

Prevalence difference of *Helicobacter pylori* infection between Tibetan and Han ethnics: A meta-analysis on epidemiologic studies

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Abstract

Background *Helicobacter pylori* (Hp) appears worldwide prevalent as a primary carcinogenic pathogen of human gastric cancer. China is a multi-ethnic country, and the prevalence of Hp infection may be diverse among ethnics. This meta-analysis was conducted to compare the prevalence of Hp infection between Tibetan and Han ethnics.

Methods The databases, PubMed, Web of Science, Blackwell Journals, CNKI, and Wanfang were searched. Those studies which reported the prevalence of Hp infection between Tibetans and Hans in China were eligible. There were no limitation to Hp detection method, publication language, and observation period. RevMan 5.3 and Stata 12.0 softwares were used for heterogeneity tests and meta-analyses. Meanwhile, subgroup analysis, sensitivity analysis and publication bias evaluation were performed where applicable.

Results Totally, 11 studies with 3,826 Tibetans and 19,787 Hans were analyzed. The pooled prevalence of Hp infection were 62.2% and 55.3% among Tibetans and Hans, respectively. Tibetans had higher risk of Hp infection than Hans (OR=1.38, 95% CI 1.05-1.80). In subgroup analysis, those Tibetans with upper gastrointestinal symptoms (OR=1.51, 95% CI 1.06-2.16), inhabiting in Tibet (OR=1.51, 95% CI 1.22-1.87), or in Northwestern region (OR=1.15, 95% CI 1.00-1.31) had significantly higher risk of Hp infection. Additionally, in recent ten years, Hans appeared a decreased risk of Hp infection (OR=1.81, 95% CI 1.42-2.30). Heterogeneity was common, while sensitivity analyses showed partially inconsistent results against main findings.

Conclusions This study demonstrated the higher prevalence of Hp infection in Tibetans compared with Hans, especially in recent years, or in the Tibet and the northwest China, as well as symptomatic Tibetans. It suggests tailored strategy and robustness need further consider for Hp screening and eradication among Tibetans.

Trial registration: The present systematic review and meta-analysis was registered in the PROSPERO International Prospective Register of Systematic Reviews supported by the National Institute for Health Research of the National Health Service (NHS), UK (registration number: CRD42019121192).

Background

Helicobacter pylori (Hp) have been defined as a class-I carcinogenic pathogen of human gastric cancer according to the World Health Organization.[1] The association between Hp infection and gastric cancer risk was identified both in western and eastern countries.[2, 3] In low incidence countries of gastric cancer, Hp was approved to increase the risk of precancerous lesion atrophic gastritis.[2, 4] In Japan, the massive screening and eradication of Hp may conceivably decrease the incidence of gastric cancer. [5] Till now, in the world, only Japan and South Korea established the nationwide organized screening of Hp infection and gastric cancer,[6] which resulted in higher proportion of early diseases and better population survival of gastric cancer.[7]

China is a multiethnic country with diverse prevalence of Hp infection in different ethnics or regions. In the 2002–2004 nationwide survey, the overall prevalence of Hp infection was decreased to 56.2%, but the highest prevalence of Hp infection was found in Tibet (84.6%).^[8] It would be informative to understand the prevalence difference in Hp prevalence among ethnics, and useful to consider tailored screening and eradication strategy for Hp infection. As far as we know, there was no systematic review or meta-analysis focused on the incidence of Hp between Tibetans and Hans. Therefore, we comprehensively retrieved the available data on the prevalence of Hp infection involving both Tibetans and Hans, and aimed to compare their prevalence of Hp infection through meta-analyses.

Methods

Reporting

This meta-analysis were conducted according to the MOOSE 2000 statements,^[9] and a flow diagram was drawn.^[10]

Literature search

The databases, PubMed, Web of Science, Blackwell NRC Online Journals, China National Knowledge Infrastructure (CNKI), and Wanfang. CNKI and Wanfang databases collected the domestic literature published in Chinese were comprehensively searched till April, 2018. The PubMed was searched with the following search terms, "(((Han[Title/Abstract]) OR Han nationality[Title/Abstract])) AND ((Tibet[Title/Abstract]) OR Tibetan)) AND (((HP[Title/Abstract]) OR H. pylori[Title/Abstract]) OR Helicobacter Pylori[Title/Abstract])". A similar search strategy was applied in searching published literatures in Web of Science, Blackwell NRC Online Journals, CNKI and Wanfang.

Eligibility

The studies that simultaneously reported the prevalence of Hp both in Tibetans and Hans were potentially eligible. Any pattern of cohort study, cross-sectional study, or case-control study conducted in China was acceptable. The participants could be originated from a hospital-based research or a massive population-based research. There was no limitation on Hp detection method (biopsy, breath test, stool test, or serological test), publication language, and period of study conduction.

Selection and assessment

The search results from 5 databases were combined by a reviewer (DB), and then the duplicate literature was eliminated. Two reviewers (DB and AMW) separately browsed the titles/abstracts, and assessed the potentially eligible full-texts, according to the predefined inclusion and exclusion criteria. Discrepancies

were resolved by consensus with a third reviewer (KL). Risk of bias assessment of all included studies was independently performed by two reviewers (DB and AM W), according to the Newcastle-Ottawa Scale (NOS).[11] The scale contains 8 criteria of 3 categories to evaluate the sample selection, comparability on the bases of design or analysis, outcome assessment.

Data extraction

Data were extracted independently by two reviewers (DB and KL). The basic information of analyzed studies included publication year, sample size, sample region, Hp detection method, average age, sex proportion, and symptoms of upper gastrointestinal tract presenting or not. The subtotal of Tibetans or Hans, and the corresponding event numbers of Hp positivity were extracted. Where applicable, the events numbers could be calculated through the reported percentages.

Statistics

The Cochrane Reviewer Manager (RevMan) 5.3, the STATA 12.0 softwares, and the PASS 11 were used for statistical analysis, where applicable. [12–14] The pooled prevalence of Hp infection in Tibetans and Hans was combined in meta-analysis for rate, with 95% confidence intervals (CIs). The pooled odds ratios (ORs) and their 95% CIs for Hp prevalence were calculated between Tibetans and Hans by fixed or random effect model where suitable. The Mantel-Haenszel test or the DerSimonian-Laird test was used for fixed or random model respectively, and two-sided p values for the pooled ORs < 0.05 were considered as statistical significance. I-square was estimated to evaluate the heterogeneity of meta-analyses. If the p values of heterogeneity test < 0.1 , random effect model should be considered. Funnel plots were drawn by the STATA 12.0 software to evaluate the publication bias.[13] Both the continuity corrected Begg's rank correlation test and Egger's linear regression test were used.[15] Any p value < 0.05 of Begg's or Egger's test was considered as significance of publication bias. In Egger's test, the intercept and its 95% CI was estimated. In sensitivity analysis, the leave-one-out method was applied for those meta-analyses pooling at least two studies. Additionally, L'Abbé plot and Galbraith plot were used to observe the heterogeneity. For an individual study, the power $(1 - \beta)$ was estimated by the PASS 11 software.[14] The category of two independent proportions to test inequality was selected, and parameter module of proportions was used for calculation.[16] Two-sided Z test (pooled) was provided with $\alpha = 0.05$. Additional sensitivity analysis was performed by excluding the studies with the power < 0.70 , or < 0.80 .

Ethics

The ethical approval was not required due to the nature of literature-based research.

Results

Literature and general information

Totally, 1,412 citations were searched from the 5 electronic databases, and there were 868 citations after consolidation of databases. After remove citations that have nothing to do with Hp infection about ethnic groups, there are 27 citations remained for full-text review. Finally, 11 studies were eligible,^[17–27] and 3,826 Tibetans and 19,787 Hans were analyzed. The PRISMA flow chart of this meta-analysis was shown in the Figure 1. The general information of included studies and corresponding estimated power were shown in the Table 1. The quality assessment according to the NOS was display in the Table 2.

Overall prevalence comparison

The pooled prevalence of Hp infection in Tibetans and Hans were 62.2% (95% CI 54.5%–70.0%, random model, heterogeneity $p < 0.001$) and 55.3% (95% CI 45.2%–65.4%, random model, heterogeneity $p < 0.001$), respectively. The overall comparison on the prevalence between Tibetans and Hans showed a higher prevalence in Tibetans (OR = 1.38, 95% CI 1.05–1.80, $p = 0.02$) (Figure 2).

Subgroup analysis by periods

Regarding the different periods, the subgroup analysis demonstrated that in the recent years (2010–2018) Hans had lower prevalence (OR = 1.81, 95% CI 1.42–2.30, $p < 0.0001$) (Figure 3). Over 1990–1999, 2000–2009, and 2010–2018 periods, the pooled prevalence was decreased among Hans from 61.0% (95% CI 40.8%–81.1%), 57.4% (95% CI 40.6%–74.2%) to 45.3% (95% CI 36.1%–54.5%). In contrast, the prevalence of Tibetans did not experience the similar decrease.

Subgroup analysis by regions

The subgroup analysis by regional difference demonstrated Tibetans had higher prevalence of Hp infection in Tibetan Autonomous Region (OR = 1.51, 95% CI 1.22–1.87, $p = 0.0002$) and the Northwestern region (OR = 1.15, 95% CI 1.00–1.31, $p = 0.04$). But subgroup analysis by regional difference in Sichuan Province is not the same as that in Tibetan Autonomous Region and the Northwestern region (Figure 4). Moreover, the pooled prevalence demonstrated Tibetan Autonomous Region was a high prevalent area for both Tibetans (71.3%, 95% CI 63.3%–79.2%) and Hans (64.5%, 95% CI 50.7%–78.2%).

Subgroup analysis by symptomatic presence

Among those with upper digestive tract symptoms, the prevalence of Hp infection was significantly higher in Tibetans than in Hans (OR = 1.51, 95% CI 1.06–2.16, $p = 0.02$) (Figure 5). However, the pooled

prevalence was not increase among symptomatic Tibetans (62.1%, 95% CI 52.0%–72.3%), against asymptomatic Tibetans (62.4%, 95% CI 47.7%–77.2%).

Sensitivity analysis

The results of sensitivity analysis were shown in Table 3. In the leave-one-out re-analysis, only the subgroups 1990–1999 period and asymptomatic subpopulation had always consistent results, i.e. no significant differences between Tibetans and Hans. The remanent subgroups had certain substantial changes against primary results in all-included meta-analysis. Additional sensitivity analysis including only studies with power \geq additional sensitivity found overall comparison and symptomatic subgroup were changed to non-significance, but in subgroups 2000–2009 and 2010–2018 periods, as well as Tibet and Northwestern regions, Tibetans still had significantly higher prevalence of Hp infection (Table 3)

Publication bias and heterogeneity

The Begg's funnel plot and Egger's regression plot of all-included meta-analysis were shown in Figure 6. The continuity corrected Begg's test demonstrated no significant publication bias ($p = 0.640$). Likewise, the Egger's test also found no significant publication bias (coefficient = 1.02, 95% CI $-5.137.16$, $p = 0.717$). Consistent results of publication bias tests were found in the leave-one-out sensitivity analyses (data not shown). However, the L'Abbé plot and the Galbraith plot demonstrated the existence of heterogeneity (Figure 6). Actually, heterogeneity comprehensively existed among the present meta-analyses. In the all-included meta-analysis, the I-square was 83% ($p < 0.00001$) (Figure 2).

Discussion

The present meta-analysis suggested that the prevalence of Hp was different between Tibetans and Hans. Tibetans had higher prevalence of Hp infection than Hans, especially among those with upper gastrointestinal symptoms. Tibetans lived in Tibet Autonomous Region and Northwest regions had higher prevalence, but not in Sichuan. The prevalence of Hp infection was comparable before the 2010, but the prevalence was higher in Tibetans after the 2010. These results would be informative for developing a tailored strong Hp infection screening and eradication strategy targeting Tibetans.

The average prevalence of Hp infection in China between 1983–2013 was 55%.^[28] Our study showed that the prevalence of Hp infection among Tibetans and Hans was 63.98% and 55.3%, respectively. The prevalence of Tibetans was higher than the average. A systematic review in New Zealand by McDonald, et al. addressed that the Hp prevalence were 39%–83% and 7%–35% in pacific and European population, respectively.^[29] In a large cross-sectional nationwide multicenter study in Korea, 10,796 subjects were enrolled, and the Hp infection rate was 54.4%.^[30] In Japan, a cross-sectional study including 14,716 subjects showed that the prevalence of Hp was 37.6% in women and 43.2% in men.^[31] In contrast, the prevalence of Hp infection among Tibetans in China was also higher than the prevalence of the ethnic

minority in Vietnam (38.1%) and Thailand (54.5%).[32, 33] Besides, the difference in target population and regions, we think different diet, lifestyle and sanitary were also responsible for those results.

There has been a proven strong association between Hp infection and gastric cancer. A systematic review and meta-analysis including randomized controlled trials from China, Japan, USA, and UK showed that eradicating Hp could reduce the incidence of gastric cancer among healthy asymptomatic infected Asian individuals, but this result was considered unable to be extrapolated to other populations.[34] Other literatures demonstrated that Hp eradication prevented the development of gastric cancer, to some extent.[35, 36] Besides, there were some literatures considering that patients with early gastric cancer after endoscopic resection had a lower incidence of metachronous gastric cancer due to the eradication of Hp.[37–39] In a word, we may potentially reduce the incidence of gastric cancer in certain specific population through screening and eradication of Hp.

Chronic atrophic gastritis (CAG), a precancerous lesion, plays a significant role in the development of gastric cancer in the initial stage. The association between CAG and Hp has been described.[40] The cytotoxin-associated gene product (cag A), the vacuolating toxin (vac A) and adhesion protein BabA2 are three major virulent factors of Hp. Studies from Brazil, Saudi, Mexican, Japan and Laos showed that the three virulent factors might be meaningful markers of the toxicity of Hp and clinical outcome of patients.[41–45] Providing combining with detection of precancerous lesion and Hp virulent factors, it may improve the individualized and precise screening, treatment and surveillance strategy for high-risk subpopulation of gastric cancer. In Tibet, with the high prevalence of Hp and related limited finance, the design of screening strategy in a cost-effective manner should be more practical.

These data provided us with evidence that Tibetans had a higher prevalence of Hp than Hans, especially among the patients with upper gastrointestinal symptoms and living in Tibet Autonomous Region and the northwestern China. By now, it is hard to establish the nationwide organized population screening program for gastric cancer. However, the government can emphasize and promote the health education of Hp infection screening and eradication, as well as the endoscopic screening and surveillance for precancerous lesion and early gastric cancer. In particular, as a high-risk subpopulation of gastric cancer, incorporation of Hp screening and eradication into medical insurance may subsequently improve the control of gastric cancer in the future.

The results need interpret with caution due to some limitations. Although multiple databases were comprehensively searched, the limited sample size impaired the power of results. Some other confounding data, such as sex, age and detection methods, were unavailable to perform further subgroup analysis. The various virulent factors were not employed in Chinese studies, and additional identification of those really high-risk subpopulation would be not feasible. Finally, the nature of multi-ethnics in China, the understanding of Hp prevalence in ethnic minorities other than Tibetans would be more informative to design a domestic screening strategy.

Conclusions

This meta-analysis demonstrated that Tibetans had higher prevalence of Hp infection than Hans, especially among those Tibetans with upper gastrointestinal symptoms. The Tibetans in Tibet Autonomous Region and the northwestern China had higher prevalence compared to Hans. After the 2010, the prevalence of Tibetans became higher than that of Hans. A tailored strong screening and eradication strategy for Hp infection need consider among Tibetans.

Abbreviations

Hp: Helicobacter pylori

CAG: Chronic atrophic gastritis

cag A: the cytotoxin-associated gene product

vac A: the vacuolating toxin

BabA2: Blood group antigen-Binding Adhesion2

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The authors have all contributed to this manuscript and approve this submission. JK H and XZ C equally contributed to the conception and design of the study, and drafting the manuscript; DB, KL, AM W and SY-D participated in acquisition of data and the analysis and interpretation of the data and statistical analysis; WH Z and PM B participated in the study concept, interpretation of the data, drafting the manuscript, critical revision of the manuscript.

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Figures

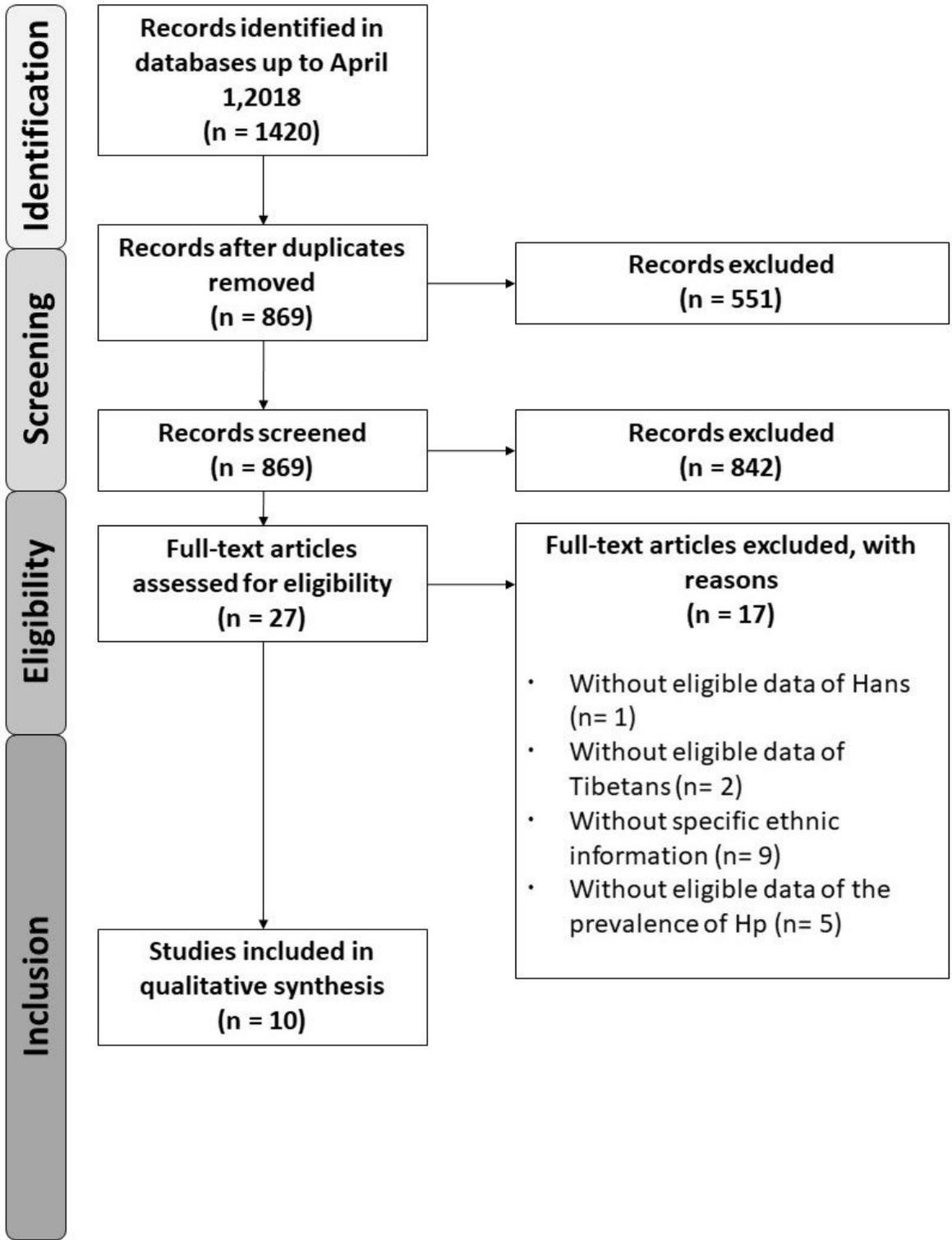


Figure 1

The PRISMA flow chart of the meta-analysis.

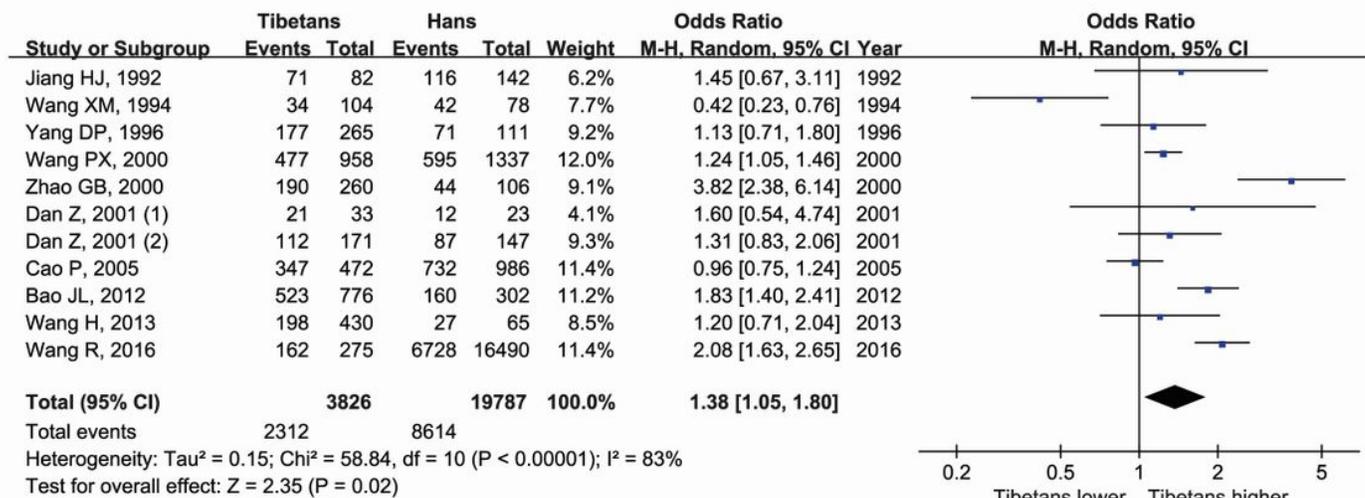


Figure 2

The forest plot of the overall comparison on Hp prevalence between Tibetans and Hans.

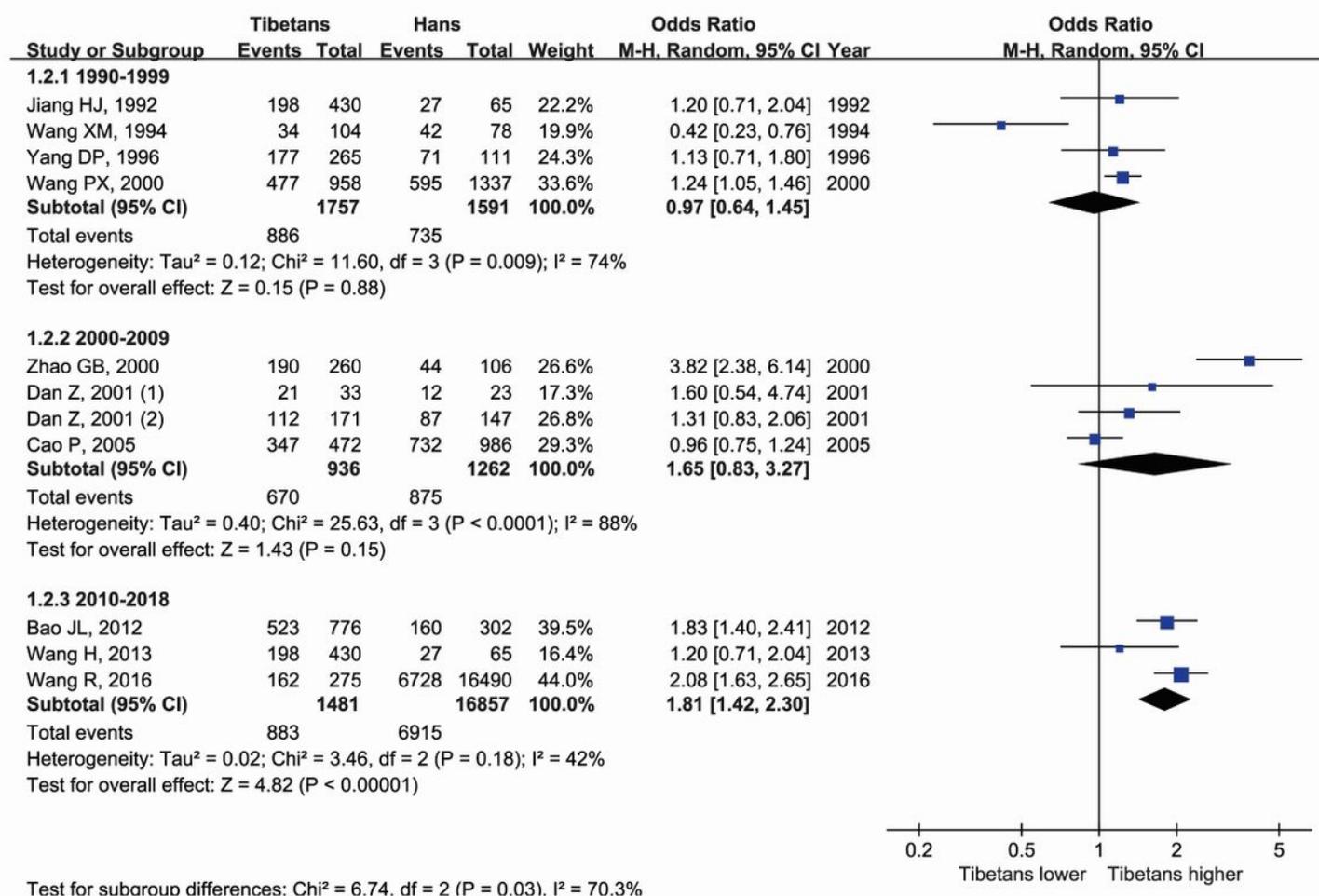


Figure 3

The forest plot of the subgroup analysis by study periods.

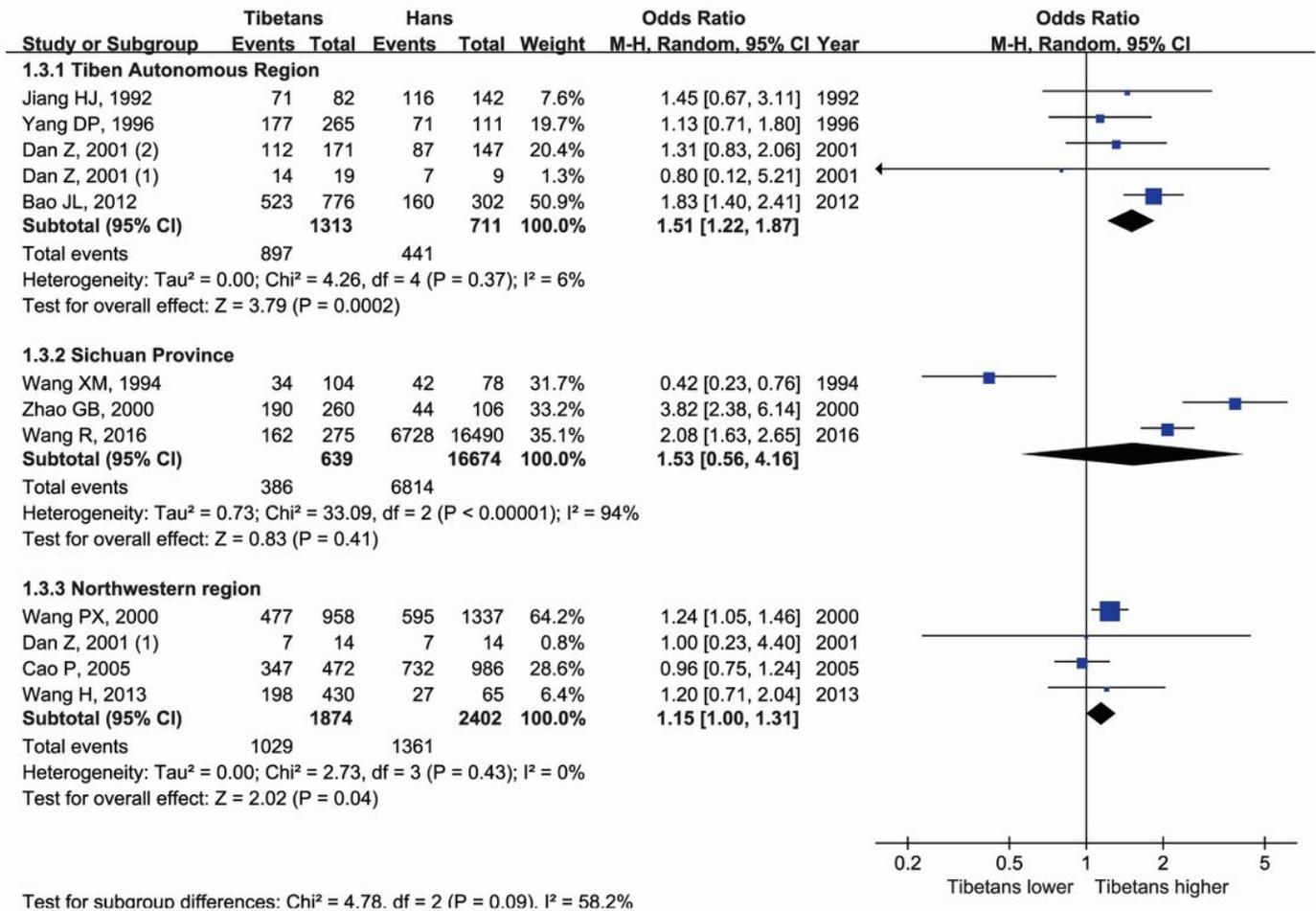


Figure 4

The forest plot of the subgroup analysis by residence regions.

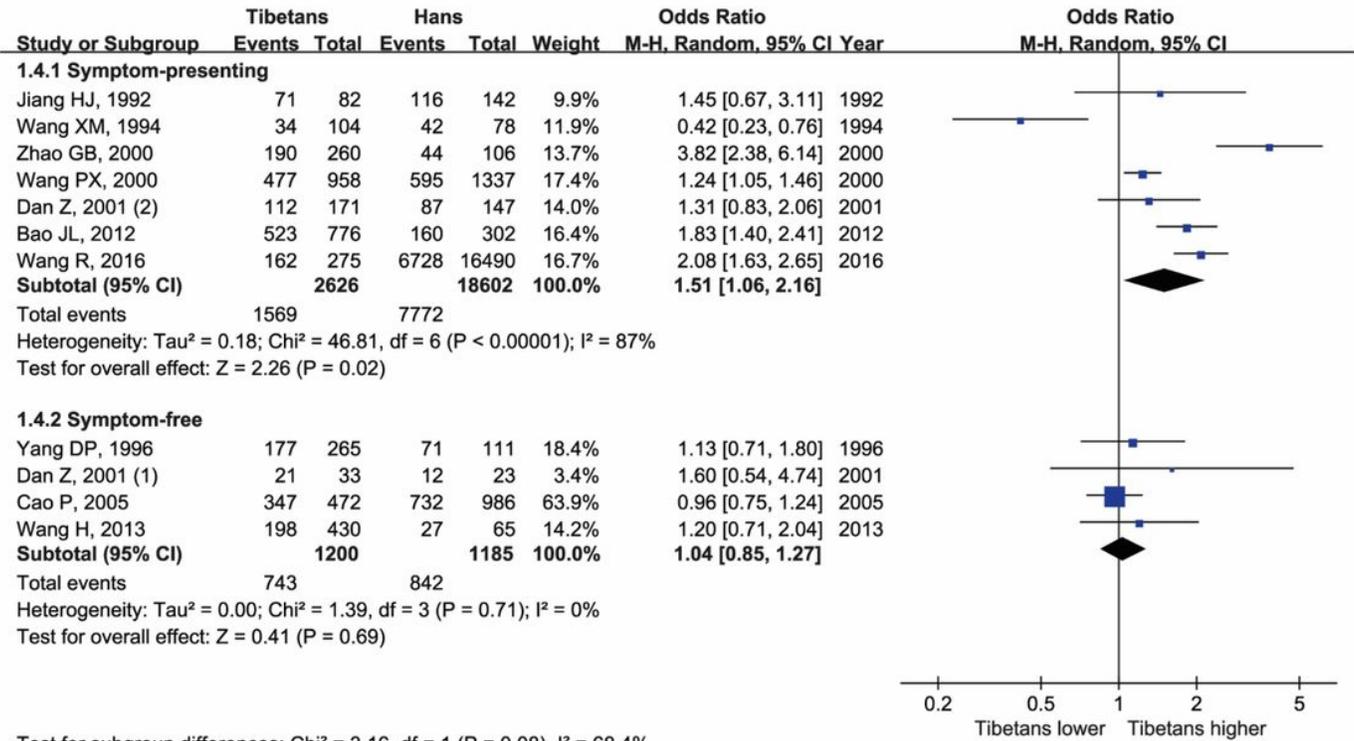


Figure 5

The forest plot of the subgroup analysis by symptomatic presence.

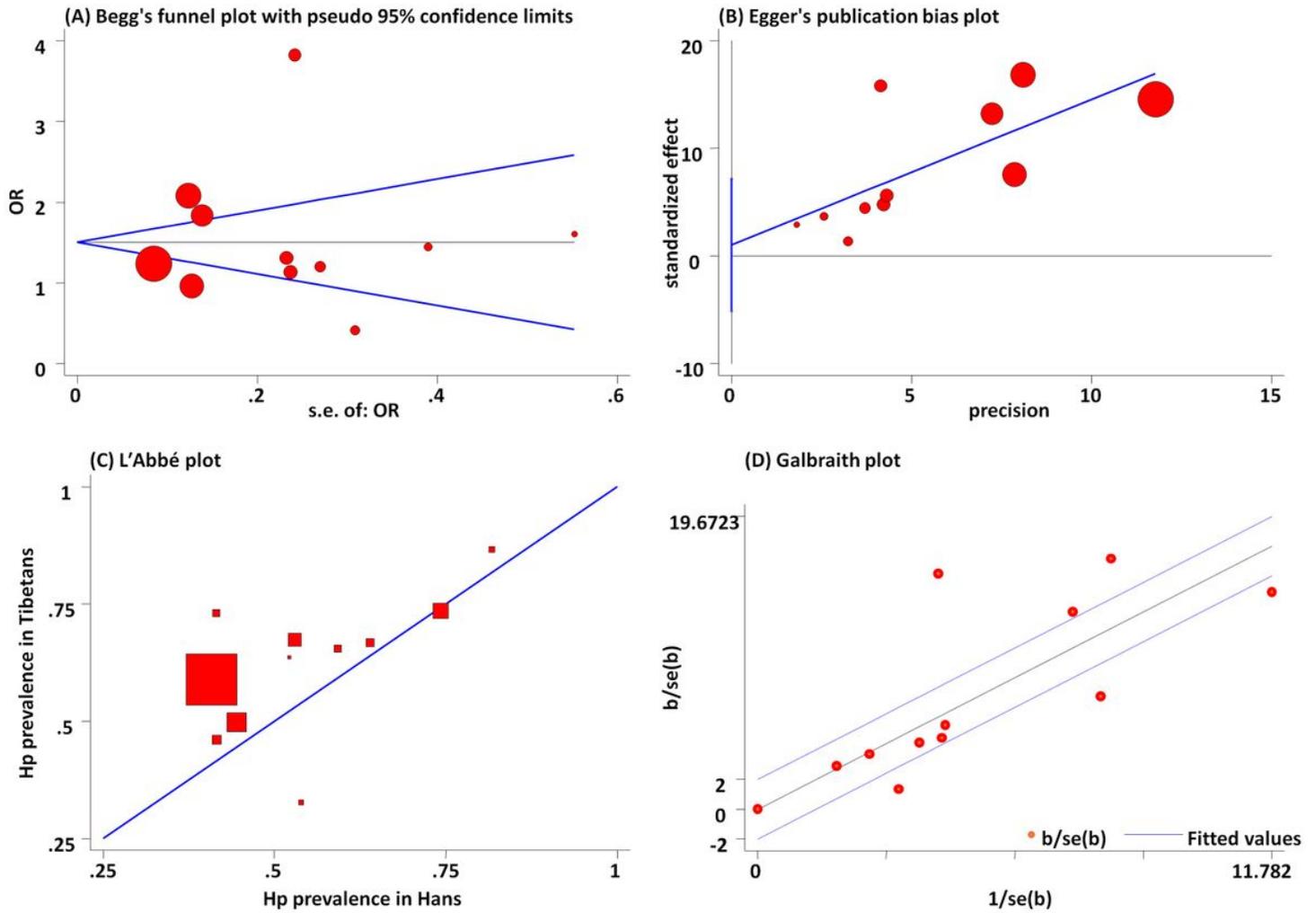


Figure 6

(A) Begg's funnel plot, (B) Egger's regression plot, (C) L'Abbé plot, and (D) Galbraith plot of the all-included meta-analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table3.docx](#)
- [Table1.doc](#)
- [Table2.doc](#)