

Review Article**Prevalence of chronic hepatitis B infection in Iran: a review article***Jalal Poorolajal^{*a}, Reza Majdzadeh^a***Abstract**

Hepatitis B virus infection is a major public health problem worldwide. Islamic Republic of Iran is a country in which hepatitis B prevalence is intermediate. The aim of this study is to assess prevalence of chronic hepatitis B infection in Iran according to demographic characteristics. All cross-sectional studies concerning prevalence of chronic hepatitis B infection in Iran were included irrespective of date and language. The outcome of interest was prevalence of chronic hepatitis B infection confirmed by blood specimen positive for HBsAg. The prevalence of chronic hepatitis B infection was estimated about 1.7% or lower in general population; 0.8% (95% CI: 0.6% to 0.9%) in blood donors and 3.2% (95% CI: 2.3% to 4.1%) in intravenous drug users and varied from zero to 1.5% in beta thalassemic patients. Since mass vaccination in 1993, prevalence of chronic hepatitis B infection has been reduced among children and adolescents. This reduction can be attributed to the effectiveness of the national immunization program and it may impact on reduction of prevalence of hepatitis B infection in general population.

KEY WORDS: Hepatitis B, Prevalence, Blood Donors, Thalassemia, Drug Users, Iran.

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Hepatitis B virus (HBV) infection is one of the major public health problems in the world.¹ Approximately 45% of the world population live in hyper-endemic where prevalence of hepatitis B surface antigen (HBsAg) is greater than 8%; 43% live in mid-endemic areas where HBsAg prevalence is 2% to 7%, and 12% live in hypo-endemic areas where HBsAg prevalence is less than 2%.^{2,3} According to the report of World Health Organization (WHO) in 2001 and Centers for Disease Control and Prevention (CDC) in 2005, prevalence of chronic hepatitis B infection in Iran is between 2-7%.^{2,3} In hyper-endemic areas, the lifetime risk of HBV infection is more than 60% and infection occurs mostly through perinatal and child-to-child transmission. In mid-endemic areas (such as Iran) the lifetime risk of HBV infection is 20-60% and infection involves all age groups. In hypo-endemic areas the lifetime risk of HBV infection is less than 20% and

infection occurs mostly in high-risk adults.³ At present, vaccination is the most effective and cost saving means of prevention of HBV infection.⁴ Hepatitis B vaccine was introduced within National Immunization Program (NIP) in Iran in 1993⁵ and immunization of teenagers under 18 years old integrated into NIP since 2006. In this review, we aimed to assess prevalence of chronic HBV infection in Iran and to determine high-risk populations.

Inclusion and Exclusion Criteria***Types of Studies***

We included all cross-sectional, systematic review and meta-analysis studies conducted in Iran concerning HBV infection irrespective of date and publication language.

Types of Participants in The Studies

All participants of the included studies were native of Iran with different ages, sexes and occupations.

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Types of Outcome

The primary outcome that we intended to assess was "HBV infection prevalence" confirmed by detection of blood specimen positive for HBsAg.

Search Strategy

The search strategies were developed, then searching national and international databases was conducted using a combination of the word "hepatitis B" with the words "prevalence" or "incidence" and "Iran". MEDLINE (from 1950 to 2008), EMBASE (from 1966 to 2008), Science Citation Index Expanded (from 1994 to 2008), Ovid (from 1960 to 2008), Google Scholar, IranMedex, MagIran, Scientific Information Database (SID), and Scientific Journal of Iran Blood Transfusion Organization (SJIBTO).

Methods

To assess prevalence of chronic HBV infection in Iran, not only both national and international databases were searched, but reference list were screened to find as much publication as possible.

Data Collection and Extraction

The data was extracted from the included studies, using an electronic data collection and abstraction form developed by Stata 9 computer program. The extracted variables included bibliography, type of studies, total sample size, number of HBsAg positive, demographic characteristics of the participants, date and region in which the studies were conducted.

Methodological Quality

Methodological quality and the strengths and weaknesses of the report of included studies was investigated using a modified STROBE checklist consisted of the following items: title and abstract, introduction, methods, results and conclusion.⁶ Thirty four cross-sectional studies were found, 4 of which were published as abstracts. The STROBE items reported by included studies varied from 55% to 85%. Items reported

by English and Persian articles were nearly the same (69% versus 70% respectively).

Statistical Methods

The measure of interest was "prevalence of HBV infection" with 95% confidence interval (CI). Statistical heterogeneity was explored using Cochran's Q-test and Higgins' I² statistic and the publication bias was addressed using funnel plot. The analysis was performed in Stata 9 statistical software. The random effects model was reported with 95% CI.

Characteristics of Studies

One hundred and two publications were found by searching electronic databases as well as screening the references list. After reading the titles and abstracts, 61 of these publications were excluded because they were duplicates or had objectives different from this review. The remaining 41 publications were retrieved for further assessment. Of these, 5 publications were excluded because their full texts were not available and their abstracts were not as complete as to provide necessary data for this review. Two publications were excluded after reviewing the full texts; one publication did not meet the inclusion criteria and the other one for duplication (Diagram 1). Of the remaining 34 publications, 30 studies were published as full paper articles and 4 studies as abstracts. Twenty studies were published in English and the remaining 14 studies in Persian.

We did not find any meta-analysis related to HBV infection in Iran. All included publications were cross-sectional method. Also 5 narrative reviews were identified that the references of which were checked for additional studies.⁷⁻¹¹

Thirty one studies had been conducted after introduction of hepatitis B vaccine within NIP¹²⁻⁴¹ and the remaining 3 studies were conducted theretofore.⁴²⁻⁴⁴

Four studies had been conducted at national level^{23,41,43,44}; 2 studies had been carried out as multi-center^{25,32} and the remaining 28 studies had been conducted in different provinces of Iran.^{12-22,24,26-31,33-40,42}

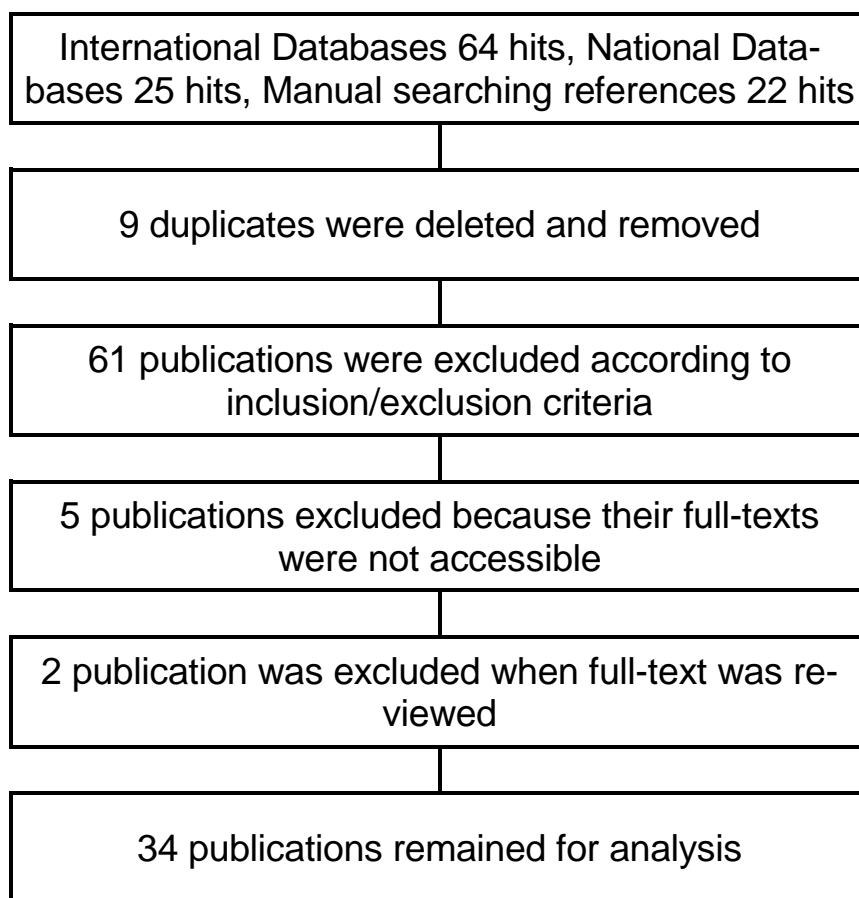


Diagram 1. Inclusion and exclusion flowchart

Characteristics of The Participants in The Studies

The 34 included studies had been conducted on the following populations: 6 studies^{13,18,35,41,42,44} on general population; 15 studies on blood donors^{12,14-17,19,20,24,28,29,31,33,34,40,43}; 5 studies on beta thalassemic patients^{21,26,32,36,38}; 3 studies were conducted in hemophilic patients^{21,30,39}, 4 studies on intravenous drug abusers^{22,25,27,37} and one study on long vehicle drivers.

The sex of the participants was not specified in one study,²⁵ two studies were restricted to males,^{23,27} one study was restricted to females²² and the remaining 30 studies included both males and females.^{12-21,24,26,28-44} Proportion of male participant's to female participants was

53% to 93%, while this proportion was opposite in one study. There was a remarkable diversity in the participants' age. The studies related to general population included all age groups. All blood donors were more than 18 years old i.e. not including children and teenagers while studies conducted on beta thalassemic patients composed mostly of children and teenagers.

Results

We were not able to pool all data to conduct meta-analyses due to the lack of homogeneity between studies' participants. Therefore, we performed a stratified meta-analysis according to the characteristics of the participants to obtain a summary measure.

Prevalence of Chronic HBV Infection in General Population

Six studies had been conducted on general population from 1989 to 2005 (Table 1) 2 of which^{41,44} were national and 4 of which^{13,18,35,42} were regional. These studies included all age groups. The sample sizes of these studies varied from 1824 to 46631. The lowest prevalence of 1.7%^{41,44} was reported by national studies and the highest prevalence of 8.9% was reported by Golestan province study.³⁵ Because of unbalanced among sample sizes (1824 to 46631), there was a prominent significant heterogeneity across these six studies (p value < 0.001). Thus we analyzed high sample size (national studies) and low sample size (regional studies) separately as well as together. The prevalence of HBV infection in general population according to the national studies was 1.7% [95% CI: 1.6% to 1.8%], according to regional studies was 3.6% [95% CI: 2.3% to 4.9%] and according to both national and regional studies was 2.7% [95% CI: 2.2% to 3.1%] using the random effect model.

Prevalence of Chronic HBV Infection in Blood Donors

Fourteen studies had been conducted to assess prevalence of HBV infection in blood donors in different provinces of Iran from 1998 to 2005.^{12,14-17,19,20,24,28,29,31,33,34,40} A national study was conducted with same purposes in 1979.⁴³ All blood donors aged 18 years or older. The proportion of male blood donors (82% to 93%) were much more than female blood donors (7% to 18%). Majority of blood donors (35% to 84%) mentioned a history of previous blood donation. There was a remarkable diversity among sample sizes (441 to 221508). The lowest and highest reported prevalence of HBV infection in blood donors was 0.4%¹⁷ and 3.4%⁴³ respectively. The later study was much older than the other studies (1979 versus 2000-2007) and looked like an outlier. We excluded this study and re-performed meta-analysis using the random effects model with 95% confidence interval (Figure 1). According to the results

obtained from the meta-analysis, prevalence of HBV infection in blood donors of Iran is 0.8% [95% CI: 0.6% to 0.9%].

Prevalence of Chronic HBV Infection in Beta Thalassemic Patients

There were five studies^{21,26,32,36,39} related to prevalence of HBV infection in beta thalassemic patients which were conducted from 2000 to 2002 in Iran (Table 2). The sample sizes of these studies were unbalanced (84 to 755). There were no HBsAg positive cases in two studies.^{22,39} In the remaining 3 studies, the lowest and highest reported prevalence were 0.3% and 1.5% respectively.^{32,36} Because of standard error (SE) of zero in two studies, we were unable to run meta-analysis. According to the results of these studies, it seems that prevalence of HBV infection in beta thalassemic patients of Iran is lower than general population.

Prevalence of Chronic HBV Infection in Hemophilic Patients

We identified only 3 studies^{21,30,38} concerning prevalence of HBV infection in hemophilic patients (Table 3). The sample sizes of these studies were small (101 to 162) and the results were very diverse (2% to 27%) due to random error. We were not able to pull the data and perform a meta-analysis due to lack of reliability and strong heterogeneity between studies' results.

Prevalence of Chronic HBV Infection in Intravenous Drug abusers

We identified 4 studies^{22,25,27,37} concerning prevalence of HBV infection in Iranian intravenous drug abusers from 2001 to 2003. The sample sizes of the studies were diverse (196 to 1431). The lowest and highest reported prevalence was 1.5% and 3.7% respectively. We performed a meta-analysis using the random effects model with 95% confidence interval (Figure 2). According to the results obtained from the meta-analysis, prevalence of HBV infection in Iranian intravenous drug abusers was 3.2% [95% CI: 2.3% to 4.1%].

Table 1. Prevalence of chronic HBV infection in general population

Study	Province	Date of study	Sample size	Prevalence
Amini 1993	Hamadan	1989	4930	0.025
Zali 1996	National	1991	39841	0.017
Zali 2005	National	1999	46631	0.017
Farhat 2003	Khorasan	1998	4528	0.036
Alizadeh 2005	Nahavand	2003	1824	0.023
Roshandel 2007	Golastan	2005	1850	0.089

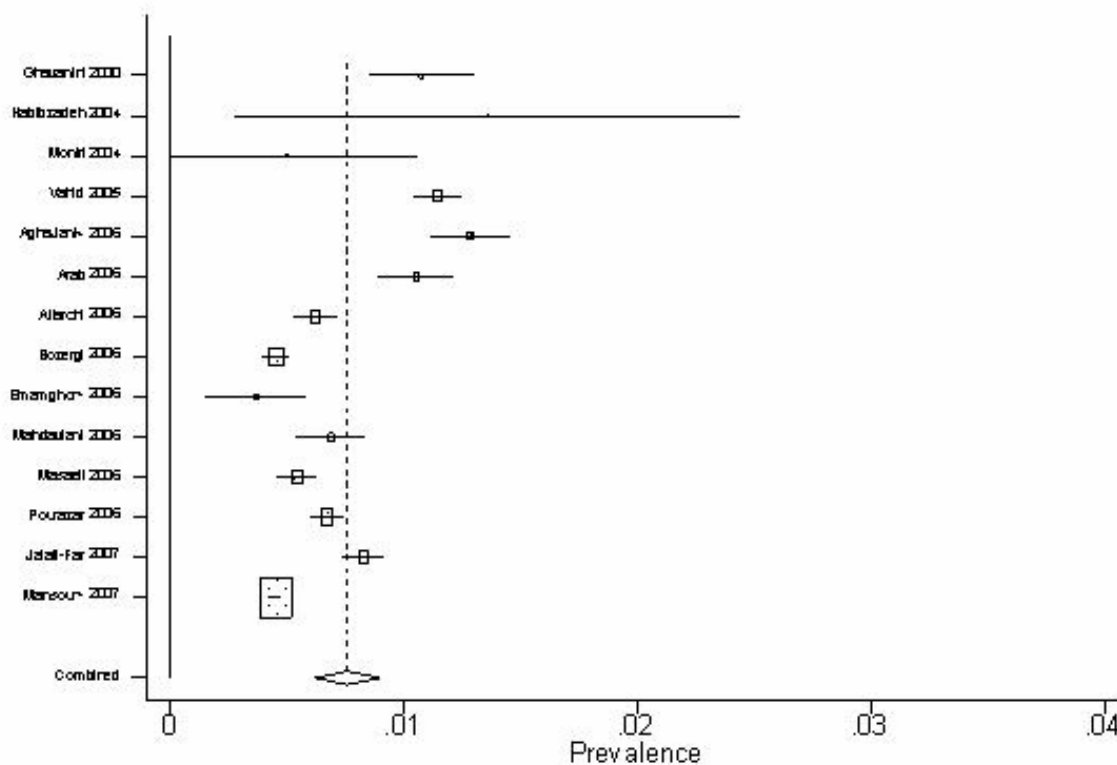


Figure 1. Forest plot for estimating of HBV prevalence in blood donors

Table 2. Prevalence of chronic HBV infection in beta thalassemic patients

Study	Province	Date of study	Sample size	Prevalence
Karimi 2001	Shiraz	2000	755	0.005
Sanei-Moghaddam 2004	Zahedan	2002	364	0.003
Torabi 2005	East Azarbijan	2003	84	0
Hariri 2006	Isfahan	2004	616	0
Mirmomen 2006	Multi-Center	2002	732	0.015

Table 3. Prevalence of chronic HBV infection in hemophilic patients

Province	Study	Date of study	Sample size	Prevalence
Guilan	Mansour-Ghanae 2002	1999	101	0.267
Isfahan	Hariri 2006	2004	120	0.017
East Azarbijan	Torabi 2006	2004	162	0.019

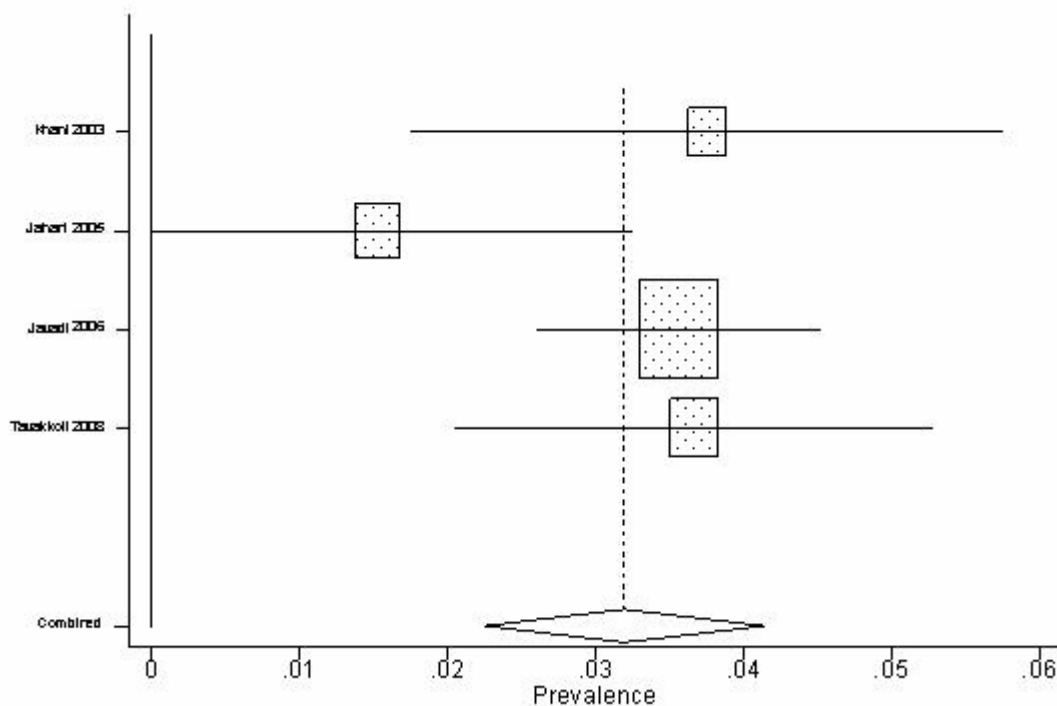


Figure 2. Forest plot for estimating of HBV prevalence in intravenous drug abusers

Prevalence of Chronic HBV Infection Related to Age and Sex

There was remarkable diversity in participants' age groups. The most prevalent age groups were not specified in 21 studies.^{13,16,17,19-22,24,26-29,31,33-36,38,39,43} Eight studies^{14,15,18,37,40-42,44} reported the most prevalence of HBV infection in participants aged over 30 while 6 studies^{15,18,23,41,42,44} reported in those aged over 40. The gender of the participants was not specified in 12 studies.^{19-21,25,26,30,31,34,36,38,39} Two studies^{23,27} restricted to males and one study²² restricted to females. Nine studies^{14-16,18,24,28,33,37,42} reported the same prevalence rate for both males and females. Infection rate was reported more prevalent in males in comparison with females in 9 studies^{12,13,17,29,32,35,41,43,44} while opposite results were reported in one study.⁴⁰ However, two national studies^{41,44} justified that infection rate in males is significantly more than females (1.9% versus 1.5% respectively).

Discussion

Hepatitis B virus (HBV) infection is a major problem of public health in the world particularly in developing countries. According to

WHO report in 2001³ and CDC report² in 2005, considered Iran as a mid-endemic region with a prevalence of 2% to 7%. A review article conducted by Merat et al¹⁰ in the 1980s indicated that 3% of Iranian population were chronic carriers of HBV infection. While two big national studies conducted by Zali et al in 1990⁴⁴ and 1999⁴¹ revealed that the overall prevalence of chronic HBV infection was 1.7% in the 1990s. Furthermore, these two consecutive studies which were carried out before and after mass vaccination of hepatitis B in 1993 indicated a significant decline in infection rate (from 1.3% to 0.8%) in children of 2-14 years old and may be attributed to hepatitis B vaccine effectiveness. Nevertheless, other regional studies in deferent provinces reported HBV prevalence more than 1.7% in last decade.^{13,18,35} However, 14 years is passed since integration of hepatitis B vaccine within NIP and now the immunization program have covered a large population of children and teenagers under 18 years old with the coverage rate of 62% in 1993 to 94% in 2005.⁸ Thus, it seems that prevalence of HBV infection is now about 1.7% or lower in general population of Iran.

According to the WHO guideline,³ serological surveys of first-time unpaid blood donors generally offer the most useful means of estimating the prevalence of HBV infection among adults in the general population. While, repeat and paid blood donors usually have a higher prevalence of HBV infection and are not representative of the general population.³ However, the serological surveys of blood donors carried out in Iran are not good representatives for assessing prevalence of HBV infection among adults in the general population due to following reasons: first, proportion of male blood donors is much more than female blood donors (82% to 93% versus 7% to 18% respectively). Second, serological findings of first-time unpaid blood donors are not separated from repeated blood donors so that majority of blood donors in these surveys are repeated donors (35% to 84% of whom had reported a history of previous blood donation).^{15,16,20,28,31,34} Indeed, repeated blood donors must be uninfected to be allowed for repeated blood donation. Thus, it is wise to expect that prevalence of HBV infection in these surveys be reported lower than general population (prevalence rate of 0.8% in blood donors versus 1.7% in general population).

In large studies a negligible amount of heterogeneity may be statistically significant, whereas in small studies a strong heterogeneity may not be statistically significant.⁴⁵ To obtain a summary measure of prevalence of HBV infection in blood donors, we pooled the data from fourteen regional and national studies and performed a random effects meta-analysis. However, because of very large sample sizes (from 3000 to 200,000) in some studies, there was a strong and statistically significant heterogeneity across studies ($p < 0.001$), whereas demographic characteristics of the blood donors such as age, sex and date of studies were nearly the same in all studies. Therefore, we performed meta-analysis and reported summary measure notwithstanding significant heterogeneity was present.

Although, thalassemic patients receive repeated blood transfusion, the infection rate in these patients was significantly lower than gen-

eral population (0.5% versus 1.7% respectively). The studies were large enough (included 2551 patients) that we could not attribute such a result to random error. We concluded that it may be due to the immunization of these patients at the beginning of disease before receiving any blood transfusion.

Intravenous drug users are at higher risk for HBV infection primarily through high-risk sexual activity and sharing unsterile needles.² According to an unpublished data in a review article, Merat et al claimed that over 25% of intravenous drug users were HBV carriers in a prison in south of Iran in 1980s.¹⁰ Nonetheless, there are 4 surveys investigated the prevalence of HBV infection in intravenous drug abusers with total sample size of 2491 during 2001 to 2003.^{22,25,27,37} These studies reported the prevalence of HBV infection from 1.5% to 3.7% with an estimated summary measure of 3.2%. Thus, very high prevalence of HBV infection in intravenous drug users reported by Merat et al seems to be over estimated.

Conclusions

According to the results of this review we drew the following conclusions. Prevalence of chronic HBV infection in general population of Iran is about 1.7% or lower. Prevalence of chronic HBV infection in Blood donors is 0.8% [95% CI: 0.6% to 0.9%]. Serological surveys of blood donors are not a good representative for estimating the prevalence of HBV infection among adults in the general population. Prevalence of chronic HBV infection in beta thalassemic patients varies from zero to 1.5%. Prevalence of chronic HBV infection in intravenous drug abusers is 3.2% [95% CI: 2.3% to 4.1%]. Prevalence of chronic HBV infection is higher in middle aged and elders than children, teenagers and youth. Prevalence of chronic HBV infection is 25% higher in males than females. Prevalence of chronic HBV infection has reduced after mass vaccination in children and teenagers.

Limitation of The Review

Iranian national databases are not useful enough due to lack of actual search tools. These

databases do not encompass all national scientific journals as well. Lack of advanced search tools and impossibility of saving search results are additional insufficiencies of national databases. Many national surveys conducted as dis-

sertations that are not registered completely in databases. Thus, in such situation, it is not possible to conduct a national comprehensive meta-analysis.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

JP developed and wrote the protocol and was responsible for the reference searching, article retrieval, study inclusion and exclusion, data extraction, assessment of risk of bias in included studies, analysis and interpretation of results and writing of the review. RM edited the protocol and was responsible for the analysis, interpretation of results and writing of the review.

All authors have read and approved the final manuscript.

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