Risk factors associated with echinococcosis in Chinese general population: a meta-analysis and systematic review

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Research

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Abstract

Background

Echinococcosis is a severe zoonotic disease that imposes a substantial burden on human life. Numerous studies on echinococcosis have involved a variety of risk factors, and it is difficult to evaluate the key risk factors. The objectives of this meta-analysis are to summarize available data on the prevalence of human echinococcosis and identify the key risk factors for echinococcosis.

Methods

Relevant studies were comprehensively searched in the PubMed, EMBASE, Web of Science, Cochrane, Chinese National Knowledge Infrastructure (CNKI), Chongqing VIP Information (VIP), Wanfang and SinoMed databases from database inception until August 22, 2020. A random-effects model was used to estimate the pooled odds ratio (OR) and 95% confidence interval (CI) by integrating the OR values of each risk factor. The I^2 and Q statistics were calculated to evaluate the heterogeneity, and potential sources of heterogeneity were identified using sensitivity analysis and subgroup analysis. Publication bias was estimated by funnel plots and Egger's test.

Results

A total of 1026 studies were identified through the database search, of which 26 were eligible for this meta-analysis. In total, 23 and 9 of the 26 studies were cystic echinococcosis (CE) and alveolar echinococcosis (AE) studies, respectively (6 papers included both AE and CE). The pooled prevalence of echinococcosis was 5.52% (95% CI: 5.47%–5.58%). Ethnicity (OR = 2.93, 95% CI: 1.81–4.75; I^2 = 0), being a herder (OR = 2.66, 95% CI: 2.25–3.14; I^2 = 8%), not washing hands before meals (OR = 2.40, 95% CI: 1.34–4.28; I^2 = 82.8%) and being female (OR = 1.45, 95% CI: 1.26–1.66; I^2 = 33.9%) were risk factors for AE. The top five risk factors for CE were ethnicity (OR = 3.18, 95% CI: 1.55–6.52; I^2 = 79.2%), nomadism (OR = 2.71, 95% CI: 1.65–4.47; I^2 = 55.8%), drinking nonboiled water (OR = 2.47, 95% CI: 1.36–4.47; I^2 = 85.7%), feeding viscera to dogs (OR = 2.35, 95% CI: 1.89–2.91; I^2 = 21.5%), and being a herder (OR = 2.19, 95% CI: 1.67–2.86; I^2 = 85.1%). The study design-specific subgroup analysis showed that the heterogeneity of CE risk factors decreased to varying degrees.

Conclusions

Specific characteristics (i.e., ethnicity and herder status) and behaviors (i.e., not washing hands before meals and feeding viscera to dogs) are possible risk factors for echinococcosis. This study provided remarkable insight for future prevention and control of echinococcosis.

Introduction

Echinococcosis is widely known as a zoonotic and natural focal disease; it occurs as a result of accidental ingestion of the larval stage of *Echinococcus granulosus* (*E. granulosus*) or *Echinococcus multilocularis* (*E. multilocularis*) and is classified into cystic echinococcosis (CE) and alveolar echinococcosis (AE)[1]. The annual numbers of new cases of CE and AE were estimated to be 188,000 and 18,200, respectively, leading to a total of 184,000 and 666,000 disability-adjusted life years (DALYs)[2]. The higher mortality rate of AE than of CE is one of the major reasons for AE's greater global burden[3]. AE is also known as "worm cancer"[4].

Echinococcus parasites can inhabit any part of the human body, mainly the liver, lung, brain and abdomen. Once the parasite attaches to the human body, it will be followed by deteriorating health conditions. CE is endemic in pastoral areas around the world, where the infection is often maintained by herders feeding viscera from infected ruminants to dogs. In contrast, human AE infection is usually associated with contact with wild animals, such as hunting foxes[5]. Therefore, compared to those of *E. granulosus*, the potential risk factors for *E. multilocularis* are more complex because its life cycle involves various wild animals as final hosts and a large number of small mammals (mostly rodents) as intermediate hosts[6].

To date, many studies on the risk factors for echinococcosis have been performed, with each study focusing on certain points. The geographical distribution and prevalence of echinococcosis vary from region to region and are mainly influenced by biological factors and abiotic factors. Biological factors include species, transmission mechanism, density and prevalence among definitive hosts[3]. Abiotic factors include environmental factors, socioeconomic factors and behavioral factors. A study[7] on environmental and socioeconomic risk factors for CE in western China showed that the grassland area ratio positively correlated with the prevalence of human CE and that gross domestic product and land surface temperature (spring) were negative independent variables. Wang Qian[8] reported that fox skin ownership, not preventing flies from landing on food, using open streams as drinking water sources and playing with dogs were statistically significant

behavior risk factors for AE. It is difficult to identify the main high-risk factors for echinococcosis because of differences in the study group, type of echinococcosis and study region among studies. Therefore, the present meta-analysis aimed to pool diversification studies and analyze the main risk factors for AE and CE.

Material And Method

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to perform the literature search. Two researchers (T.T.Z. and B.L.) independently searched for relevant articles published in four English (PubMed, Embase, Web of Science, and Cochrane) and four Chinese (China National Knowledge Infrastructure, China Science and Technology Journal Database, Wanfang Data and SinoMed) databases from their inception to August 22, 2020. The search terms were [(“echinococcosis” OR “echinococcoses” OR “echinococcus infection” OR “hydatidosis” OR “hydatidosises” OR “hydatid cyst” OR “hydatid disease” OR “echinococcus granulosus infection”) AND (“risk factor” OR “population at risk” OR “homo sapiens” OR “man” OR “human”) AND (“People's Republic of China” OR “Chinese” OR “China”)]. In addition, the references of reviews and meta-analyses were manually screened to identify additional potential studies.

Eligibility criteria

Studies were eligible if they met the following inclusion criteria: (1) the research was conducted among Chinese residents, (2) diagnoses of AE and CE were based on a combination of serological and ultrasonic detection, and (3) the odds ratio (OR) and its 95% confidence interval (CI) could be obtained directly or calculated from the study.

Studies were excluded if (1) the publications were neither in Chinese nor in English; (2) the sample size was 30 or less[9]; (3) no risk factors were reported; (4) if there were several articles based on data from one study sample, only the article with the most comprehensive results was included; and (5) low-quality literature based on the overall Newcastle-Ottawa Scale (NOS) or Agency for Healthcare Research and Quality (AHRQ) score.

Quality assessment

Two authors (T.T.Z. and B.L.) independently assessed the quality of the included studies. We employed NOS and AHRQ scores to assess the study quality. The NOS score ranges from 0–8, and scores of 7–8, 4–6 and 0–3 indicate high, medium and low quality of the included study, respectively[10, 11]. The AHRQ score is between 0 and 11, with scores of 8–11 indicating high quality and scores of 4–7 and 0–3 indicating moderate and low quality, respectively[12]. Any disagreements in the process were resolved by discussion with the third author (S.L.).

Data extraction

Two authors (T.T.Z. and B.L.) independently extracted data and information including the first author of the study, year of publication, region of study, type of echinococcosis (AE or CE), study design, sample size, positive cases, age in years, sex, race/ethnicity, herder status, raising of dogs, kind/number of animal host, hand washing status, and the OR value and its 95% CI or the original data from which the OR could be calculated.

Meta-analysis

The ORs and their 95% CIs of the associated factors were pooled using random-effects models if there were at least three studies reporting data on the same factor[13]. The results were also represented using forest plots. The Q test was used to test the level of heterogeneity between studies, and the percentage of total variation in the results due to heterogeneity was assessed based on the I^2 statistic. An $I^2 < 25\%$, 25–50%, 50–75% and 75–100% represents no, moderate, large and extreme heterogeneity, respectively[14]. In this study, $P \geq 0.05$ and $I^2 \leq 50\%$ were considered to indicate heterogeneity between studies[15]. Sensitivity analysis was performed using the leave-one-out method to evaluate the stability and reliability of the result. In addition, Egger's test[16] and funnel plots were used to test for the presence of publication bias. The prevalence of echinococcosis in epidemic areas was obtained by combining the prevalence in cross-sectional studies.

We employed subgroup analysis to explore the source of heterogeneity on the basis of the study design (case-control study and cross-sectional study) and geographic distribution of the studies (Ningxia, Qinghai and Xinjiang). Data were analyzed using the R(4.0.0) package meta[17, 18], and $p < 0.05$ was considered statistically significant.

Results

Study selection

A total of 1,026 articles were originally identified, and 449 were excluded as duplicates. A total of 577 studies were screened, and 26[8, 19-43] of them were eligible and included in this meta-analysis. The literature selection process is detailed in Figure 1. The basic characteristics of the included studies are shown in Table 1. All 20 cross-sectional studies were of medium quality. Within the case-control studies, there were three medium-quality studies and three high-quality studies (Table. 1). There were no cohort studies involved in our analysis.

Overall, the included studies covered 690,322 samples (AE=54,338, CE=635,984), of which 38,358 (AE=1,588, CE=36,770) were positive based on the combined diagnosis of ultrasound and serological methods. The included studies were from the Tibetan Autonomous Region (n=1), Qinghai Province (n=4), Western China (n=2), Yunnan Province (n=1), Gansu Province (n=3), Xinjiang Province (n=5), Ningxia Province (n=5), Sichuan Province (n=3), and the Tibetan Plateau (n=2). Three studies reported only on AE-infected patients, seventeen reported only on CE-infected patients, and six studies reported on both AE- and CE-infected patients.

Ultimately, thirteen potential risk factors reported in more than three studies were included in the meta-analysis, namely, sex, ethnicity, dog ownership, touching fox skin, lack of washing hands before meals, playing with dogs, herder status, feeding viscera to dogs, drinking nonboiled water, presence of stray dogs, number of household dogs, nomadism and eating raw vegetables.

Twenty cross-sectional studies reported the prevalence of echinococcosis until August 2020, and the pooled prevalence of echinococcosis in endemic districts was 5.52% (95% CI: 5.47%-5.58%).

Potential risk factors for AE

Seven risk factors were recognized among the studies including AE, and a meta-analysis was executed on nine cross-sectional studies[8, 25, 31, 32, 35, 39-41, 43]. The results of the meta-analysis and forest plots are summarized in Table 2 and Figure 2.

Four risk factors were statistically significant. According to the strength of correlation, they were ethnicity (Tibetan/Han) (OR=2.93, 95% CI: 1.81-4.75; $p<0.001$), herder status (OR=2.66, 95% CI: 2.25-3.14; $p<0.001$), not washing hands before meals (OR=2.40, 95% CI: 1.34-4.28; $p=0.003$) and sex (female/male) (OR=1.45, 95% CI: 1.26-1.66; $p<0.001$).

Potential risk factors for CE

Eleven risk factors were recognized among the CE studies, and a meta-analysis was performed on twenty-three[19-30, 32-42] of the included papers. These papers include six case-control studies[20, 22, 33, 34, 37, 38] and seventeen cross-sectional studies[19, 21, 23-30, 32, 35, 36, 39-42]. The results are shown in Table 2 and Figure 3.

All of the risk factors were statistically significant. According to the strength of the correlation, the top three were ethnicity (Tibetan/Han) (OR=3.18, 95% CI: 1.55-6.52; $p=0.002$), nomadism (OR=2.71, 95% CI: 1.65-4.47; $p<0.001$) and drinking nonboiled water (OR=2.47, 95% CI=1.37-4.47; $p=0.003$).

Sensitivity analysis

The sensitivity analysis revealed that for most of the risk factors, the results were stable. However, when we removed two studies (P.M. SCHANTZ 2003 and Xianglin Wu 2010) on AE, the heterogeneity of playing with dogs and dog ownership declined markedly, and their corresponding results became statistically significant. Similarly, when we removed the studies of CE He Ye 2019, AiLuo 2014 and Wenting Wu 2018, the heterogeneity of sex, ethnicity and the presence of stray dogs dropped below 50%. More details are shown in Additional file 1.

Publication bias

The publication bias test was performed for all the risk factors included in this study (see Additional file 1). Based on the results of Egger's test and the funnel chart, the CE risk factors sex, herder status and feeding viscera to dogs exhibited publication bias. Other risk factors had no bias; for instance, the p value of Egger's test for the AE risk factor sex was greater than 0.05, and the funnel chart was substantially symmetric (Figure 4).

Subgroup analysis

The study design-specific subgroup analysis was only conducted on CE risk factors because all of the AE articles were cross-sectional studies. The results are shown in Additional file 1. In the case-control studies, two risk factors were identified and were statistically significant: dog ownership (OR=1.35, 95% CI: 1.03-1.83; $p=0.029$) and feeding viscera to dogs (OR=2.76, 95% CI: 2.00-3.83; $p<0.001$). In the cross-sectional studies, seven risk factors were identified and were statistically significant. According to the strength of the correlation, the top three were ethnicity (OR=3.71, 95% CI: 1.60-8.59; $p=0.002$), not washing hands before meals (OR=2.37, 95% CI: 1.40-4.00; $p=0.003$) and herder status

(OR=2.30, 95% CI: 1.74-3.04; $p<0.001$). The heterogeneity of all the CE risk factors decreased to varying degrees. The results of sensitivity analysis and publication bias are shown in Additional file 1.

In general, the studies had a wide geographical distribution and involved seven provinces in China. The subgroup analysis based on study region was performed for Ningxia, Qinghai and Xinjiang provinces and included 3 risk factors, 2 risk factors and 1 risk factor, respectively. The CE risk factors sex in Xinjiang and drinking nonboiled water in Ningxia had high heterogeneity, and the test of their overall effect was not significant. However, the heterogeneity of other risk factors was considerably low. An additional file shows this in more detail (see Additional file 1). The results of sensitivity analysis and for publication bias are shown in Additional file 1.

Discussion

The pooled prevalence of echinococcosis was 5.52% (95% CI=5.47%-5.58%). However, the prevalence of population surveillance reached 0.41% in 2017[44], which is a significant decrease. Having a good understanding of the risk factors for the transmission of echinococcosis helps better control echinococcosis.

This meta-analysis showed that sex, ethnicity, lack of washing hands before meals, herder status and dog ownership were common risk factors for AE and CE. Females are more likely to develop echinococcosis than males. Females undertake housework, such as food preparation and pet care, and they have more opportunities for contact with dogs and sheep[45]. Moreover, females under ultrasonic tests more often than males due to reproductive health, which is called detection signal bias. An experimental study conducted by Blancas Mosqueda M[46] found that parasites may live longer in females due to the potential association between hormones and granulomatous responses, and females are more susceptible to echinococcosis than males. Tibetans have more opportunities to contract echinococcosis because most Tibetans are herders[29], and livestock and sheepdogs are common intermediate hosts of echinococcosis. Tibetans might be a confounding factor since herders contact infected mammals more frequently.

The digestive tract is the main route of human infection because echinococcosis can spread via the ingestion of food, soil, and water contaminated with the feces of infected dogs[47]. Not washing hands before meals and the CE-related risk factors drinking nonboiled water and eating raw vegetables are poor habits that can lead to mistakenly ingesting worm eggs, increasing the risk of disease. This result was consistent with those of previous studies[48, 49].

Nomadism, a lifestyle form involving animal grazing, is a risk factor for CE. The lifestyle of nomads is the opposite of collectivization; nomads live in areas with lower hygiene and economic disadvantage, where they have more exposure to infected dogs and infected foods and a higher probability of getting the infection.

This study included a number of dog-related risks since dogs are the most common host, such as dog ownership, playing with dogs, number of household dogs, feeding viscera to dogs and the presence of stray dogs. Stray dogs easily find and ingest raw offal from infected animals, and their feces is not collected from the environment. These dogs leave the echinococcus eggs behind and thereby expand the range of contamination. Infected domestic dogs carry eggs in their fur or discharge excrement that carries the eggs[50]. All of these factors will increase the chance of human echinococcosis. Furthermore, for many rural families, dogs are less likely to obtain nutritious food, so they hunt small mammals, which are intermediate hosts of echinococcus[51]. This will increase the risk of echinococcosis. On the other hand, many dog owners fed dogs the viscera of livestock, which supports the lifecycle of echinococcus[52]. Dogs, the main participants in transmission, play a key role in prevention and control. In New Zealand (1959–1991) and Tasmania (1964–1996), dogs were systematically dewormed every 45 days[53]. This strategy was extremely successful in the final elimination of CE as a public health problem. It is noteworthy that feeding dogs viscera was mentioned in both cross-sectional studies and case-control studies, and the results were basically consistent.

In the study of Schweiger[54], an increase in the fox population density started in 1985, and after a 10-15 year latency period, the number of human AE cases underwent a significant increase. A reasonable explanation may be urbanization[55], which has resulted in an increased number of foxes appearing in the living quarters of people. Increased opportunities for people to come into contact with foxes increased the infection risk for the human population. Some previous studies have also shown that exposure to foxes increases the risk of AE infection[45, 56]. However, the risk of touching fox skin was not significant in this study. After sensitivity analysis, I^2 changed to 0.00, but the test for an overall effect was still not significant. This might be caused by a lack of data, outdated studies and the poor quality of the literature.

The results of the test for an overall effect of the AE-related risk factors dog ownership and playing with dogs were not statistically significant. After sensitivity analysis, the results became significant. Thus, the studies of Xianglin Wu 2010 and P.M. SCHANTZ 2003 had an excessive influence on the result. The results of the test for an overall effect of the CE-related risk factors sex, herder status and feeding viscera to dogs revealed publication bias. After we conducted subgroup analysis based on study design, the publication bias disappeared, and heterogeneity decreased. For example, as shown in Figure 5, when we excluded the case-control study, the funnel chart became symmetric, and the result of the CE risk factor sex became significant. Therefore, differences in study design may be the source of heterogeneity. However, the region-

specific subgroup analysis did not greatly limit heterogeneity. The studies related to the risk of drinking nonboiled water in Ningxia included two case-control studies and a cross-sectional study. The sample size related to the risk factor sex in Xinjiang was smaller than that of the other factors. The different study designs and small sample sizes may explain the high heterogeneity and nonsignificant overall effects. The heterogeneity of the other risk factors was considerably low. It is not clear whether study region was the source of heterogeneity.

Our study has several limitations, most relating to the lack of literature for further analysis. Although we have identified some risk factors for echinococcosis, more factors need to be analyzed, such as environmental factors and economic factors. Some limitations are related to the study design of the included studies. All of these are observational studies (case-control and cross-sectional studies) that have intrinsic limits. For instance, observational studies are prone to selection bias and information bias[57]. In addition, the chronological sequence of exposure and outcome could not be determined in these studies. Moreover, the region of this study was found to be insufficient. Specifically, the study area included in this meta-analysis did not cover all the regions with a high incidence of echinococcosis.

Conclusion

In summary, the most active factors affecting the prevalence of echinococcosis among residents are dog-related factors, such as dog ownership, playing with dogs, feeding viscera to dogs, number of household dogs and the presence of stray dogs. There were also diet-related factors, such as not washing hands before meals, drinking nonboiled water, and eating raw vegetables, and demographic factors, such as sex and herder status. Prevention of echinococcosis in humans lies in improved personal and environmental hygiene, and echinococcosis in animals can be prevented by monthly artificial pest control[58]. A series of national control measures, including regular dog deworming, public health education and community screening, are in operation[59]. They have been proven to be effective[58, 59]. The focus of current prevention and control work is the major risk factors and implementation of these policies.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Contributors

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Drafting of the manuscript: TZ, SL.

Approval of the final version for publication: All authors.

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Not applicable

Conflict of interest

All authors declare that there are no conflicts of interest.

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Tables

Table 1 Main characteristics of the included studies.

No.	Author	Year of Publication	Region	Type of Echinococcosis	Study Design	Sample Size	Positive case	Risk Factors*	Quality score
1	Manxiang Zeng	2020	Western China	CE	Cross-sectional	470400	32928	11	4
2	Wei He	2019	SiChuan	CE	Case-control	-	-	1,11,12	8
3	Bin Li	2019	Tebit	CE	Cross-sectional	80384	1371	1,7	6
4	Wenting Wu	2018	Tibetan plateau	CE	Case-control	378	189	3,5,8,10,11	7
5	Kun Li	2017	Qinghai	CE	Cross-sectional	600	11	1	4
6	Ruixia Yuan	2017	Western China	CE	Cross-sectional	5813	90	5,8,10,9,13	4
7	Ye He	2017	Yunnan	AE CE	Cross-sectional	9460	348	1 1	5
8	Dan Li	2015	Gansu	CE	Cross-sectional	972	92	8,12	5
9	Shijie Yang	2015	Xinjiang	CE	Cross-sectional	42356	159	7	5
10	Xinwei Qi	2015	Xinjiang	CE	Cross-sectional	532	23	1,7	4
11	AiLuo	2014	Qinghai	CE	Cross-sectional	23445	1048	1,2,7	6
12	Patrick Giraudoux	2013	Tibetan plateau	AE	Cross-sectional	15614	577	1,2,7	5
13	Kechong Bai	2013	Xinjiang	CE	Cross-sectional	869	11	1	4
14	Guizhi Wang	2009	Xinjiang	CE	Case-control	5037	141	2,3,7	6
15	Junxia Yuan	2011	Gansu	CE	Case-control	75	25	3,8	6
16	Yunling Feng	2011	Ningxia	AE CE	Cross-sectional	6039	89	1 1	5
17	Xianglin Wu	2010	Ningxia	AE CE	Cross-sectional	3196	72	1,3,5 1,3,5,8	5
18	Li Zhong	2009	Xinjiang	CE	Cross-sectional	3691	56	1,7	5
19	Li Li	2008	Ningxia	CE	Case-control	303	101	3,9,13	7
20	Jv Yang	2008	Ningxia	CE	Case-control	387	129	8,9,13	6
21	Yu Rong Yang	2006	Ningxia	AE CE	Cross-sectional	4773	96 75	1 1,9	5
22	Qian Wang	2006	Sichuan	AE	Cross-sectional	7138	223	1,2,3,4,5, 6,7	5
23	P. M. SCHANTZ	2003	Qinghai	AE CE	Cross-sectional	3703	31 243	1,2,5,6,7,8,9,10 1,2,5,7,8,9,10	6
24	Qian Wang	2001	Sichuan	AE	Cross-sectional	1858	43	1,3,4,5,6	4

				CE			65	1,3,5,10,12	
25	Xianhong Wu	2001	Qinghai	CE	Cross-sectional	817	38	1,2	4
26	P.S. Craig	2000	Gansu	AE	Cross-sectional	2482	84	3,4	5

*1. Sex (Female/Male); 2. Ethnicity (Tibetan/Han); 3. Dog ownership; 4. Touched fox skin; 5. Not washing hands before meals; 6. Playing with dogs; 7. Herder status; 8. Feeding viscera to dogs; 9. Drinking nonboiled water; 10. Presence of stray dogs; 11. Number of household dog (with each addition); 12. Nomadism; 13. Eating raw vegetables

AE: alveolaris echinococcosis; CE: cystic echinococcosis.

Table 2 Result of echinococcosis risk factors meta-analysis

Risk factor	Number of studies included	Type of echinococcosis	Sample size	positive cases	Test of heterogeneity			OR	95% CI	Test of overall effect	
					Q	P	I ² (%)			Z	P-value
Sex(Female/Male)	8	AE	51781	1479	10.59	0.158	33.9	1.45	1.26-1.66	6.73	<0.001
Ethnicity(Tibetan/Han)	3	AE	26455	831	1.92	0.382	0	2.94	1.81-4.75	4.38	<0.001
Dog ownership	4	AE	14674	422	8.15	0.043	63.2	1.52	0.96-2.39	1.78	0.075
Playing with dogs	3	AE	12699	297	24.44	<0.001	91.8	1.72	0.45-6.52	0.8	0.424
Touch fox skin	3	AE	11478	350	4.82	0.090	58.5	1.19	0.70-2.02	0.64	0.523
Not washing hands before meals	4	AE	15895	369	17.49	0.001	82.8	2.40	1.34-4.28	2.96	0.003
Herder status	3	AE	26455	831	2.17	0.337	8	2.66	2.25-3.14	12.63	<0.001
Sex(Female/Male)	14	CE	139367	3450	89.4	<0.001	85.5	1.30	1.11-1.53	3.27	0.001
Ethnicity(Tibetan/Han)	4	CE	33002	1470	14.44	0.002	79.2	3.18	1.55-6.52	3.16	0.002
Dog ownership	6	CE	10847	593	9.88	0.079	49.4	1.54	1.09-2.17	2.46	0.014
Not washing hands before meals	5	CE	14948	659	21.44	<0.001	81.3	2.05	1.35-3.10	3.39	0.001
Herder status	7	CE	159148	3041	40.25	<0.001	85.1	2.19	1.67-2.86	5.71	<0.001
Feeding viscera to dogs	7	CE	14524	840	7.64	0.266	21.5	2.35	1.89-2.91	7.78	<0.001
Drinking nonboiled water	5	CE	14979	638	27.91	<0.001	85.7	2.47	1.36-4.47	2.99	0.003
Presence of stray dogs	4	CE	11752	587	6.11	0.106	50.9	1.75	1.15-2.65	2.64	0.008
Number of household dog(with each addition)	3	CE	470778	33117	7.48	0.024	73.2	1.66	1.17-2.34	2.85	0.004
Nomadism	3	CE	2830	157	4.53	0.104	55.8	2.71	1.65-4.47	3.92	<0.001
Eating raw vegetables	3	CE	6503	320	0.84	0.658	0	1.86	1.47-2.35	5.16	<0.001

Figures

Figure 1
Summary of the literature search and study selection

Figure 2

The forest chart of AE factors. A: Sex (Female/Male); B: Ethnicity (Tibetan/Han); C: Dog ownership; D: Playing with dogs; E: Touch fox skin; F: Not washing hands before meals; G: Herder status.

Figure 3

The forest chart of CE factors. A: Sex (Female/Male); B: Ethnicity (Tibetan/Han); C: Dog ownership; D: Not washing hands before meals; E: Herder status; F: Feeding viscera to dogs; G: Drinking nonboiled water; H: Presence of stray dogs; I: Number of household dog (with each addition); J: Nomadism; K: Eating raw vegetables.

Figure 4

Funnel chart of AE risk factor sex

Figure 5

Funnel chart of CE risk factor sex before and after study design subgroup analysis.

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