Prevalence of human alveolar echinococcosis in China: a systematic review and meta-analysis

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Abstract

Background Human alveolar echinococcosis (HAE) is a severe parasitic disease that is a major public health concern. A review has indicated that new HAE cases in China account for 91% of the global HAE burden every year. Although there are a few studies and systematic reviews (SRs) on the prevalence of HAE in China, trends in the prevalence have not been estimated. Therefore, this study aims to describe the overall variation in the trend of HAE prevalence, and provide evidence for preventive measures in the future.

Methods Thirty-five eligible studies were retrieved from PubMed, Web of Science, EMBASE, CNKI, Wanfang Data, and VIP, and included in the SR and meta-analysis. An adjusted Agency for Healthcare Research and Quality checklist was used to evaluate study quality. We used the arcsine transformation to adjust the individual reported prevalences and also calculated the pooled HAE prevalence. We evaluated heterogeneity using the chi-square test and I² statistic, as well as random-effects models and fixed-effects models. We generated forest plots for the meta-analysis results and assessed publication bias of the studies using the Egger’s test and funnel plots. We conducted subgroup analyses, sensitivity analyses, and meta-regression analyses to analyze the source of heterogeneity and factors potentially influencing the prevalence of HAE.

Results The meta-analysis indicated that the pooled HAE prevalence in China was 0.96% (95% CI: 0.71 to 1.25%). Factors potentially influencing HAE prevalence are female sex (OR=1.60, 95% CI: 1.35 to 1.91), being ≥30 years of age (OR=4.72, 95% CI: 2.29 to 9.75), and being farmers and/or herdsmen (OR=2.54, 95% CI: 1.60 to 4.02). The results of the meta-regression analysis (R² =38.11%, P < 0.01) indicated that HAE prevalence is on a downward trend.

Conclusions HAE prevalence has decreased over time and maintained low levels after 2005 in China. This decline was influenced by the utilization of One Health strategies as intervention measures. Therefore, these One Health strategies should be used as references to formulate future programs for HAE control. More high-quality epidemiological investigations and surveillance programs ought to be conducted in order to improve HAE control in the future.

Background
Alveolar echinococcosis (AE) is a severe zoonosis caused by the larva of Echinococcus multilocularis that has an adverse impact on human and animal health [1]. Parasite eggs are excreted through the feces of the definitive hosts, which are usually foxes and dogs. Once the eggs are ingested by the intermediate hosts such as rodents and humans, oncospheres released from the eggs under the action of gastrointestinal digestion go on to form metacestodes in the liver or other organs. A large number of protoscolices (PSCs) are usually generated by metacestodes through asexual reproduction. After the definitive hosts ingest the viscera that include the metacestodes, the PSCs attach to the definitive hosts’ intestine wall and develop into adult worms to complete the life cycle [2]. As one of the intermediate hosts, humans can contract hydatid disease through contaminated food or water, with the liver primarily being the infected organ. If not treated in time, the disease will lead to jaundice, cirrhosis, and other clinical symptoms, which can result in liver failure or even death. The mortality of untreated human alveolar echinococcosis (HAE) patients or inadequately untreated patients is 90% at 10–15 years after diagnosis [3, 4]. Hence, HAE is also known as "the parasite cancer" [5].

HAE has become a global threat to public health [6-8]. There are 18,235 new cases of HAE every year in the world, with the disease burden reaching 666,433 disability-adjusted life years (DALYs) [9, 10]. In the past, it was generally believed that HAE cases were mainly distributed across the northern hemisphere, especially in Asia [11]. However, in recent years, new cases of HAE have been found in some European countries; the incidence of HAE has doubled in France and Germany [12-14]. Some regions of Canada have also reported cases of HAE [15]. China is one of the countries seriously affected by HAE, accounting for 91% of the global burden of new HAE cases every year [10]. The prevalence increased to 9.43% in Banma County, Qinghai in 2014 [16] and 3028 cases were reported in Shiqu County, Sichuan between 2015–2017 in China [17]. HAE has also become a burden in endemic regions and has constrained the development of animal husbandry in China [18]. Although a few studies and systematic reviews (SRs) have explored HAE in China, the trend in the variation of HAE prevalence remains unclear. As a consequence, it is important to depict the overall trend in the variation of HAE prevalence, which will help provide evidence for preventive measures
and HAE studies in the future. Therefore, this SR and subsequent meta-analysis aim to estimate the characteristics and trends in the variation of HAE prevalence in China and to explore potential influencing factors.

Methods

Search strategy and study selection
The SR and meta-analysis were performed according to the guidelines of PRISMA [19]. The online search was carried out using 6 databases (PubMed, Web Of Science, EMBASE, CNKI, Wanfang Data, and VIP) with keywords and Boolean operators AND/OR: “((((((alveolar echinococcosis) OR alveolococcosis) OR echinococcus multilocularis infection) OR alveolar hydatid disease) OR multilocular echinococcosis)) AND ((prevalence) OR epidemiology)) AND ((human OR people OR person OR man OR men OR women OR woman OR patient)) AND ((China) OR Chinese).” All the screened articles were published before December 1, 2019.

The study selection was performed independently by two researchers (XZW and GDD). Disagreements were resolved by consensus. First, we inspected the titles and abstracts of all the studies. Studies were included if they were screening studies, cross-sectional studies, case-control studies, and cohort studies regarding HAE in China. Subsequently, we browsed through all full-text articles. Studies were included if they used both imaging examinations (B-ultrasonography) and serological examinations as diagnostic methods for HAE [20, 21]. Studies were excluded if they had been published repeatedly with the same samples, had inaccessible full texts, or had no data on HAE prevalence in China. We also identified relevant papers from the reference lists of the articles for the meta-analysis.

Data extraction and quality assessment
We used Microsoft Excel (version 2016) to record data that included the first author, published year, language, years during which the study was conducted, study areas, the sample size, number of HAE patients, and patient demographic details (sex, age, occupation) for each of the studies included. All the data were extracted independently by two researchers (XZW and ML). Disagreements were resolved by consensus.

The Agency for Healthcare Research and Quality (AHRQ) checklist was used to evaluate the quality of
the studies. Of the 11 items in the AHRQ checklist, two items were unsuitable for these studies: item 4 ("Indicate whether or not subjects were consecutive if not population-based") and item 11 ("Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained"). Therefore, 9 items were used to score the studies (Additional file 1). If an item was answered with a "yes," it was scored "1"; if it was answered with a "no or unclear," it was scored "0." The quality of the studies was classified using a number system, where low-quality studies scored 0–2, medium-quality studies scored 3–5, and high-quality studies scored 6–9.

**Statistical analysis**

R software (version 3.6.1) was used for all analyses. The arcsine transformation was calculated for the prevalence of each study and the pooled prevalence of HAE was calculated as part of the meta-analysis. Heterogeneity was evaluated using the chi-square test and $I^2$ statistic. If the $P$-value $\leq 0.10$ and $I^2 \geq 50\%$, substantial heterogeneity between studies was indicated, and the random-effects model was used [21]; otherwise, we used the fixed-effects model. The results of the meta-analysis were presented using forest plots, and publication bias of the studies was assessed by the Egger’s test and funnel plots. Subgroup analyses, sensitivity analyses, and meta-regression analyses were performed to analyze the source of heterogeneity and factors potentially influencing the prevalence of HAE.

**Ethical Approval**

Not applicable.

**Results**

**Literature search results**

Based on the screening strategy, 426 studies were considered, of which 87 were from Chinese databases. Ninety-seven studies that were duplicates were excluded by the document management software NoteExpress (version 3.2). After screening the titles and abstracts, 254 studies were removed. The full texts of the remaining 75 papers were then screened by the selection criteria. A total of 35 eligible articles were included in the meta-analysis after screening, according to the inclusion and exclusion criteria. The details of the selection process are shown in Fig. 1. Due to the
study discussed in literature 7 being conducted across two time periods (1997 and 2003), we treated the data from the two periods as two different studies (literature 7-1, 7-2) in the meta-analysis. Similarly, the data for the study discussed in literature 33 were acquired from 6 areas (Gansu, Ningxia, Qinghai, Sichuan, Tibet, and Xinjiang), therefore literature 33 was regarded as 6 separate studies (literature33-1, 33-2, 33-3, 33-4, 33-5, 33-6).

**Basic information of included literatures**

Of the 41 selected studies (the splitting up of literature 7 and literature 33 were included), 11 (27%) were in English and 30 (73%) in Chinese (Table 1). The periods of time during which these studies were carried out and published were from 1991 to 2016 and from 1992 to 2019, respectively. All surveys were cross-sectional studies and were conducted in 6 provinces in China: 9 in Gansu, 3 in Ningxia, 8 in Qinghai, 8 in Sichuan, 9 in Tibet, and 4 in Xinjiang. A total of 2,032,811 subjects were included, of which 7522 were HAE patients. Table 1 shows the general features of the included studies.

**Table 1** List of included articles in the meta-analysis

**Literature quality evaluation**

The quality of the cross-sectional studies was evaluated by the adjusted AHRQ checklist (9 items). The results (Table 1) showed that there were 7 low-quality studies (17%), 27 medium-quality studies (66%), and 7 high-quality studies (17%). The details of the quality evaluation were shown in Additional file 2.

**Meta-analysis of the prevalence of HAE in China**

Substantial heterogeneity was observed among the included studies ($I^2=100\%, P<0.01$, Fig. 2), which is common in most meta-analyses studying prevalence. Therefore, we used a random-effects model to calculate the pooled prevalence. The result indicated that the pooled prevalence of HAE in China was 0.96% (95% confidence interval [CI]: 0.71 to 1.25%) (Table 2). The funnel plot was shown in the Additional file 3 and the Egger’s test did not indicate any publication bias ($P=0.06$). The sensitivity analysis indicated that despite excluding studies, the pooled prevalence remained stable (Additional file 4).
All the studies were divided into 6 groups based on the geographical areas for the subgroup analysis. The prevalences of HAE in these 6 areas were statistically significant \( (P<0.01, \text{Table 2}) \). The highest prevalence of HAE was in Sichuan (2.03%, 95% CI: 1.30 to 2.92%), while the lowest was in Xinjiang (0.013%, 95% CI: 0.001 to 0.036%). There were not enough studies based in Xinjiang (4 studies) and Ningxia (3 studies), therefore it is possible the pooled prevalences of these two areas may not be accurate.

**Table 2 Meta-analysis of HAE prevalence in China**

**Factors potentially influencing HAE prevalence**

Three factors potentially affecting HAE prevalence were considered in our meta-analysis: sex, age, and occupation. Due to the small number of articles addressing “age” and “occupation” (<10 articles), publication bias was only evaluated for “sex.” Heterogeneity was indicated within all groups (sex, age, and occupation) (Additional file 5), with statistically significant differences observed \( (P<0.01) \) (Table 2).

Of the included studies, 11 articles (1-3, 8-11, 13, 14, 18, 22) reported data on sex in their study populations. The meta-analysis showed that the prevalence of women with HAE (3.47%, 95% CI: 2.69 to 4.34%) was higher than that of men with HAE (2.14%, 95% CI: 1.55 to 2.82%) (Table 2). The overall pooled odds ratio (OR) for women with HAE was 1.60 (95% CI: 1.35 to 1.91, \( P<0.01 \)). After excluding literature 1 from the sensitivity analysis, we found that the heterogeneity reduced \( (I^2=27\%, \ P=0.20) \) and the adjusted OR was 1.50 (95% CI: 1.30 to 1.73, \( P<0.01 \)), as shown in Additional file 6. The funnel plot (Additional file 3) and Egger’s test did not indicate the existence of publication bias.

Five articles (1, 13, 14, 16, 22) had data on the age of the subjects. The prevalence of HAE was higher in those whose age was \( \geq 30 \) years old (6.41%, 95% CI: 3.50 to 10.12%) than those whose age was <30 years old (1.64%, 95% CI: 0.36 to 3.83%) (Table 2). Being in the \( \geq 30 \) years old age group was associated with an increase in HAE prevalence \( (\text{OR}=4.72, \ 95\% \text{ CI}: 2.29 \text{ to } 9.75, \ P<0.01) \). The sensitivity analysis (Additional file 7) indicated that the OR was relatively stable when any study was excluded.

The occupations of the subjects were investigated in 4 articles (3, 9, 18, 22). The analysis showed
that HAE prevalence was higher in farmers and/or herdsman (2.90%, 95% CI: 1.82 to 4.21%) than in people in other occupations (1.20%, 95% CI: 0.63 to 1.94%), and the OR was 2.54 (95% CI: 1.60 to 4.02, \( P<0.01 \)). The sensitivity analysis indicated that heterogeneity decreased (\( I^2=50\%, P=0.14 \)) when literature 22 was excluded; the adjusted OR was 3.01 (95% CI: 2.02 to 4.48, \( P<0.01 \)) (Additional file 8).

**Trend in the variation of HAE prevalence in China**

Fig. 3 shows the trend in the variation of HAE over time. The overall HAE prevalence has remained low since 2005—despite its resurgence in prevalence from 2005–2010, it remained stable after 2010. Additionally, the meta-regression analysis indicated that there was negative correlation between the time period during which the studies were conducted and the HAE prevalence in China (\( R^2=38.11\%, P<0.01 \)) (Fig. 4).

**Discussion**

This SR and meta-analysis included 41 studies published in 1992–2019, including 2,032,811 subjects and 7,522 HAE patients. All included studies were cross-sectional studies, however, only seven were high-quality (17%). This means that researchers need to improve the quality of their studies for more reliable results. In the process of the literature search, we found that although researchers have carried out epidemiological investigations on HAE in recent years, there were very few nationwide epidemiological studies [22]. Therefore, this SR and meta-analysis summarized the HAE prevalence and provided epidemiological data about HAE in China for future prevention.

In China, we found that the overall HAE prevalence was 0.96% (95% CI: 0.71 to 1.25%). The subgroup analysis indicated that there were 6 provinces (Table 2) with high HAE prevalence, which aligns with results from another study [10]. Of the 6 provinces, the prevalences in Sichuan and Qinghai were higher than in other provinces; since most of the included studies in Sichuan and Qinghai were conducted in communities residing in Tibetan autonomous prefectures, it is possible the higher prevalence is related to the proximity to the Tibetan plateau [23]. The low-temperature climate caused by the high altitude in the Tibetan plateau makes survival easier for the *E. multilocularis* eggs
in the environment, which is conducive to the spread of HAE [22]; additionally, certain religious beliefs such as not killing dogs, and the poor health habits of Tibetan residents also allow for the spread of HAE [24]. However, the results of the meta-analysis indicated that the HAE prevalence in Tibet was relatively low (0.19%, 95% CI: 0.13 to 0.25%). This may be due to the Tibetan studies being conducted after 2010, when the national prevention and control project of echinococcosis was popularized in China. It is indicated that prevention measures should be implemented in the Tibetan plateau as well as the surrounding areas.

Female sex, being ≥30 years of age, and working as a farmer and/or herdsman were the three influencing factors discussed in the context of HAE prevalence in our meta-analysis. A higher odds of HAE infection was observed in women (OR=1.60, 95% CI: 1.35 to 1.91) than men. This may be due to the women being responsible for feeding dogs in some Tibetan farming and pastoral areas, leading to frequent contact with a definitive host, which would explain the higher risk of HAE in women [25].

Women are also more involved in housework, such as collecting yak feces and sheep-shearing. As a result, they are exposed to possible contaminants in dog feces and/or *E. multilocularis* eggs [26, 27]. Thus, specific living habits are a likely cause for the increase in the potential HAE risk in women. Five articles indicated that being ≥30 years of age increased the odds of an HAE infection (OR=4.72, 95% CI: 2.29, 9.75). This may be because older people have a greater chance of being infected [28, 29], and the long incubation period (5–15 years) of HAE can lead to a delayed onset of clinical symptoms [2, 30], which would make the disease more detectable in age groups ≥30 years. Sex and age are typically regarded as confounding factors, therefore it is important for investigators to distinguish confounders with well-designed studies and analyses. Regardless, it is still important for concerned departments to focus on women and individuals older than 30 years for the prevention of HAE.

Regarding occupation, the odds of HAE infection were higher in farmers and herdsmen (OR=2.54, 95% CI: 1.60 to 4.02) than in people in other occupations. It is assumed that farmers and herdsmen are more easily exposed to dogs as a result of their occupation, which could increase the risk of infection. Yang et al. presented a similar result [31].

The sensitivity analysis indicated that literature 1 likely caused heterogeneity in the 11 articles
addressing sex. The OR decreased to 1.50 (95% CI: 1.30 to 1.73) and the heterogeneity decreased ($I^2=27\%$, $P=0.20$) when literature 1 was excluded. With regards to the sensitivity analysis for articles concerning occupations, literature 22 was regarded as one of the sources of heterogeneity. The heterogeneity decreased ($I^2=50\%$, $P=0.14$) after literature 22 was excluded, and the OR shifted to 3.01 (95% CI: 2.02 to 4.48). The sensitivity analysis for age suggested that the heterogeneity was not from any of the articles and that the pooled OR was stable (Additional file 7).

Compared to earlier years, the overall HAE prevalence has remained low since 2005, and there has been no indication that it has surged since 2010 (Fig. 3). However, it is necessary to keep monitoring levels through continuous surveillance and investigation in the future [8]. Additionally, the meta-regression analysis suggested that there was a negative correlation between the time period during which the studies were conducted and the HAE prevalence, which corroborates the variation trend of HAE prevalence. A national echinococcosis control project has been carried out in China since 2005 [2], with new control programs and targets being formulated every five years since 2010 [32]. The measures of these programs were developed from three aspects: the population (screening and treatment), animals (dog management and deworming), and the environment (drinking water safety and rodent control). Based on the declining trend in HAE prevalence, it is proven that these prevention and control measures were effective and have resulted in the HAE prevalence being effectively controlled. Given the massive size of population, the magnitude of the susceptible population in China is still higher than in other countries [10, 22]. As a result of this, we should continue to implement One Health strategies that focus on the human control measures and establish a continuous surveillance system for HAE prevention [33-35].

In this SR and meta-analysis, we found that the prevalence of HAE in most studies was close to 0. This would have resulted in the confidence intervals spanning negative numbers, if the prevalence was directly used in this meta-analysis [36]. Therefore, the arcsine transformation was performed on the prevalence reported in each study to make the pooled results more reasonable. This method of data transformation also applies to other meta-analyses addressing disease prevalence. However, the
literature included in this meta-analysis has substantial heterogeneity that may cause the pooled results to be inaccurate. Additionally, there was limited information available about HAE for data extraction, leading to insufficient information for the subgroup analysis.

Conclusions
The prevalence of HAE varied in different areas in China. We found female sex, being ≥30 years of age, and working as a farmer and/or herdsman were the three influencing factors of HAE prevalence in our meta-analysis. It is important to focus on these people who may be with high risk of prevalence. We also described trends in the variation of HAE prevalence in China. HAE continues to pose a threat to public health in some regions of China, and several echinococcosis prevention programs utilizing One Health control strategies have been proposed to combat it. The One Health strategies emphasize interdisciplinary, cross-sectoral, and trans-regional cooperation as well as comprehensive control measures focused on the human-animal-environment relationship. Since One Health strategies were utilized for the preventive measures, HAE prevalence has been on a downward trend and has maintained low levels after 2010. Therefore, these One Health approaches should be used as reference points to formulate programs. High-quality epidemiological investigations and continuous surveillance programs ought to be conducted in the future in order to establish more measures for HAE control.

Abbreviations
AE, Alveolar echinococcosis; PSCs, protoscolices; HAE, human alveolar echinococcosis; DALYs, disability-adjusted life years; SR, systematic review; AHRQ, Agency for Healthcare Research and Quality; OR, odds ratio; CI, confidence interval

Declarations
Ethics approval and consent to participate
Not applicable.

Consent to publish
Not applicable.

Availability of data and materials
All the data associated with this article are included in the supplementary information files.
Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
JH L, WZ J, XZ W conceived and designed the study. XZ W, GD D, M L performed the literature research/quality evaluation/statistical analysis. XZ W, WZ J, ZM G contributed to the writing and revising of the manuscript. All authors read and approved the final manuscript.

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Table 1 List of included articles in the meta-analysis

| Study ID | Reference | Language | Conducted year | Study areas | Sample size | Cases | Score |
|----------|-----------|----------|----------------|-------------|-------------|-------|-------|
| 1        | [37]      | English  | 1991           | Gansu       | 1312        | 65    | 4     |
| 2        | [38]      | English  | 1997           | Gansu       | 2482        | 84    | 6     |
| 3        | [39]      | Chinese  | 1998           | Sichuan     | 3999        | 76    | 4     |
| 4        | [40]      | Chinese  | 2000           | Qinghai     | 1046        | 3     | 3     |
| 5        | [41]      | English  | 1998           | Sichuan     | 1858        | 43    | 2     |
| 6        | [42]      | English  | 1998           | Qinghai     | 3703        | 29    | 5     |
| 7-1      | [43]      | Chinese  | 1997           | Gansu       | 3116        | 113   | 2     |
| 7-2      |            | Chinese  | 2003           | Gansu       | 393         | 6     | 2     |

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|    |   |     |   |   |   |
|----|---|-----|---|---|---|
|    |   | Language | Year | Region | No. of Cases | No. of Deaths | Cases/Deaths |
|    |   | English   | 2002 | Sichuan | 3199 | 198 | 3 |
| 8  | [44] | Chinese   | 2003 | Sichuan | 3018 | 37 | 3 |
| 9  | [45] | English   | 2003 | Sichuan | 7138 | 223 | 3 |
| 10 | [26] | Chinese   | 2005 | Qinghai | 6528 | 125 | 2 |
| 11 | [46] | English   | 2002 | Ningxia | 159 | 8 | 3 |
| 12 | [47] | English   | 2003 | Ningxia | 4773 | 96 | 5 |
| 13 | [48] | Chinese   | 2006 | Qinghai | 1723 | 141 | 3 |
| 14 | [49] | Chinese   | 2007 | Xizang  | 712 | 2 | 2 |
| 15 | [50] | English   | 2008 | Sichuan | 10186 | 311 | 3 |
| 16 | [51] | Chinese   | 1997 | Gansu   | 2485 | 86 | 3 |
| 17 | [52] | Chinese   | 2009 | Sichuan | 538208 | 4386 | 3 |
| 18 | [53] | English   | 2007 | Tibet   | 1511 | 11 | 2 |
| 19 | [54] | Chinese   | 2008 | Qinghai | 1561 | 34 | 3 |
| 20 | [55] | Chinese   | 2013 | Xizang  | 532 | 2 | 4 |
| 21 | [56] | Chinese   | 2011 | Gansu   | 257823 | 3 | 3 |
| 22 | [57] | Chinese   | 2013 | Xizang  | 42356 | 2 | 3 |
| 23 | [58] | Chinese   | 2015 | Gansu   | 118476 | 40 | 5 |
| 24 | [59] | Chinese   | 2016 | Tibet   | 10287 | 3 | 4 |
| 25 | [31] | Chinese   | 2016 | Tibet   | 21497 | 26 | 4 |
| 26 | [60] | Chinese   | 2016 | Tibet   | 77049 | 136 | 5 |
| 27 | [61] | Chinese   | 2016 | Tibet   | 11897 | 33 | 4 |
| 28 | [62] | Chinese   | 2016 | Tibet   | 14289 | 39 | 5 |
| 29 | [63] | Chinese   | 2016 | Tibet   | 5016 | 5 | 5 |
| 30 | [64] | Chinese   | 2016 | Sichuan | 112605 | 301 | 6 |
| 31 | [65] | Chinese   | 2016 | Tibet   | 80384 | 153 | 6 |
| 32 | [66] | Chinese   | 2016 | Gansu   | 198131 | 10 | 6 |
| 33 | [22] | Chinese   | 2016 | Qinghai | 109122 | 573 | 6 |
| 34 | [67] | Chinese   | 2016 | Xizang  | 62348 | 13 | 6 |
| 35 | [33] | English   | 2006 | Gansu   | 302121 | 24 | 6 |
| Groups       | Number of studies | Sample size | Prevalence,% (95%CI) | $\hat{\text{i}}^2,\%$ | $P$ heterogeneity |
|--------------|------------------|-------------|----------------------|-------------------|------------------|
| Overall      | 41               | 2032811     | 0.96(0.71-1.25)      | 100               | 0.01             |
| Areas        |                  |             |                      |                   |                  |
| Gansu        | 9                | 586718      | 1.24(0.81-1.75)      | 99                | 0.01             |
| Ningxia      | 3                | 67280       | 1.49(0.02-5.19)      | 99                | 0.01             |
| Qinghai      | 8                | 126211      | 1.55(0.65-2.82)      | 99                | 0.01             |
| Sichuan      | 8                | 680211      | 2.03(1.30-2.92)      | 100               | 0.01             |
| Tibet        | 9                | 226670      | 0.19(0.13-0.25)      | 86                | 0.01             |
| Xinjiang     | 4                | 345721      | 0.013(0.001-0.036)   | 75                | 0.01             |
| Sex          |                  |             |                      |                   |                  |
| female       | 11               | 22595       | 3.47(2.69-4.34)      | 91                | 0.01             |
| male         | 11               | 23147       | 2.14(1.55-2.82)      | 91                | 0.01             |
| Age group    |                  |             |                      |                   |                  |
| ≥30 years    | 5                | 4720        | 6.41(3.50-10.12)     | 95                | 0.01             |
| <30 years    | 5                | 6198        | 1.64(0.36-3.83)      | 96                | 0.01             |
| Occupation   |                  |             |                      |                   |                  |
| farmer and/or herdsman | 4 | 9987 | 2.90(1.82-4.21) | 90 | 0.01 |
| others       | 4                | 8777        | 1.20(0.63-1.94)      | 86                | 0.01             |

Figures
Records identified through database searching: PubMed 35, Web of Science 267, EMBASE 37, CNKI 23, Wanfang DATA 53, VIP 11 (n=426)

Duplicates removed (n=97)

Articles screened after duplicates removed (n=329)

Records excluded by title and abstract (n=254):
- Reviews, case reports, studies not relevant with AE (n=181)
- Subjects were not human (n=59)
- Study regions were not in China (n=14)

Full-text articles assessed for eligibility (n=75)

Articles excluded by criterion (n=40):
- The samples were used repeatedly (n=12)
- Only one method was used for diagnosis (n=18)
- No prevalence of HAE reported (n=8)
- Lack of full texts (n=2)

Fig. 1 Flow diagram of the selection of studies

Figure 1
Flow diagram of the selection of studies
|                | n   | OR    | 95% CI       | p    | Fixed effect model | Random effects model | Heterogeneity | Random effects model | Heterogeneity |
|----------------|-----|-------|--------------|------|-------------------|----------------------|--------------|----------------------|---------------|
| **subgroup = Ningxia** |     |       |              |      |                   |                      |              |                      |               |
| Yang et al.(2005)[12] | 8   | 1.55  | [0.996; 2.46] | 0.056| 0.002             | 0.175                | 0.195        |                      |               |
| Yang et al.(2006)[13] | 12  | 1.59  | [0.982; 2.59] | 0.055| 0.002             | 0.175                | 0.195        |                      |               |
| Wu et al.(2018)[33-3] | 13  | 2.49  | [1.20; 5.14]  | 0.045| 0.002             | 0.175                | 0.195        |                      |               |
| Fixed effect model    |     |       |              |      |                   |                      |              |                      |               |
| Random effects model  |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **subgroup = Qinghai** |     |       |              |      |                   |                      |              |                      |               |
| He et al.(2001)[4]    | 3   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Schranz et al.(2003)[6] | 29  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wang et al.(2005)[11] | 21  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wu et al.(2018)[34]   | 13  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Fixed effect model    |     |       |              |      |                   |                      |              |                      |               |
| Random effects model  |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **subgroup = Sichuan** |     |       |              |      |                   |                      |              |                      |               |
| Cui et al.(2000)[3]   | 76  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wang et al.(2006)[5]  | 43  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Li et al.(2005)[8]    | 198 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Yu et al.(2006)[9]    | 37  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wang et al.(2006)[10] | 223 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Li et al.(2010)[18]   | 311 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Diao et al.(2015)[20] | 436 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wu et al.(2016)[33-1] | 301 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Fixed effect model    |     |       |              |      |                   |                      |              |                      |               |
| Random effects model  |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **subgroup = Tibet**   |     |       |              |      |                   |                      |              |                      |               |
| Feng et al.(2015)[21] | 11  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Baima et al.(2018)[27] | 3   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Banxian et al.(2018)[23] | 26  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Chen et al.(2018)[25] | 136 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Danzhen et al.(2018)[30] | 33  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Gongsheng et al.(2018)[31] | 39  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wang et al.(2018)[32] | 5   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wu et al.(2018)[33-2] | 153 | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Xiao et al.(2018)[34] | 13  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Fixed effect model    |     |       |              |      |                   |                      |              |                      |               |
| Random effects model  |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **subgroup = Xining**  |     |       |              |      |                   |                      |              |                      |               |
| Wang et al.(2009)[17] | 2   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Qi et al.(2015)[23]   | 2   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Yang et al.(2015)[25] | 2   | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Wu et al.(2018)[33-3] | 24  | 1.04  | [0.91; 1.21]  | 0.001| 0.002             | 0.175                | 0.195        |                      |               |
| Fixed effect model    |     |       |              |      |                   |                      |              |                      |               |
| Random effects model  |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **Fixed effect model** |     |       |              |      |                   |                      |              |                      |               |
| **Random effects model** |     |       |              |      |                   |                      |              |                      |               |
| Heterogeneity: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
| **Residual heterogeneity**: $I^2 = 39$, $Q = 0.45$ | | | | | | | | | |
Figure 2
Forest plot of the meta-analysis for the pooled HAE prevalence in China

Figure 3
Trend in the variation of HAE prevalence in meta-analysis between 1991-2016
Figure 4

Meta-regression result of the time period during which the studies were conducted

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