91.8). Loss of consciousness, in 27.6% (95% CI: 15.2 to 42, I^2 = 97.5%) and seizures in 4.2% (95% CI: 2.9 to 5.6, I^2 = 0) were the most and the least common CNS complications, respectively. After CNS signs, gastrointestinal signs and symptoms with a percentage of 27.6 % in all cases were the most common (95%, CI: 14.3 to43.4, I^2 =98.7%). 13.2% of the cases were asymptomatic. Most of the children (92.1 %) (95% CI: 88.6 to 95, I^2 = 89.5%) were poisoned through oral ingestion (**Table 4**).

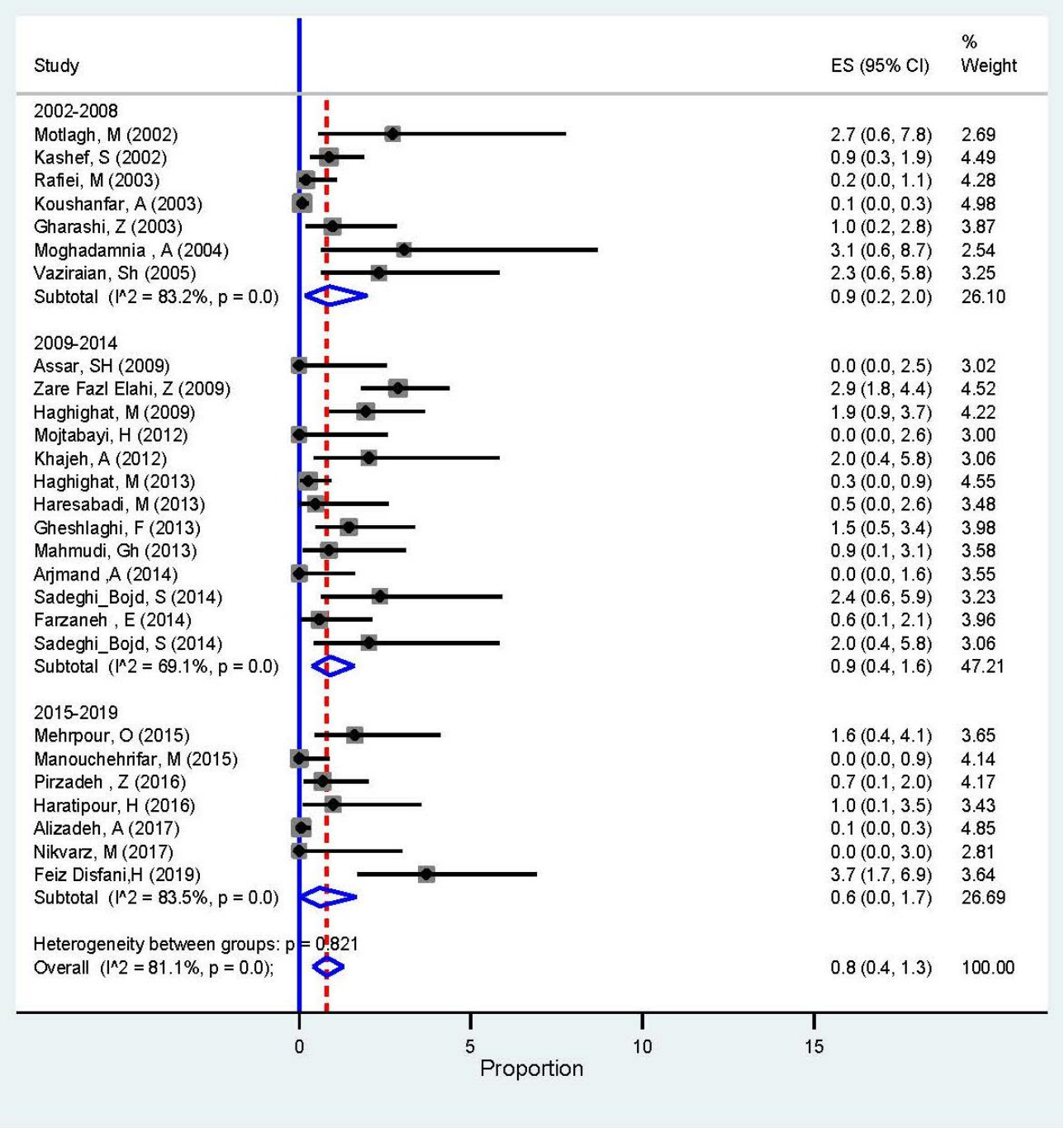

Fig. 3: Forest plot of death trend proportion during 2002-2019

3-2-4. The effects of season and climate

Pediatric poisonings were more frequent in summer (28.2 %) (95% CI: 23.8 to 32.9, I^2=75.5%); although, there was not a significant difference between various seasons. In addition, poisonings occurred more in hot and dry climates. More detailed information is presented in **Table 5**.

4- DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis,

reviewing pediatric poisoning epidemiology in all provinces of Iran.

Table-4: Signs and Symptoms, Route of poisonings

Variables		N	Pooled proportion (95% CI)	I^2
Signs and symptoms	Asymptomatic	11	13.2 (8.4-18.9)	95.7
	Gastrointestinal	10	27.6 (14.3-43.4)	98.7
	CNS	10	51.8 (44.5-59)	91.8
	Loss of consciousness	6	27.6 (15.2-42)	97.5
	Seizure	2	4.2 (2.9-5.6)	0
	Other	4	25.1 (17.1-34)	93
	Respiratory	7	14 (9.4-19.4)	87.7
	Cardiovascular	4	4.6 (0-14.9)	96.9
	Other	7	19(11.2-28.3)	94.7
Route of poisoning	Ingestion	10	22.1 (88.6-95)	89.5
	Inhalation	6	5.2 (1.9-9.8)	91.5
	Transdermal	4	2.4 (0.3-6.2)	90.6
	Injection	2	2.2 (0.9-4)	0
	Other	3	10.1 (6.8-14)	68

CNS, Central Nervous System.

4-1. Demographic data

The most common age range of the participants was 3 to 5 years old (**Table 1**). As shown in our meta-analysis and in the studies from other countries, ingestion is the most common route of poisoning in this age group. Children are generally curious and hyperactive at these ages and tend to put objects in their mouths to explore their environment (23-25). This can describe the high rate of unintentional poisoning in our study. Thus, poisoning prevention education is important for the parents of children in this age group. Males were the dominant group affected by poisoning in our study. This is in agreement with a WHO report released in 2004. This is likely because boys are naturally more energetic and curious than their female counterparts (26, 27). On the other hand, females were the dominant group in intentional poisonings (2, 5, 28, 29). Studies from other countries have shown the same results (30, 31). The reason for more attempts at self-harm in females could include higher rates of psychiatric problems, especially depression, more emotional crisis in adolescence, and earlier puberty and hormonal changes (3, 25, 32-34).

Children living in urban areas were more exposed to poisoning than those from rural regions (**Table 1**) (3, 5, 35, 36). Some explanations for this issue include more child negligence due to busier mothers, more availability of toxic substances in cities, larger populations in urban areas, and easier access to the hospital (3). In addition, more poisoning cases in our study took place in summer, which could be because of spending more time outdoors and thus lesser parental supervision (37, 38).

4-2. Pattern of intoxicants

Overall, non-drug toxicity accounting for 59.2% of the cases was the most common cause of poisoning in our study. Pharmaceuticals, illicit drugs, and hydrocarbons were the next most common causes of poisoning, respectively.

Table-5: The status of poisoning in different seasons and climates

Variables		N	Pooled proportion (95% CI)	I^2
Season	Autumn	7	24.7 (15.9-34.6)	94.1
	Summer	8	28.2 (23.8-32.9)	75.5
	Spring	7	22.3 (17.6-27.5)	77
	Winter	6	23.7 (20.3-27.2)	43.8
Climate Pharmaceutical	Hot and dry	12	41.6 (34.6-48.8)	94.3
	Cold and dry	4	48.7 (38.2-59.3)	94
	Moderate	11	36.9 (29.4-44.7)	97.3
Hydrocarbon	Hot and dry	9	18 (11.2-26)	94.8
	Cold and dry	4	16 (7.3-27.3)	96.4
	Moderate	8	15 11.2-19.3)	90.7
CO	Hot and dry	10	20.3 (13-28.6)	96.1
	Cold and dry	4	6.2 (0.9-15.3)	97
	Moderate	8	26.5 (5.7-55.2)	99.8
Illicit	Hot and dry	10	16.8 (10.4-24.3)	95.7
	Cold and dry	3	5.9 (1-18.7)	97.5
	Moderate	8	25.7 (6-52.9)	99.8
Pesticide	Hot and dry	9	6.3 (4.1-8.9)	82.5
	Cold and dry	4	5.2 (2-9.8)	90.9
	Moderate	6	4.4 (1.5-8.6)	94.9
Plants	Hot and dry	7	2.6 (2-3.4)	1
	Cold and dry	3	5.5 (0.6-14.7)	96.4
	Moderate	4	1.7 (0.5-3.6)	92.9
Bites and stings	Hot and dry	3	9.1 (3.2-17.5_	94.7
	Cold and dry	2	2.7 (1.8-3.9)	97.3
	Moderate	4	3.2 (1.8-5.1)	89.2
Detergents	Hot and dry	5	4.8 (2.3-8)	83.5
	Cold and dry	3	3.4 (0.7-7.8)	90.7
	Moderate	7	6.5 (4-9.5)	89.1
Raticide	Hot and dry	2	3.8 (1.6-6.8)	68.9
	Cold and dry	2	3.2(1.8-4.8)	68.9
	Moderate	2	3.9 (2.3-5.8)	68.9

4.-2-1. Pharmaceuticals

Some reasons for the high rate of pharmaceutical poisoning in our study are negligence of families in storing drugs, children's interest in colored medications, tendency to imitate adults, and immature organs for metabolizing the drugs (34, 39). This was in line with studies conducted in Taiwan, Brazil, and Australia (23, 40, 41). Among medications, CNS drugs, especially BZDs, were the most responsible ones for pediatric poisoning. Their use has increased among families for the treatment of anxiety, sleep disorders, and epilepsy. Thus, they are more accessible to children now than they were previously (42). Benzodiazepines can cause drowsiness and loss of consciousness in children, explaining why these neurologic effects were reported as the most common sign in our study (43). Analgesics, especially acetaminophen, were the second most common pharmaceutical agents causing poisoning in our study (30, 41). The lowest rate of

drug poisoning was related to antibiotic agents. This may be because pharmacies are obligated to sell these drugs with a physician prescription or because they tend to have a low order of toxicity.

4-2-2. Illegal drugs

Illicit drugs, especially opioids, were the second most common cause of drug poisoning after pharmaceuticals. The significant rise in opioid poisoning from 2002 to 2019 indicates the increase in the availability of them in the country. This is in contrast with reports from other parts of the world (44-46). The main reasons for this availability are the neighboring countries like Afghanistan and Pakistan, which use the strategic situation of Iran for smuggling these drugs into Europe (2, 25, 47-51).

According to studies from different parts of Iran, the pattern of traditional opium poisoning has decreased and has been somewhat replaced by methadone overdose, which may be due to the increased availability of methadone, new medical treatment programs such as methadone maintenance therapy, and home storage of this drug in insecure containers that seem attractive to children (33, 52, 53). Finally, alcohol poisoning had the lowest rank among illicit drugs in our results. Alcohol poisoning showed a decreasing trend from 2002 to 2019, which could be related to the religious ban on its consumption; or the legal ban which might have led to underreporting due to social issues (2).

4-2-3. Hydrocarbon toxicity

Hydrocarbon toxicity was the third common cause of poisoning, after pharmaceuticals and illicit drugs. Commonly being colorless like water, hydrocarbons are frequently used as a fuel in developing countries and stored under unsafe conditions, making them a hazard to children (27, 50, 54). This finding is in agreement with the high prevalence of gastrointestinal and respiratory symptoms in our study. There was a downward trend in the prevalence of hydrocarbon poisoning in our study from 2002 to 2019 due to changing lifestyles and a decrease in kerosene use in houses (25). This result was in contrast to the findings from other countries, like India, Pakistan, and Kuwait (55-57).

4-2-4. Other poisonings

Envenomation is also a noteworthy intoxication among children, especially in Iran's southern parts (58-60). Although its frequency was not high in our meta-analysis, we noted an increasing trend from 2002 to 2019. Pesticide poisoning is always a concern, and if left untreated can lead to death. Children may consume them because pesticides may be stored in unsafe containers. Although it is still common in some developing countries, pesticide poisoning has a low prevalence in Iran and our study demonstrated a trend of decreasing exposures (61, 62).

4-3. Patient outcomes

One reason that children tend not to ingest large amounts of poisons is because many have unpleasant tastes. When these are ingested, rapid and effective management can prevent mortality and morbidity (63, 64). In our study, hospitalization, PICU admission, and mortality rate decreased from 2002 to 2019. The overall mortality rate in Iran was 0.8%, which is less than the rates reported from Kuwait (3.22%) and Turkey (2%) (57, 65). Increased knowledge of the parents, technological advances in PICUs, and expeditious management may be the reasons for these low rates (50).

4-4. Strengths and Limitations

The strengths of the present study include focusing on the hitherto poorly studied pediatric age group in Iran, addressing nearly all aspects of pediatric poisoning epidemiology such as geographical data,

time, and site of poisonings. We were able to accomplish this systematic review and meta-analysis because we located 27 separate studies from which to draw data. However, our study does have some limitations. Among these are relying on studies not recording all risk factors that made the patients susceptible to poisoning, including the location of the toxic agents, the number of siblings, and the parents' profession. Importantly, there is a high degree of heterogeneity in multiple endpoints. However, in prevalence studies, heterogeneity is inherently high due to the increased sample size. In order to resolve this, we performed subgroup analysis and meta-regression to determine the sources of heterogeneity among studies. Finally, poisoning was not discussed in terms of the spectrum of pediatric age groups, which could be addressed in future studies.

5- CONCLUSION

Overall, acute pediatric poisoning has been found to be the third most common injury in children under the age of 16 admitted to emergency departments in Iran. Furthermore, non-pharmaceutical toxicity was recognized as the most common cause of poisoning. But if we consider agents separately, pharmaceuticals, illicit drugs, and hydrocarbons were the most common causes of poisoning respectively. In contrast to the decreasing trend in hydrocarbons, pesticides, and pharmaceutical poisonings, we found an increase in opioid poisoning during our study period. Thus, training parents on keeping drugs in safe locations and child proof packages coupled with early referral to medical centers could continue the trend of decreasing pediatric morbidity and mortality resulting from poisonings. Moreover, knowledge of regional poisoning patterns can play an important role in planning for prevention, care, and treatment of the patients.

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