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The Prevalence of Hepatitis A in Iranian Children and Adolescents

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ABSTRACT

Background and Objective: Hepatitis A is considered a disease with high prevalence in developing countries, and the spread of this disease in children is considered an important alarm for societies. The aim of this systematic review and meta-analysis is to investigate the prevalence of hepatitis A in Iranian children and adolescents.

Methods: In this systematic review and meta-analysis, a systematic search was performed on PubMed, ScienceDirect, SID and Google Scholar databases using the keywords “Iranian children and adolescents” and “hepatitis A infection” in the time frame of 2000-2022. In this study, the age range of 1 to 19 years, which includes the prevalence reported in children and adolescents, was investigated.

Findings: In 39 studies with a sample size of 11,795 children and adolescents aged 1 to 19 years based on meta-analysis, the prevalence of hepatitis A in Iranian children and adolescents was reported as 37.3% (95% CI: 29.6-45.7). Based on subgroup analysis by age, in a total of 24 studies with a sample size of 6739 adolescents, the prevalence of hepatitis A in Iranian adolescents was 54.8% (95% CI: 47-62.4). In a total of 9 studies with a sample size of 2055 children, the prevalence of hepatitis A in Iranian children was reported as 14.6% (95% CI: 8.8-23.4).

Conclusion: The results of this study showed that the prevalence of hepatitis A is relatively high in Iranian children and adolescents, and accordingly, it requires the attention of health policy makers.

Keywords: *Hepatitis A, Children, Adolescents, Meta-Analysis.*

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Introduction

Hepatitis is considered a disease with high prevalence in the world. Although the prevalence of this disease is small in developed countries, it causes a heavy burden on governments and society in other countries (1). Depending on the severity of the disease, hepatitis is classified into acute and chronic types (2). Drugs, alcoholic beverages, viruses, and in general any factor that causes inflammation or replacement of liver cells with fatty tissue, play a role in causing hepatitis. Various types of viruses cause this disease, including types A, B, C, D, E and G (2, 3).

Type A is a hepatovirus and member of the Picornaviridae family (3) which has a polyribonucleotide chain containing 7470 ribonucleotides. Different types of this virus have different sequences, but all these sequences have the same antigens and are inhibited and destroyed by a similar type of antibody that the body makes against all of them. The antibody made against this virus usually remains permanently in the body's serum and provides permanent immunity to the person against this disease (2). Furthermore, this virus is surrounded by an icosahedral protein capsule; The presence of this strong but flexible capsule, in addition to playing a protective role by facilitating the entry of the virus into the liver cells, causes hepatitis A (4).

The most common way of transmission of this virus is fecal-oral. After entering the mouth, the viruses enter the internal environment through the pharynx or in the intestine and through the absorption of cells, and after entering the blood, they go to the liver. By entering the parenchymal and immune cells of the liver, they force the cell to reproduce on its own. Finally, some of the cells enter the bile and enter the feces through the excretion of bile matter, and this transfer cycle continues (5).

The clinical symptoms of this disease in adults include jaundice, severe liver necrosis, lethargy, fatigue, and increased body temperature; In rare cases, contracting this disease leads to death (3-5). In general, cells infected with viruses cause relative resistance in nearby cells against viral agents by secreting type 1 interferon. Since this resistance has a time limit, T lymphocytes and natural killer cells destroy cells infected with the virus in the next step, which causes inflammation of the liver (3-6).

The average incubation period of this virus in type A is about four weeks in human body, and due to the lack of clinical symptoms in the person, he/she will have the potential to spread this virus in the society in this period. Since this virus is resistant to heat, disinfectants and acidic environments to a large extent and can even maintain its pathogenic effect for a long time in bad environments such as sewage (4, 7), if a small part of the society is infected, it is expected that the transmission cycle of this disease continues with higher intensity and power (7).

The spread of this disease in children is considered an important alarm for societies. Although the death rate in children is very small and close to zero, but due to the occurrence of subtle symptoms or even the absence of clinical symptoms in children, the possibility of an endemic disease increases in communities that are unaware of the spread of this disease in children. Since the symptoms of this disease increase with age, we will see the deterioration of the situation in adults after a while. In explaining this, it can be said that unlike other types of hepatitis, hepatitis A is not chronic and does not cause long-term liver damage, and hepatitis A rarely causes sudden severe liver damage, especially in adults with chronic liver diseases. As a result, people with chronic liver disease are at risk of more severe disease and more complications with hepatitis A virus infection. Therefore, active vaccination of these patients against this infection is recommended (7). In the studies conducted in Iran and based on the quality assessment conducted in these studies (8) in different cities, the prevalence is 11.6% in Yasuj (9), the prevalence is 81.2% in the study conducted in Ahvaz (10) and in the study conducted in Sanandaj, the prevalence of 50% is reported (4), indicating diverse prevalences. Therefore, considering the wide range of articles in this field and the

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heterogeneity of information obtained from different articles, the aim of this systematic review and meta-analysis is to investigate the total prevalence of hepatitis A in Iranian children and adolescents.

Methods

In this systematic review and meta-analysis, systematic search of the investigated databases, screening of articles, selection of studies according to the criteria entered by the authors, extraction of data, analysis and finally presentation of the final report according to the PRISMA 2020 statement were carried out.

Search strategy: A systematic search of articles was conducted in PubMed, ScienceDirect, SID and Google Scholar databases and the keywords used for searching in this study were selected based on initial published studies and also (MESH Terms) in PubMed database. The keywords were selected according to the criteria of population, exposure, comparison and outcome (PECO). It includes the target population: Iranian children and adolescents, exposure: to hepatitis A infection, comparison: whether or not they have hepatitis A infection, outcome: the prevalence of hepatitis A infection in children and adolescents. The keywords selected in this study were in English and their Persian equivalents were used in Persian search databases. Also, Boolean search method was used to combine keywords. The search was done in different databases between January 2000 and November 2022.

Inclusion and exclusion criteria: In this review, cross-sectional studies that emphasized the prevalence of hepatitis A in Iranian children and adolescents who did not have any other diseases were considered, and case studies, case-control studies, cohort studies, clinical trials, systematic reviews and Meta-analyses were excluded.

Selection of studies and data extraction: After entering the collected studies into EndNote software, the reviews were started by the authors. The evaluations in this study were performed independently and they were blinded. At first, two authors checked the title and abstract of the articles according to the inclusion criteria. If there was a difference of opinion among the authors in relation to each of the reviewed articles in terms of inclusion criteria, the final opinion of the third person was considered.

Quality assessment: The quality of observational studies was evaluated using the STROBE checklist. This checklist examines various aspects of writing an article, including the title, statement of the problem, objectives of the study, type of study, statistical population, sampling method, data collection tool, and statistical analysis methods. Since the evaluations in this checklist are done using 32 different items, the studies were given a score in the range of 0-32. In this study, the articles that received a score of 16 and above from the authors were included as medium and high-quality studies (8).

Data analysis: The data extracted from the studies were entered into Comprehensive Meta-Analysis Version 2 (CMA 2) software. The heterogeneity of the studies was examined by I^2 test, and considering the obtained heterogeneity, random effects model was used to analyze the results. The publication bias in the studies was also evaluated by Egger test and funnel plot. Also, in order to investigate the effective factors in creating heterogeneity in studies, meta-regression test was used and $p<0.05$ was considered significant. Furthermore, in order to better display the data, they were reported according to different geographic regions based on the ArcMap software (ArcGIS 10.3).

Results

After searching in databases, 211 articles were found in PubMed database, 229 articles in ScienceDirect, 890 articles in Google Scholar, and 152 articles in SID, and finally, 1482 articles in all databases. After removing 988 duplicate articles and removing 411 articles based on the inclusion and exclusion criteria, 83

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articles were included in the secondary evaluation, and finally, after removing 44 articles unrelated to the subject, 39 articles were included in the meta-analysis (Figure 1 and Table 1).

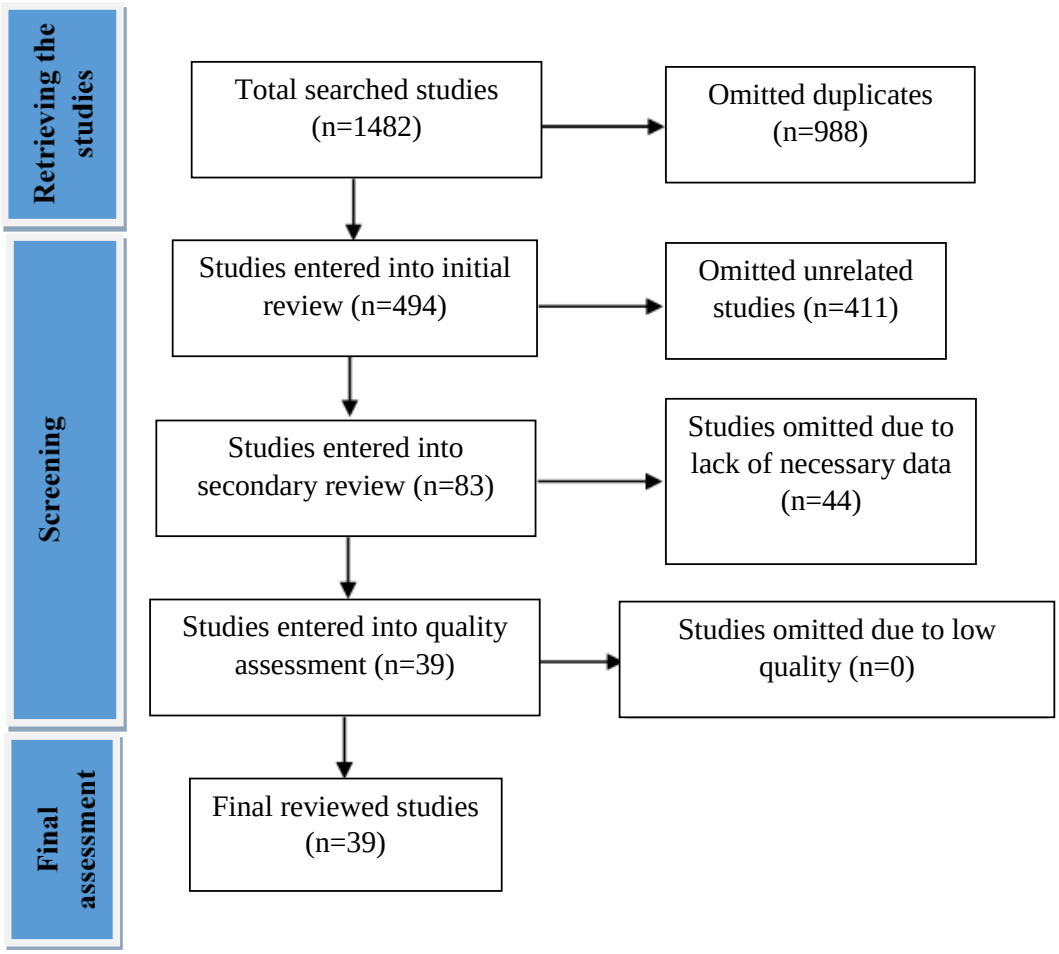


Figure 1. The results of the reviewing and retrieving studies and their screening based on PRISMA

Table 1. Data extracted from the reviewed studies

Row	First author (reference)	Year of publication	Age	Place of study	Sample size	Antibody titer HAV^+	Prevalence (%)	Quality assessment (STROBE)
1	Ghadimi-Moghaddam (9)	2020	1 month to 15 years	Yasuj	379	44	11.6	High
2	Shamsizadeh Hayat Davoudi (10)	2005	10-15 years	Ahvaz	800	649	81.2	Average
3	Yousefinejad (4)	2019	Below 20 years	Sanandaj	56	28	50	High
4	Ayatollahi (11)	2001	13-16 years	Yazd	226	208	92	Average
5	Alian (12)	2011	1-5 years	Sari	192	18	8.9	Average
6	Alian (12)	2011	5-15 years	Sari	330	54	15.8	Average

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7	Hoseini (13)	2015	10-18 years	-	2494	1596	64	Average
8	Mostafavi (14)	2016	10-18 years	Ardabil	205	138	67.6	High
9	Mostafavi (14)	2016	10-18 years	West Azerbaijan	142	95	67.2	High
10	Mostafavi (14)	2016	10-18 years	Fars	100	50	50	High
11	Mostafavi (14)	2016	10-18 years	Guilan	133	86	64.9	High
12	Mostafavi (14)	2016	10-18 years	Esfahan	147	99	67.4	High
13	Mostafavi (14)	2016	10-18 years	Kermanshah	231	142	61.5	High
14	Mostafavi (14)	2016	10-18 years	North Khorasan	120	77	64.2	High
15	Mostafavi (14)	2016	10-18 years	Khorasan Razavi	167	88	52.8	High
16	Mostafavi (14)	2016	10-18 years	South Khorasan	125	76	61.3	High
17	Mostafavi (14)	2016	10-18 years	Khuzestan	195	115	59.4	High
18	Mostafavi (14)	2016	10-18 years	Kurdistan	145	76	52.8	High
19	Mostafavi (14)	2016	10-18 years	Lorestan	146	107	73.7	High
20	Mostafavi (14)	2016	10-18 years	Markazi	93	73	78.8	High
21	Mostafavi (14)	2016	10-18 years	Tehran	250	144	57.9	High
22	Mostafavi (14)	2016	10-18 years	Yazd	145	98	67.6	High
23	Mostafavi (14)	2016	10-18 years	Zanjan	92	55	60.2	High
24	Asaei (15)	2015	6-15 years	Shiraz	356	65	18.3	Average
25	Behzadi (16)	2019	Below 14 years	Hormozgan	30	1	5.3	High
26	Sofian (17)	2010	6-20 years	Tehran	1065	656	61.6	Average
27	Kazemi (18)	2007	7-10 years	Zanjan	273	121	44.3	Average
28	Namakin(19)	2018	7-18 years	Birjand	300	111	37	High
29	Ataei (1)	2007	6-19 years	Esfahan	235	25	10.6	Average
30	Noroozi (20)	2011	15-19 years	Qom	128	32	25	Average
31	Taghavi Ardakani (21)	2013	1-15 years	Kashan	666	26	3.9	Average
32	Saffar (22)	2012	1-2 years	Savadkuh	316	101	32.1	Average
33	Saffar (22)	2012	3-6 years	Savadkuh	254	65	25.8	Average
34	Saffar (22)	2012	1-10 years	Savadkuh	201	41	20.4	Average
35	Saffar (22)	2012	11-17 years	Savadkuh	115	13	11.7	Average
36	Ramezani (23)	2018	1-5 years	Tehran	228	13	5.7	High
37	Ramezani (23)	2018	6-10 years	Tehran	231	4	1.7	High
38	Ramezani (23)	2018	11-15 years	Tehran	283	12	4.2	High
39	Ramezani (23)	2018	16-19 years	Tehran	201	11	5.5	High

After reviewing 39 studies with a sample size of 11,795 children and adolescents aged 1 to 19 years, the I^2 heterogeneity test showed high heterogeneity (I^2:98.3) and based on this, the random effects model was used to analyze the results. Therefore, according to the meta-analysis, the prevalence of hepatitis A in Iranian children and adolescents was reported as 37.7% (95% CI: 29.6-45.7) (Figure 2).

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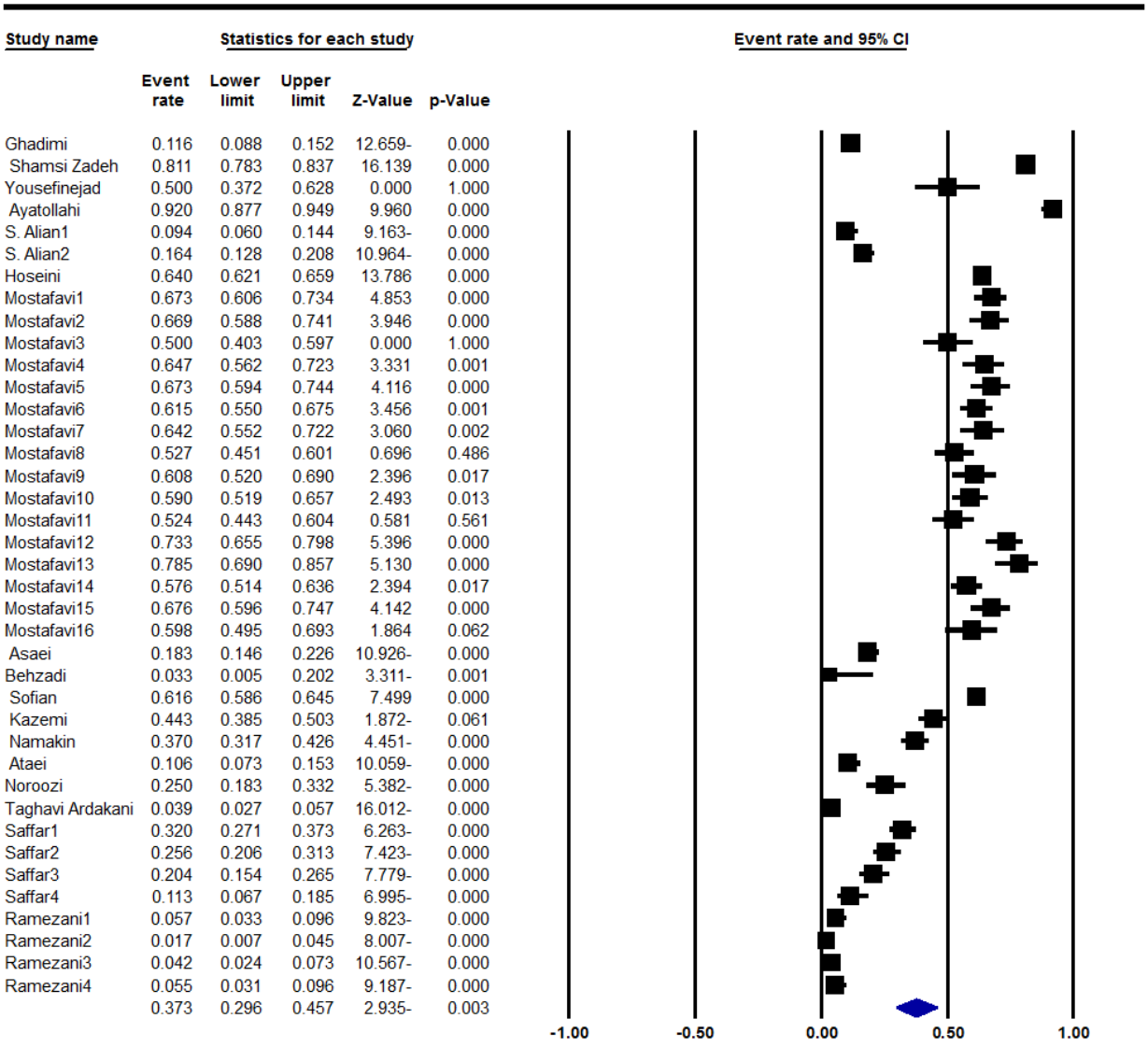


Figure 2. Forest plot of hepatitis A prevalence in Iranian children and adolescents based on random effects model

According to the reported age range, the overall prevalence was reported in the form of hepatitis A prevalence in Iranian children and adolescents. But for a more precise range, subgroup analysis was also performed based on age range. In a total of 24 studies with a sample size of 6739 adolescents, the prevalence of hepatitis A in Iranian adolescents was 54.8% (95% CI: 47-62.4) and in a total of 9 studies with a sample size of 2055 children, the prevalence of hepatitis A in Iranian children was 14.6% (95% CI: 8.8-23.4). Also, checking the publication bias in the studies through the Egger test indicates the existence of publication bias in the studies (p=0.001), on the basis of which the reported prevalence based on the meta-analysis should be examined with caution (Figure 3).

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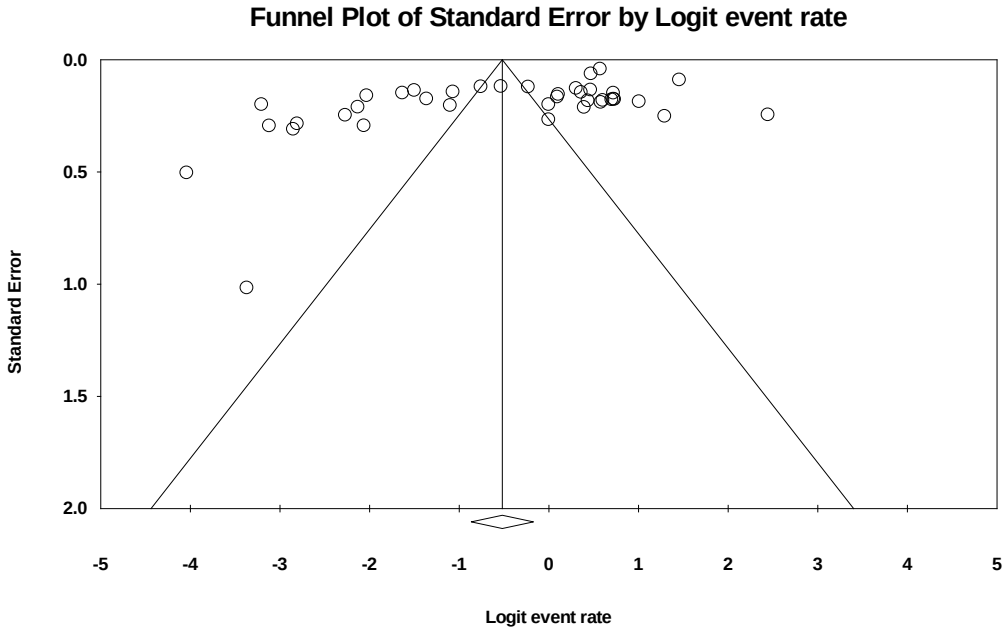


Figure 3. Funnel plot of the publication bias in the reviewed studies

In examining the factors affecting the heterogeneity of studies and investigating the effect of sample size on this heterogeneity, it was reported that with the increase in sample size, the prevalence of hepatitis A in Iranian children and adolescents increased (p=0.05) (Figure 4). Moreover, with the increase in year of publication, the prevalence of hepatitis A in Iranian children and adolescents decreased (p=0.05) (Figure 5). Based on the subgroup analysis, the reported prevalence was 36.7% in the north of the country (95% CI: 6.23-52.1), 28.4% in the center of the country (95% CI: 15.3-46.6), 54.3% in the west of the country (95% CI: 37.2-70.4), 44.5 in the east of the country (95% CI: 30-60) and 3.3% in the south of the country (95% CI: 0.5-20.2), which was reported based on ArcMap software (Figure 6).

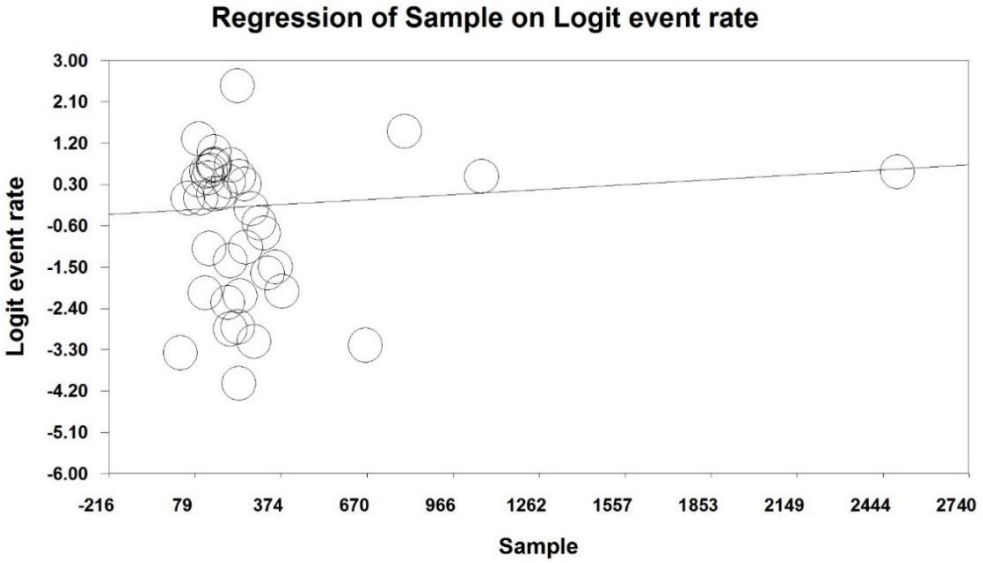


Figure 4. Meta-regression of the effect of sample size on the prevalence of hepatitis A in Iranian children and adolescents

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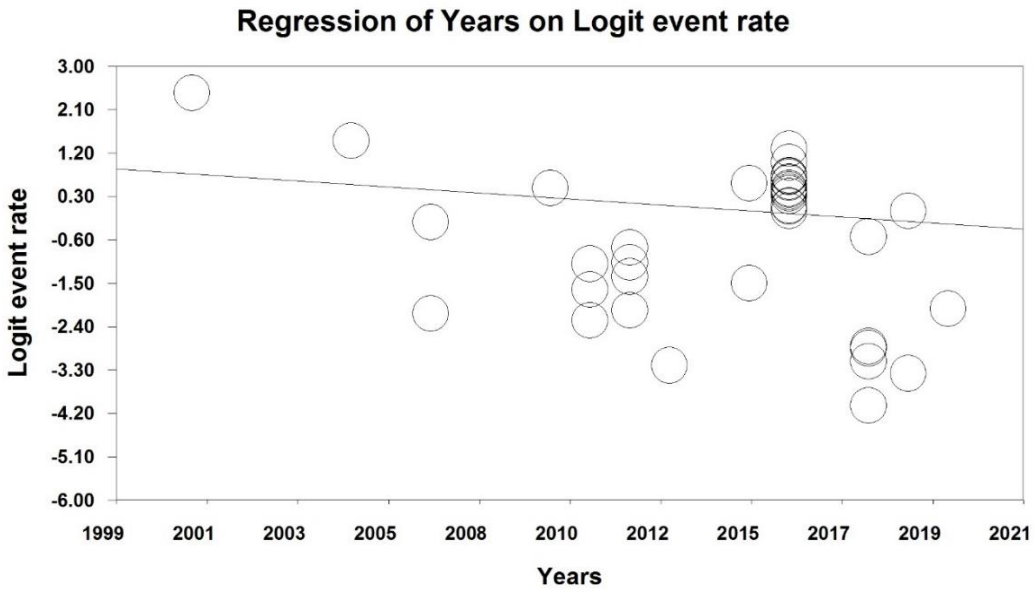


Figure 5. Meta-regression of the effect of the year of publication on the prevalence of hepatitis A in Iranian children and adolescents

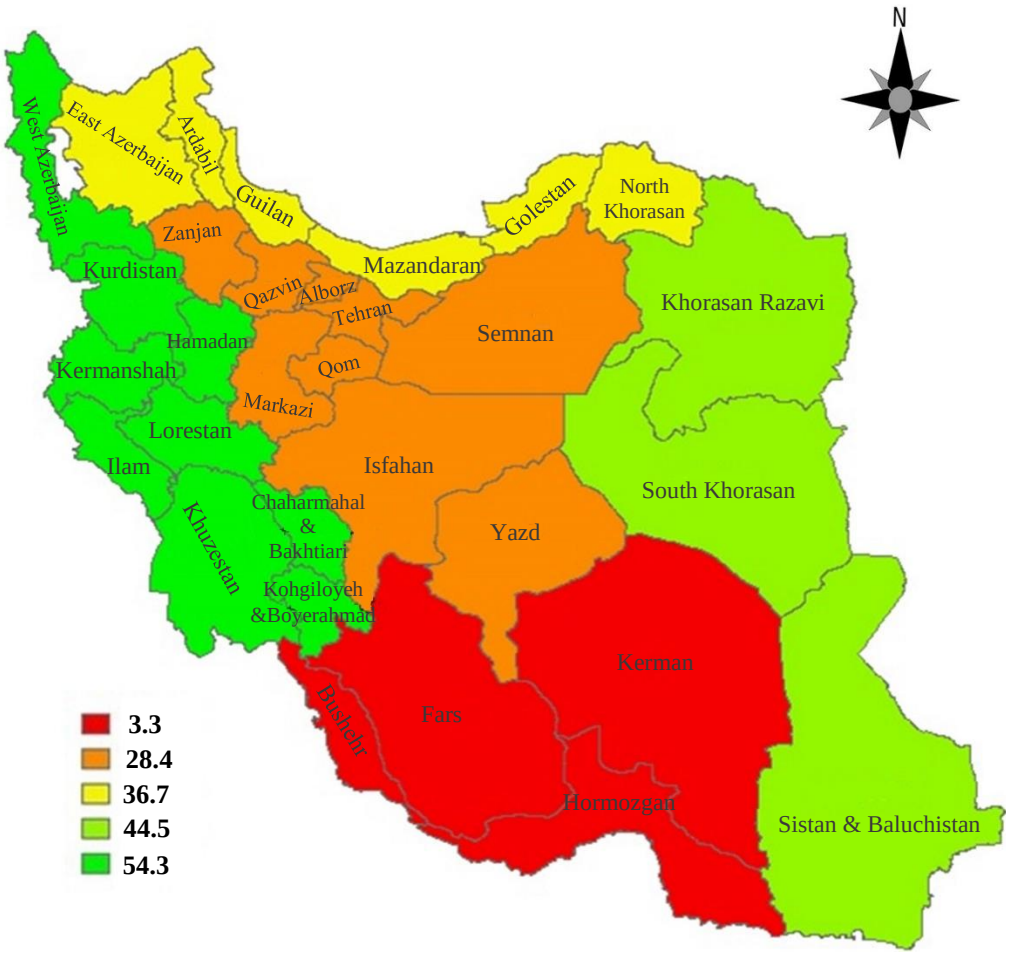


Figure 6. Prevalence of hepatitis A in Iranian children and adolescents by regions of the country

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Discussion

According to the data collected in the present study, the prevalence of hepatitis A in Iranian children and adolescents was reported as 37.3%. A study conducted in Peru on children aged one to fifteen years reported a prevalence of 50.5% (24). In this age group, a study was also conducted in Turkey, which stated the overall prevalence of 47.2% (25). In Moroccan children and adolescents aged six months to fourteen years, this rate was 51% (26). A study conducted by Stroffolini et al. on children aged six to thirteen years in an Italian city shows that the prevalence of this virus is 10.6% (27). In a study conducted in Portugal, this statistic reached 27.9% in children aged six to nineteen (28). The most important difference in the results of different studies is the different sample size, year of conducting the studies, different age groups and different races in studies conducted around the world (27-30).

In a systematic review, it was reported that the data related to anti-HAV IgM serum prevalence show the risk of acute hepatitis A infection among all age groups. The findings of this study suggest that priority should be given to collecting HAV seroprevalence data and reassessing current hepatitis A control strategies in Africa to prevent future outbreaks (30). In developing countries, hepatitis A is still a common disease, and the lower the economic and social conditions, the lower the age of contracting this disease. A prevalence between 4.7-6.3% has been reported in children and adolescents of that country (30).

In a study conducted in Iran, factors such as gender, education, drug use, race and ethnicity showed a significant relationship with the prevalence of this disease (31). Groups that are at risk and need control and diagnostic measures include children in kindergartens and schools, as well as injecting drug users and users of contaminated water and food (30).

The results of various studies report that hepatitis A disease has a global spread and the best prevention method is the administration of immunoglobulin as well as informing people about the ways of transmission and prevention methods (31). Health improvements in the past years have caused the prevalence of this disease to decrease significantly in the world (31). Furthermore, despite the high rate of prevalence in Asian countries, the Middle East and Latin America compared to developed countries, this rate shows a significant decrease compared to previously reported statistics due to the improvement of health quality, use of safe drinking water and proper waste disposal (31).

It is suggested that the health policy makers educate children about health issues and promote a healthy lifestyle in schools in order to prevent this virus, so that in the future, we will see a decrease in the spread of hepatitis A virus, rather than high costs imposed on the healthcare sector. The results of our study show that the prevalence of hepatitis A in Iranian children and adolescents is high and requires the attention of health policy makers and actions to educate families about health, teach the principles of personal hygiene methods, and also raise public awareness about this disease. In this regard, mass media will make preventive measures more effective.

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