Seroprevalence of Hepatitis E Virus in Iran:
A Systematic Review and Meta-analysis

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ABSTRACT

BACKGROUND

Hepatitis E virus (HEV) is one of common causes of viral hepatitis worldwide with higher prevalence in tropical and subtropical regions. Although epidemics of HEV have been reported from Iran, there are variable reports of this infection out of epidemics from different parts of Iran. This study aimed to determine the seroprevalence of HEV in Iran.

METHODS

In this systematic review and meta-analysis we searched PubMed, Scopus, Science direct, Google Scholar, Scientific Information Databank (SID), IranMedex, and Magiran for all relevant studies published in either English or Persian languages, up to 2015. Pooled seroprevalence estimates with a DerSimonian-Laird random-effects model were calculated. Statistical heterogeneity among the included studies was evaluated by Cochrane Q statistic and I2.

RESULTS

38 studies fulfilled the inclusion criteria compromising 18461 participants. The pooled seroprevalence rate of HEV in Iran was estimated about 10% (95% CI=0.09-0.12) with maximum and minimum of 46% (95 % CI=0.42-0.50), and 0.01% (95 % CI=0.000-0.002), respectively.

CONCLUSION

HEV is common in Iran although the prevalence is lower than some neighbor countries.

KEYWORDS

Hepatitis E Virus; Seroprevalence; Meta-analysis; Systematic review; Iran

INTRODUCTION

Hepatitis E virus (HEV) is a common cause of community acquired viral hepatitis.[1] The infection is endemic in many developing countries [2] with a prevalence of as high as 50% .[3] In non-endemic countries, the prevalence varies between 1% to 20% .[4] This virus like hepatitis A does not lead to chronic hepatitis or carrier state in immunocompetent hosts. A special feature of HEV is its high mortality among pregnant women, which may reach up to 20-25%

of cases.[5] The infection could also become chronic in immunocompromised hosts specially recipients of solid organ transplantation.[6]

HEV has been reported worldwide, but it is more common in Central and South-West Asia.[5] At least two epidemics of HEV have been reported from Iran in 1990 in Kermanshah province in western border of the country and in 1992 in Chahar Mahal and Bakhtiari province in central Iran.[7]

Out of these epidemics there are different reports of HEV prevalence in Iran.[8] As HEV could cause both acute hepatitis in general population, and chronic disease in immunocompromised hosts, it is of utmost importance to have an estimate of this infection in the whole nation. This is not only of importance for Iran but could also help to better understand the epidemiology of this infection in other transitional societies. This study aimed to determine the seroprevalence of HEV in Iran in a systematic review and meta-analysis.

MATERIALS AND METHODS

Databases:

We performed a literature search on PubMed, Scopus, Science direct, Google Scholar, Scientific Information Databank (SID), IranMedex, and Magiran till March 2015 for HEV. Studies published in either English or Persian languages were included in the systematic review. The references of all selected published articles from the above databases were also searched to find more relevant studies. The abstract book of national and international conferences with the topic of liver disease, hepatology, hepatitis, and infectious diseases were also searched for HEV.

Search strategy:

Search strategy was based both on Medical Education Subject Headings (Mesh) terms as well as free text words and words in the title or abstract of studies. We used the following search strategy "HEV" OR "Hepatitis E Virus" AND "seroepidemiology" OR "Epidemiology" OR "Prevalence" AND "Iran", in Persian or English languages.

Study Selection:

The inclusion criteria were: studies that had data indicating the seroprevalence of HEV using standard meth-

ods. The exclusion criteria were: studies that did not clearly separate the prevalence of HEV form other viral diseases, studies with unknown sample origins, studies with overlapping time, subjects and place of sample collection, case reports and case series, studies focusing on treatment, studies reporting on HEV among patients with non-Iranian nationality.

Data Extraction:

Two investigators (Masoud.Behzadifar and Meysam. Behzadifar) independently applied inclusion criteria and selected studies and extracted the data. Data from the included studies, including the name of the first author, year of publication, location of study, age, sex, type of study, sample size, and number of the infected cases and conflicts were recorded for further analysis.

Assessment of studies:

STROBE questionnaire was used [9] to assess the quality of the studies. All studies were scored by two investigators (Gholamreza.Ghoreishinia, Abouzar.Keshavarzi) separately and mean score was calculated for each study. The studies with score less than 7.5 were considered as poor quality. For 38 articles in this review, the obtained score was 18.11.

Statistical Analysis:

In studies where the SE (standard error) was not reported we calculated it from the prevalence using the following formula:

$SE = \sqrt{(P(1-P)/N)}$ (P=prevalence, N=sample size)

Confidence interval (CI) 95% = $P \pm 1.96 \times SE$

Studies were estimated with respect to the prevalence with CI and P value. Statistical heterogeneity among the included studies were measured by Cochrane Q statistic and I2.10 Rank of I2 was predefined as a Cochrane Q of 25%=low heterogeneity, 50%=medium heterogeneity, and 75%= high heterogeneity, respectively. P<0.05 was considered as statistically significant. We considered studies reporting HEV in Iran using random effects model. Meta-regression analysis of the variables of each study such as sample size, and the year of publication, sex, type of study, and the subgroup analyses were done when possible. Publication bias was assessed by Egger's [11] and Begg's [12] tests and graphically depicted by a funnel plot. All data analy-
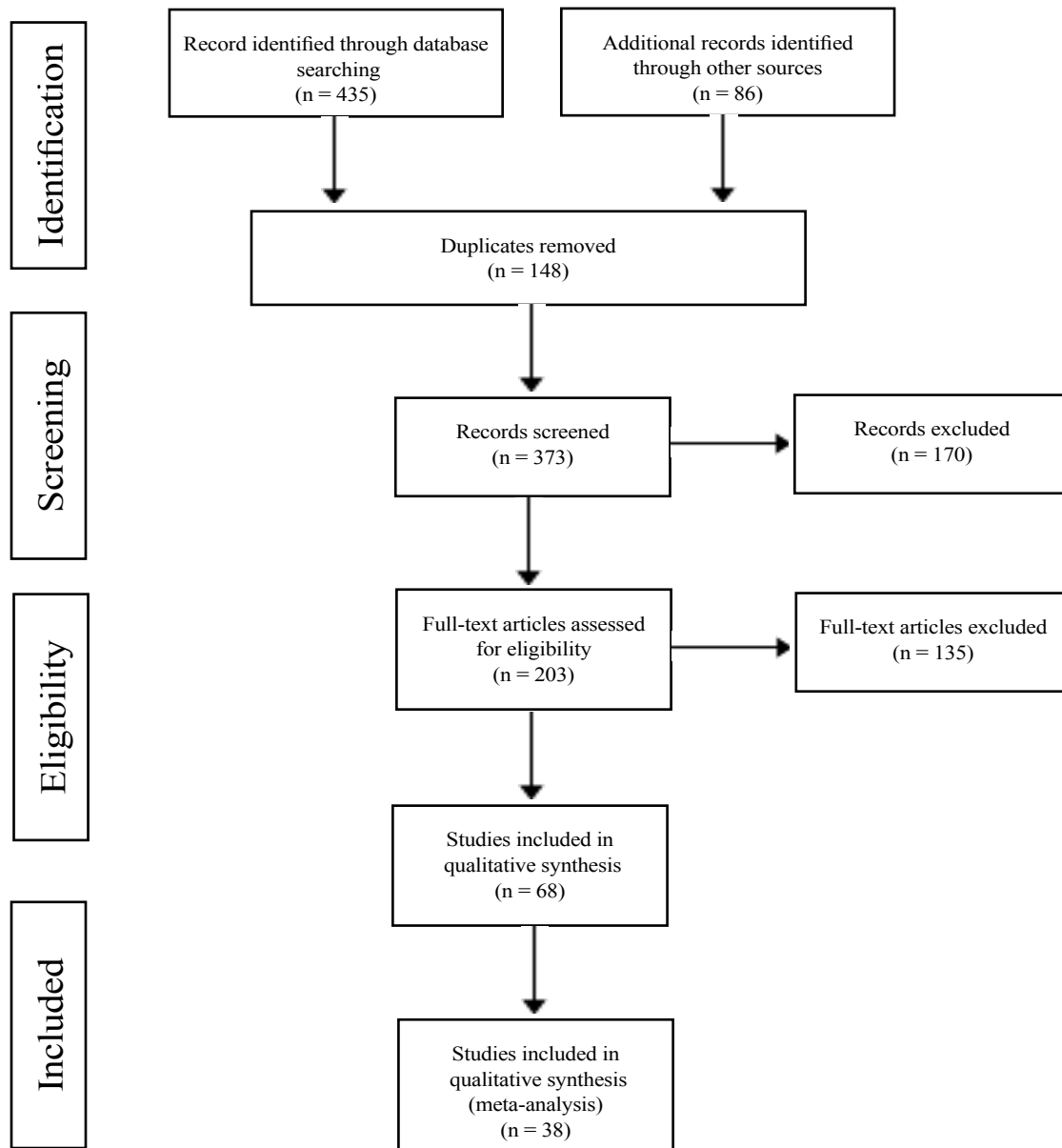
Fig.1: Flowchart of search and studies selection

ses were conducted with STATA software Version 11.0 (Stata Crop LP, College Station, Texas, USA).

RESULTS

Based on our search strategy described above 521 articles were initially retrieved. Of them, 148 articles were excluded as duplicate publications. We carefully read the titles and abstracts of the remaining 373 articles and further 170 records were excluded based on the exclusion criteria mentioned above. After reading the full text of the remaining 203 articles, an additional 135 articles were further found to have one of the exclusion criteria. Finally, 38 studies[13-50] were found eligible for final analysis and were used for this meta-analysis. This systematic review and meta-analysis is reported according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines 51 are shown in figure 1.

Included studies consisted of cross sectional and case control designs. The characteristics of all studies are

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

Author	Year	Sample	Location	Sample population	Sex	Type of study	Age
Eini	2015	153	Hamedan	Hemodialysis patients	M/F	Cr-Sec	>40 - <60
Beladi Mousavi	2014	47	Ahvaz	Hemodialysis patients	M/F	Cr-Sec	55.27 ± 8.1
Rostamzadeh	2013	136	Urmia	Pregnant Women	F	Cr-Sec	25.12 ± 4.91
Ahmadi	2013	1582	Mashhad	General population	M/F	Cr-Sec	29.06 ± 18.513
Ehteram	2013	530	Arak	Blood donors	M/F	Cr-Sec	18-50
Zekavat	2013	356	Jahrom-Shiraz	Hemodialysis patients	M/F	Cr-Sec	24-80
Rostamzadeh	2011	91	Urmia	Renal Transplant Recipients	M/F	Cr-Sec	35.4 ± 14.5
Sepanlou	2010	1423	Tehran-Golestan	General population	M/F	Cr-Sec	37.9±13.4
Mobaien	2013	93	Zanjan	Hemodialysis patients	M/F	Cr-Sec	57.0 ± 18.5
Saffar	2009	1102	Sari	General population	M/F	Cr-Sec	2–25
Taremi	2008	1824	Nahavand	General population	M/F	Cr-Sec	34.7 ±19.5
Ataei	2009	816	Isfahan	General population	M/F	Cr-Sec	6 - >50
Assarehzadegan	2008	400	Khuzestan	Blood donors	M/F	Cr-Sec	18-60
Taremi	2007	399	Tabriz	Blood donors	F	Cr-Sec	31.4±9.8
Taremi	2005	324	Tabriz	Hemodialysis patients	M/F	Cr-Sec	53.5 ± 15.1
Ramezani	2013	152	Tehran	Patients HIV	M/F	Cr-Sec	38.73 ± 0.78
Mohebbi	2012	551	Tehran	General population	M/F	Cr-Sec	41.28 ±16.96
Nazer	2012	400	Khorramabad	General population	M/F	Cr-Sec	36
Tahamtan	2013	150	Gorgan	Hemodialysis patients	M/F	Cr-Sec	>30 - <70
Ghadir	2007	697	Golestan	General population	M/F	Cr-Sec	43±15.1
Moradi	2010	1200	Gorgan	Pregnant Women	F	Cr-Sec	27±6.3
khoshbaten	2001	324	Tabriz	Hemodialysis patients	M/F	Cr-Sec	53±15.11
Gachkar	2005	399	Tabriz	Blood donors	F	Cr-Sec	40.7±12.4
shavakhi	2007	200	Tehran	liver cirrhosis	M/F	Ca-Con	ca=43±14.6,cl=44.9±17.5
Eslamifar	2012	184	Tehran	Patients HIV	M/F	Ca-Con	38.82±0.8
Rezazadeh	2006	280	Hamedan	Blood donors	M/F	Cr-Sec	>40 - <40
Alavi	2007	228	Ahvaz	Drug addiction	F	Cr-Sec	ca=33.24±7.59,cl=31.2±7.59
Sharif	2013	558	Kashan	Children	M/F	Cr-Sec	1 to 15
Noroozi	2012	740	Qom	General population	M/F	Cr-Sec	>15
Mohebbi	2012	493	Tehran	General population	M/F	Cr-Sec	40.98±17.10
Ghorbani	2007	800	Tehran	Military	M	Cr-Sec	19±1
Somi	2007	200	Azerbaijan	Blood donors	M/F	Cr-Sec	48.26±18.19
Pourahmad	2009	43	Jahrom	Hemodialysis patients	M/F	Cr-Sec	59.3 ± 14.4
Shamsizadeh	2009	566	Ahvaz	Children	M/F	Cr-Sec	6 to 15
Aminiafshar	2004	90	Tehran	Blood donors	M/F	Cr-Sec	31.8±11
Keramat	2014	262	Hamedan	Drug addiction	M/F	Cr-Sec	IDUs=35.57 ± 8.13,non IDUs=31.57 ± 8.19
Joulaei	2015	158	Shiraz	Patients with HIV	M/F	Cr-Sec	39.1 ± 8
Farshadpour	2015	510	Ahvaz	community-based	M/F	Cr-Sec	45.89 ± 14.63

M/F: Male – Female, Cr-Sec: Cross – Sectional, Ca-Con: Case-Control, IDUs= Injection Drug Users
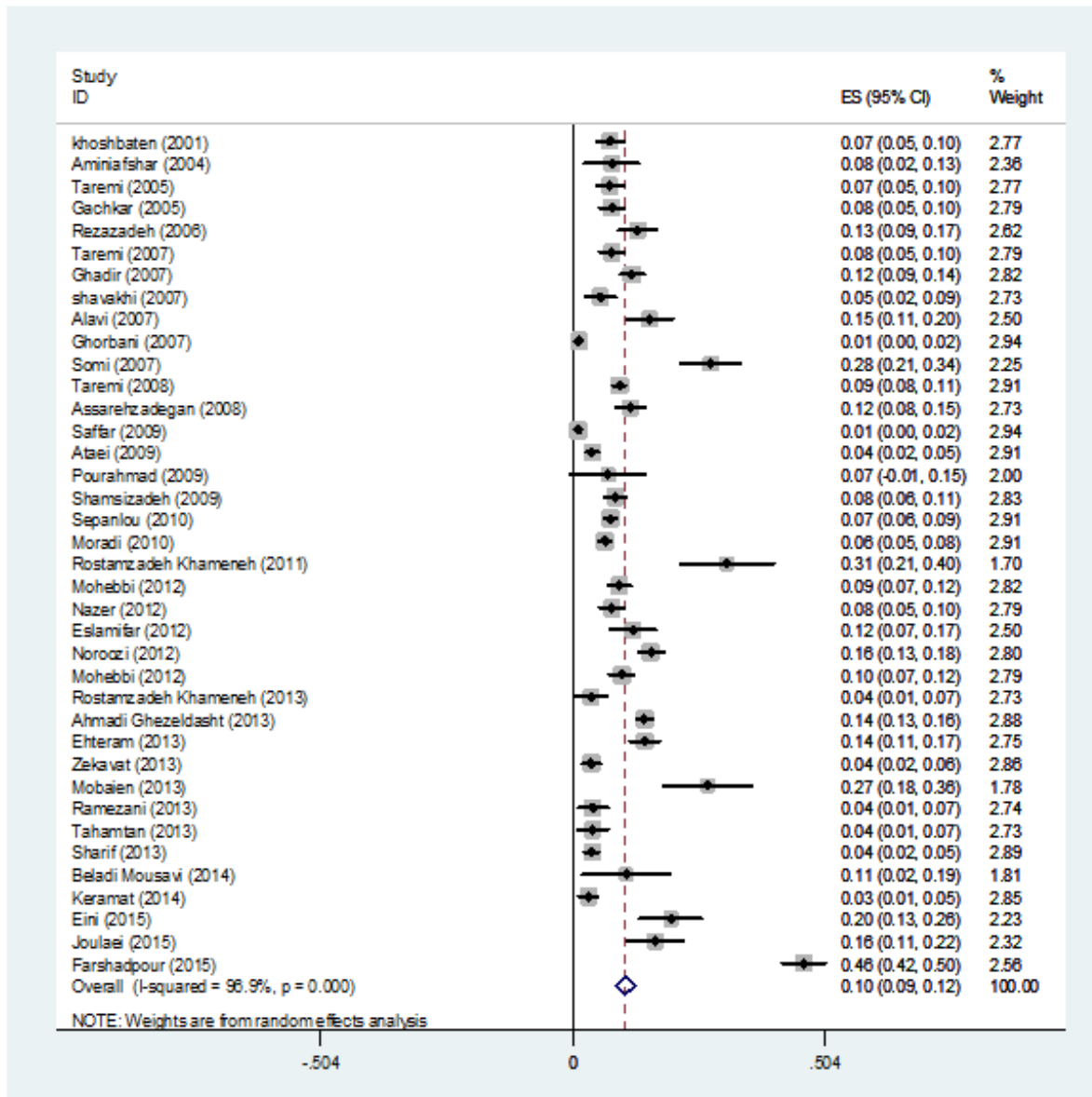
Fig.2: Forest plots of seroprevalence rate of hepatitis E virus infection in Iran and 95% confidence interval

demonstrated in table1.

The total sample size included 18,461 participants from 38 studies. The result of Q Cochran test (chi squared=1194.08, D.F =37, p=0.000 and I2=96.9 %.) indicated strong heterogeneity among the 38 studies. According to the random model analysis, the overall seroprevalence of HEV in Iran was estimated 10% (95 % CI=0.09-0.12) with a maximum and minimum value of 46% (95% CI=0.42-0.50), and 0.01% (95 % CI=0.000-0.002), respectively (figure 2).

In all included studies, individuals were entered ran-

domly. The maximum seroprevalence rate of 46% was reported by Farshadpour from Ahvaz (2015) in southwest border of Iran and Iraq. The minimum seroprevalence rate of 1% was reported by Ghorbani in Tehran and by Saffar in Yazd located in the central desert of Iran in 2010 and 2006, respectively. Seroprevalence rate in both sexes (female-male) was 11% (95% CI=0.09-0.14), the seroprevalence rate in female patients was 8% (95 % CI=0.05-0.10), and the seroprevalence in male patients was 1% (95% CI=0.00-0.02) (figure 3A). The seroprevalence rate was 11% (95% CI=0.09-0.13)
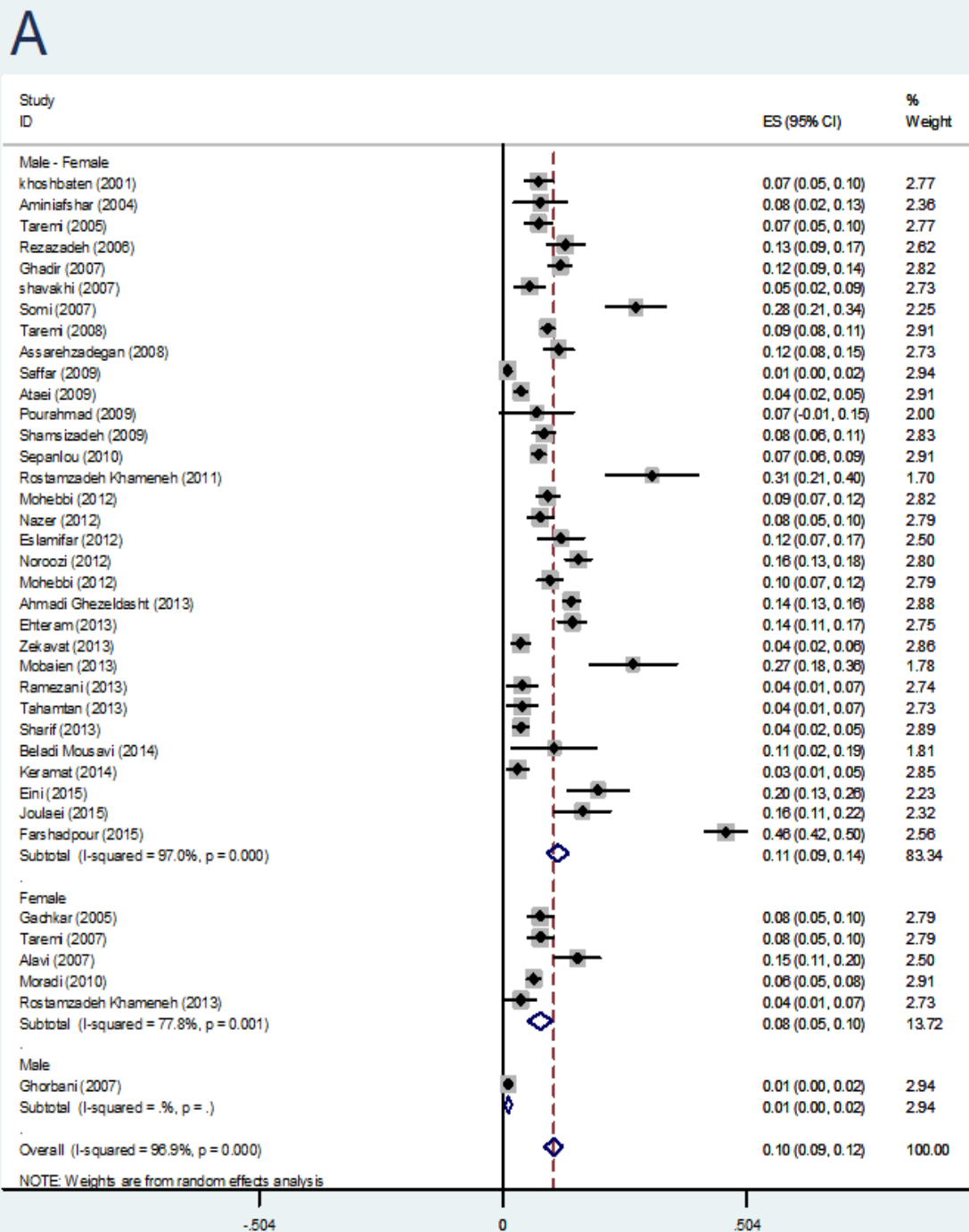
Fig. 3A : Forest plots of hepatitis E virus prevalence in Iran by sex (A)

in cross sectional studies and 8% (95% CI=0.02-0.15) in case control studies (figure 3B).

To assess publication bias by a funnel plot, we used

Begg's and Egger test. The results of Begg's was *p*=0.068 and Egger tests was *p*=0.000. This finding indicates a significant publication bias (figure 4).

B

Study ID	ES (95% CI)	% Weight
Cross-Sectional		
khoshbaten (2001)	0.07 (0.05, 0.10)	2.77
Aminiafshar (2004)	0.08 (0.02, 0.13)	2.36
Taremi (2005)	0.07 (0.05, 0.10)	2.77
Gachkar (2005)	0.08 (0.05, 0.10)	2.79
Rezazadeh (2006)	0.13 (0.09, 0.17)	2.62
Taremi (2007)	0.08 (0.05, 0.10)	2.79
Ghadir (2007)	0.12 (0.09, 0.14)	2.82
Alavi (2007)	0.15 (0.11, 0.20)	2.50
Ghorbani (2007)	0.01 (0.00, 0.02)	2.94
Somi (2007)	0.28 (0.21, 0.34)	2.25
Taremi (2008)	0.09 (0.08, 0.11)	2.91
Assarehzadegan (2008)	0.12 (0.08, 0.15)	2.73
Saffar (2009)	0.01 (0.00, 0.02)	2.94
Ataei (2009)	0.04 (0.02, 0.05)	2.91
Pourahmad (2009)	0.07 (-0.01, 0.15)	2.00
Shamsizadeh (2009)	0.08 (0.06, 0.11)	2.83
Sepanlou (2010)	0.07 (0.06, 0.09)	2.91
Moradi (2010)	0.06 (0.05, 0.08)	2.91
Rostamzadeh Khameneh (2011)	0.31 (0.21, 0.40)	1.70
Mohebbi (2012)	0.09 (0.07, 0.12)	2.82
Nazer (2012)	0.08 (0.05, 0.10)	2.79
Noroozi (2012)	0.16 (0.13, 0.18)	2.80
Mohebbi (2012)	0.10 (0.07, 0.12)	2.79
Rostamzadeh Khameneh (2013)	0.04 (0.01, 0.07)	2.73
Ahmadi Ghezeldasht (2013)	0.14 (0.13, 0.16)	2.88
Ehteram (2013)	0.14 (0.11, 0.17)	2.75
Zekavat (2013)	0.04 (0.02, 0.06)	2.86
Mobaien (2013)	0.27 (0.18, 0.36)	1.78
Ramezani (2013)	0.04 (0.01, 0.07)	2.74
Tahamtan (2013)	0.04 (0.01, 0.07)	2.73
Sharif (2013)	0.04 (0.02, 0.05)	2.89
Beladi Mousavi (2014)	0.11 (0.02, 0.19)	1.81
Keramat (2014)	0.03 (0.01, 0.05)	2.85
Eini (2015)	0.20 (0.13, 0.26)	2.23
Joulaei (2015)	0.16 (0.11, 0.22)	2.32
Farshadpour (2015)	0.46 (0.42, 0.50)	2.56
Subtotal (I-squared = 97.0%, p = 0.000)	0.11 (0.09, 0.13)	94.77
.		
Case-Control		
shavakhi (2007)	0.05 (0.02, 0.09)	2.73
Eslamifar (2012)	0.12 (0.07, 0.17)	2.50
Subtotal (I-squared = 80.0%, p = 0.025)	0.08 (0.02, 0.15)	5.23
.		
Overall (I-squared = 96.9%, p = 0.000)	0.10 (0.09, 0.12)	100.00

NOTE: Weights are from random effects analysis

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           -.504            0            .504
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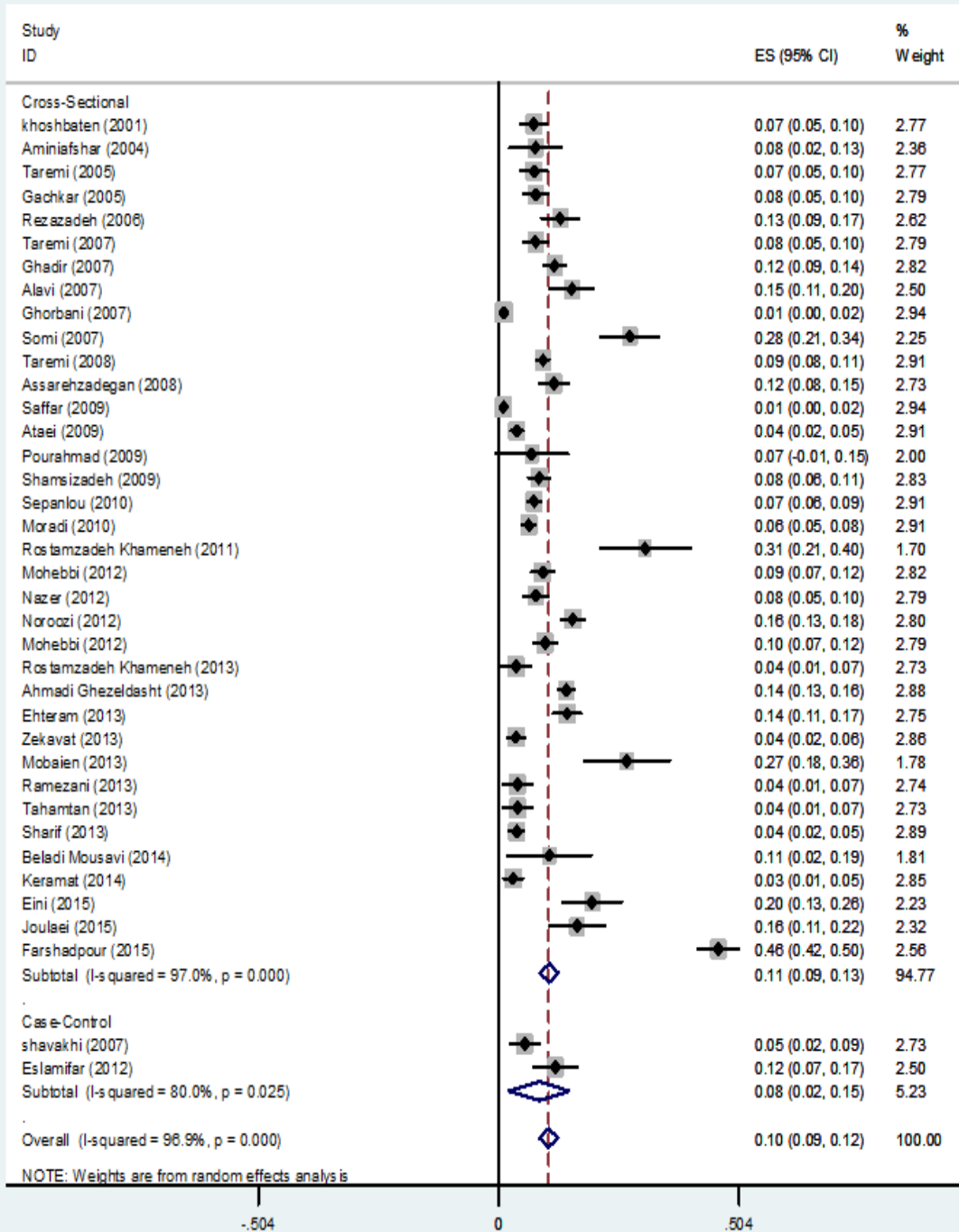
Fig. 3B : Forest plots of hepatitis E virus prevalence in Iran by study type (B)

Table 2: Characteristics of study population and percentage in 38 studies included in meta-analysis of hepatitis E virus prevalence in Iran

Subgroups	No. of studies	Sample size	Prevalence % (95%CI)	Heterogeneity	
				I²	*p*
Blood donors	7	2298	12.3% [0.087 to 0.160]	87.0%	0.000
General population	11	10138	12.1 [0.078 to 0.164]	98.8%	0.000
Military	1	800	11% [0.004 to 0.019]	-	-
Patients with HIV	3	494	10.5% [0.029 to 0.181]	88.6%	0.000
Hemodialysis patient	8	1490	9.5% [0.059 to 0.132]	85.6%	0.000
Drug addiction	2	490	9% [-0.030 to 0.211]	95.5%	0.000
Children	2	1124	6% [0.014 to 0.107]	90.9%	0.000
liver cirrhosis	1	200	5.5% [0.023 to 0.087]	-	-
Pregnant women	2	1336	5.4% [0.029 to 0.079]	56.1%	0.131
Renal transplant recipients	1	91	3.8% [0.213 to 0.403]	-	-

Seroprevalence of HEV decreased by reduced sample size and later publication year but it was not significant. In table 3, a summary of data related to meta-regression is shown.

Table 3: Result of Meta- regression investigating the effect of sample size and year on seroprevalence of hepatitis E virus in Iran

	Coefficient	Standard error	T	*p*	L CI	UCI
Sample size	-.0000275	.0000329	-0.84	0.409	-.0000942	.0000392
Year	.005872	.0041553	1.41	0.166	-.0025636	. .0143076
Cons	-11.68132	8.353102	-1.40	0.171	-28.63902	5.276378

LCI: Lower Confidence Interval   UCI: Upper Confidence Interval   Cons=Index is calculated in this study, SE (Standard Error)

DISCUSSION

Studies in different parts of the world show a wide variation in the seroprevalence of HEV. The present study estimated the overall seroprevalence of HEV in Iran as 10%. There was a wide variation in HEV seroprevalence in the included studies in this meta-analysis. The highest report belonged to Ahvaz, the center of Khozestan province in our border with Iraq. The population in this region travel frequently to Iraq. There are several reports of endemicity of HEV in Iraq even in Baghdad, the capital.[52,53] Interestingly although the general trend of the publications shows a lower prevalence in recent years, the situation is reverse in Khozestan and Ahvaz showing an increase in the prevalence from 11.5% in a study in 2008 to 46% in 2015. This corresponds to a period of more mobility along Iran / Iraq border in recent years. The disposal of waste water in Ahvaz also has faced many challenges especially after the recent cycles of drought and flood in the province in contrast to the lowest prevalence reported from Tehran with much better sanitation. The other region with much lower prevalence is Yazd with its surrounding deserts and dry weather.

In our meta-analysis the prevalence of HEV among children and pregnant women was 6% and 5.4% respectively. This is probably because of higher exposure of people with advanced age but as we had limited data we could not confirm the effect of age on seroprevalence.

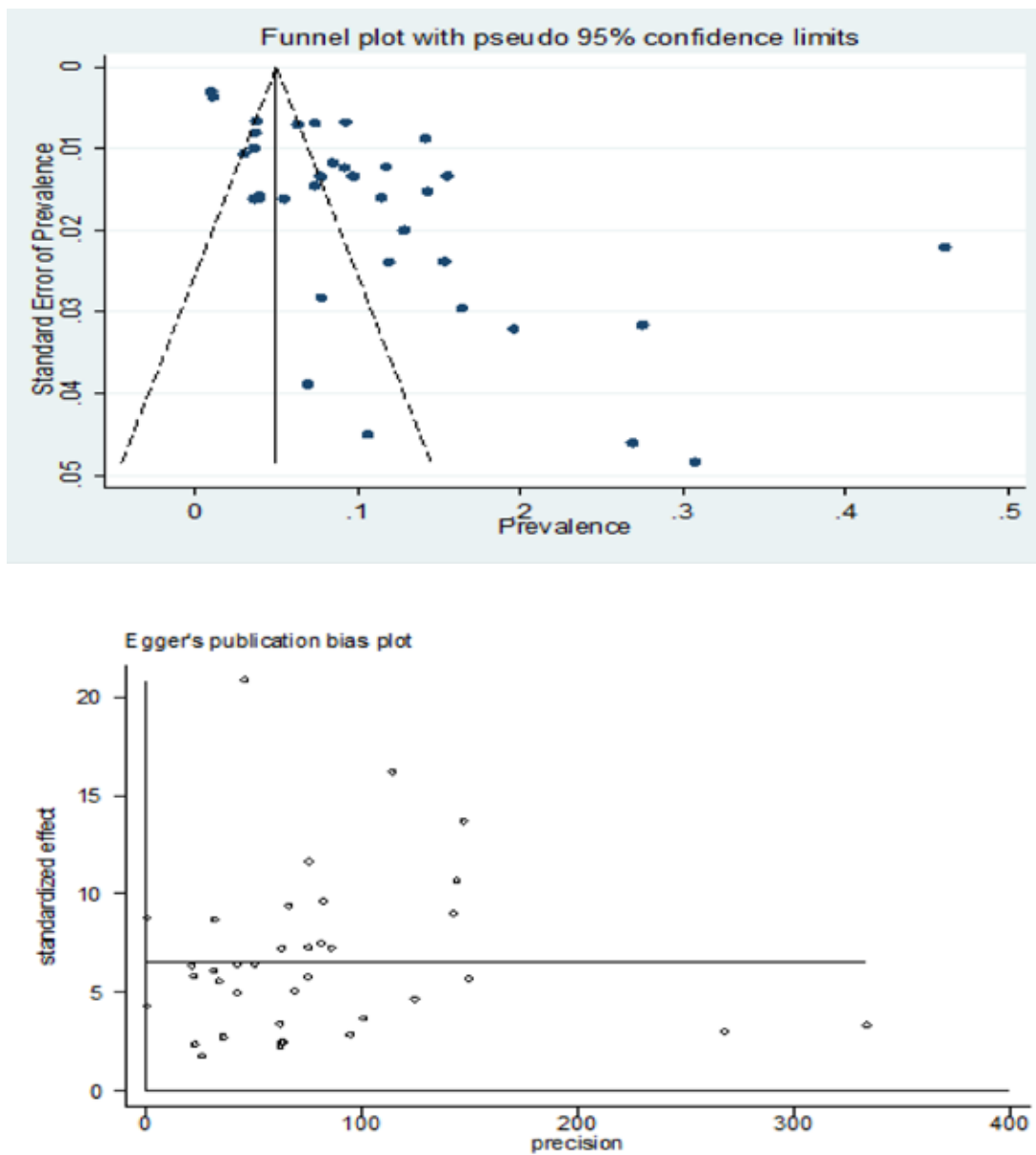The prevalence of HEV was not different among

Fig. 4 : Funnel plot and Egger's funnel plot test to assess publication bias

patients receiving hemodialysis, intravenous drug users, and HIV infected patients compared to the general population. One should realize that the most common route of HIV infection in Iran is still intravenous drug use, although the trend is moving toward sexual route.[54] This indicates that in concordance with other reports, the major route of transmission of HEV is fecal oral rather than parenteral.

It is of interest that in patients with cirrhosis the prevalence was 5.5% and in renal transplant recipients it was 3.8%. As these reports were based on serology and these patients might have exposure to HEV with loss of antibody over time due to malnutrition or immunosuppression, our estimates in these special groups might be incorrect.

This systematic review and meta-analysis has advantage of a relatively large sample size with merging data of good quality studies but it also has several limitations. Although the included studies were from many parts of the country, there were some regions with no data. For

instance we could not find any eligible study from two regions with confirmed epidemics of HEV in Iran naming Kermanshah and Chahar Mahal Bakhtiari provinces. The studies analyzed in this systematic review used several different types of serology for HEV from different sources, and their comparability is not known. There was a lack of appropriate data on the age and sex in some of the included studies. Consequently, we were not able to analyze the data by stratifying these variables. Using the information on sex and age, we could better estimate the prevalence of hepatitis E among subgroups in our society. Substantial heterogeneity of 95.7%, according to the I^2 statistic is another limitation. Of utmost importance is that none of the studies reported the prevalence of HEV among patients suffering from acute hepatitis. Despite these limitations, our study reveals that HEV in Iran is not rare and is not limited to epidemics.

HEV in Iran has an estimated prevalence of 10%. The infection seems to have a decreasing trend overtime, which might be related to improved sanitation and better access to safe water but the pattern is not uniform across the entire country with existence of certain confounders such as mobility along borders especially to countries with high endemicity of HEV. Further prospective studies on incidence of infection, especially in patients suffering from acute hepatitis in non-epidemic conditions are required to obtain better knowledge on the dynamics of this virus in our country.

Authors' contributions:

All of the authors significantly contributed to this systematic review and meta-analysis. All made the search in databases. Masoud Behzadifar, Meysam Behzadifar, Abouzar Keshavarzi, and Maryam Saran reviewed the literature, selected and assessed the articles. Masoud Behzadifar analyzed the data. Kamran B Lankarani provided critical comments for the subsequent drafts. All of the authors reviewed the final manuscript and approved the final version.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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