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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79803

Title: A Meta-analysis on the Epidemiology of Gastroesophageal Reflux Disease in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03009727
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Professor
Reviewer's Country/Territory: Russia
Author's Country/Territory: China

Manuscript submission date: 2022-09-07

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-09-07 14:06

Reviewer performed review: 2022-09-14 14:18

Review time: 7 Days

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This article is very relevant, allowing to objectify the prevalence of GERD in China. The meta-analysis was compiled in full accordance with the PRISM recommendations. Methods and results are described in detail and well illustrated. The Discussion section reflects a good interpretation of the results. The quality of the organization and presentation of the material is very high.

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Position: Editorial Board
Academic degree: MD
Professional title: Assistant Professor, Staff Physician
Reviewer's Country/Territory: United States
Author's Country/Territory: China

Manuscript submission date: 2022-09-07
Reviewer chosen by: AI Technique
Reviewer accepted review: 2022-09-29 09:45
Reviewer performed review: 2022-10-06 09:21
Review time: 6 Days and 23 Hours

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SPECIFIC COMMENTS TO AUTHORS

thank you for submitting to the journal the article is very interesting. however, please see my comments below and in the attached article. 1. english language editing is required. 2. please follow prisma workflow 3. please follow quadas-2 chart

A Meta-analysis on the Epidemiology of Gastroesophageal Reflux Disease in China

Running Head: Epidemiology of GERD in China

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Word count: 3143(Exclude abstracts, references, and forms)

ABSTRACT

Background: No large-scale epidemiological survey on the prevalence of gastroesophageal reflux disease (GERD) in China has been conducted. China has a large population and a complex geographical environment. It is important to understand the prevalence and spatial distribution of GERD in China. Therefore, we conducted this meta-analysis to explore the prevalence and the spatial, temporal, and population distribution of GERD in the natural Chinese population.

Methods: We searched Chinese and English databases for literature on the prevalence of GERD in the natural Chinese population. The prevalence of GERD was pooled using a random-effects meta-analyses model. Subgroup analysis was performed according to time, region, and population. We used ArcGIS software to draw statistical maps and trend analysis charts. Spatial autocorrelation analysis was carried out using Geoda software. Spearman correlation analysis discussed the spatial distribution relationship between GERD and upper respiratory tract tumors.

Results: Altogether, 70 studies involving 276,014 from 24 provinces of China were enrolled. The overall pooled prevalence of GERD was 8.7% (95% CI: 7.5–9.9%) in mainland China. Over the past two decades, the prevalence of GERD in China has increased from 6.0% to 10.6%. GERD was more common in people aged 40-60, with BMI ≥ 24, and of Uygur ethnicity. The prevalence was higher in the West and East than in the Center, and there may be local spatial autocorrelation in the Qinghai Tibet Plateau and the southeast. GERD was correlated with gastric (r=0.421, P=0.041) and esophageal tumors (r=0.511, P=0.011) in spatial distribution.

Conclusion: GERD is becoming common in China. The prevalence is different in different areas and different populations. Appropriate strategies for the prevention and treatment of GERD need greater attention.

Keywords: China, Meta-analysis, Gastroesophageal reflux disease, Spatiotemporal trends

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A Meta-analysis of the Epidemiology of Gastroesophageal Reflux Disease in China

INTRODUCTION

Gastroesophageal reflux disease (GERD) refers to the symptoms or complications caused by the reflux of gastric contents into the esophagus or further, into the oral cavity (including larynx) or Longfield[1]. The main symptoms of GERD are heartburn, reflux, bulbar sensation, dysphagia, chest pain, hiccups, etc[2]. And it may also present extraesophageal symptoms, including chronic cough, laryngitis, asthma, and tooth erosion[3]. GERD is a common disease with a global prevalence of approximately 13%[4, 5]. According to reports, The prevalence of GERD was highest in North America, ranging from 18.1% to 27.8%, followed by 8.8% to 25.9% in Europe and the lowest from 2.5% to 7.8% in Asia[6, 7]. As a chronic disease with a high prevalence rate, GERD has brought substantial economic and health burdens to patients and society[8, 9], and may lead to tumors[10]. In addition to laboratory methods[11], several standard scales are used to evaluate GERD, including the gastroesophageal reflux disease questionnaire (GerdQ)[12], reflux disease questionnaire (RDQ) [13], etc.

The prevalence of GERD in China is lower than the worldwide rates[4, 5]. However, no ethnicity wise large-scale epidemiological survey or meta-analysis on the majority of GERD in China has been conducted to date. Due to the differences in regions, periods, populations, sampling methods, and diagnostic criteria, there are significant differences in the survey results of existing studies. China has a vast area and many races, which will lead to significant differences in the prevalence of GERD. Therefore, we conducted this meta-analysis to explore the prevalence of GERD in the natural Chinese population, analyze its spatial, temporal, and population distribution, and explore its geographical connection with upper gastrointestinal cancer.

MATERIALS AND METHODS

Subject design

We searched the literature on GERD in adults in the Chinese Mainland, conducted a meta-analysis to explore the prevalence of GERD, and understood the disease's spatial, temporal, and population distribution through subgroup analysis. Then, using the pooled prevalence of different provinces as the dependent variable, we analyzed the

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spatial trend and spatial aggregation of GERD; Using the pooled prevalence in other cities, we analyzed the correlation between GERD and upper gastrointestinal tumors.

Literature search

PubMed, EMBASE, WanFang, VIP, and China National Knowledge Internet (CNKI) databases were systematically and independently searched for studies reporting the prevalence of GERD in Chinese adults from database inception to January 1, 2022. The following search terms were used: ('China' or 'Chinese') and ('Gastroesophageal reflux' or 'GERD') and ('prevalence' or 'epidemiology survey'). All literature have been officially published. There were no language restrictions or publication date restrictions on this search. We also manually searched the references of the selected papers to avoid omission. In addition, the incidence rate of upper gastrointestinal tumors came from the "China cancer registration annual report 2019", which reported the tumor monitoring data of more than 200 cities.

Study selection

Original studies that fulfilled the following criteria were included in the meta-analysis: the subjects were adults in the Chinese Mainland; the study type was ca ross-sectional epidemiological survey; the sample size and the number of patients could be obtained, and the sample size was more than 200. The following articles were excluded: the same data were reported in multiple articles; case reports, or reviews; and surveys for particular groups, such as hospital patients, students, soldiers, and miners.

Quality evaluation

According to the references [14], we developed a quality rating scale with eight items. For each item, 1 point was awarded for meeting the standard requirements, and 0 points were awarded for not mentioning or not conforming to the standard. The score of each article was between 0 and 8. Literature ≤ 3 points were considered as low quality and shall be excluded.

Data extraction

LTL and ZJM independently searched for literature, evaluated literature quality, and extracted data. In case of disagreement, CCW will participate in the discussion and

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finally form an agreement. The extracted information included the survey period, the survey location (province and city), sampling method, diagnostic tools and standards, sample size, number of patients, demographic data (including ethnicity, sex, gender, body mass index (BMI), residence, marital status, education, income, occupation, smoking, alcohol consumption, tea drinking, physical exercise, Helicobacter pylori, and life stress). In addition, the incidence rate of five tumors in the oral cavity, nasopharynx, throat, esophagus, and stomach of the cities involved were collected from the "2019 annual report on cancer registration in China".

Statistical analyses

The statistical methods of this study referred to another literature published by us before[15]. We used R software (version 4.0.1) for meta-analysis and subgroup analysis according to study design, survey period, survey area, and other informations. The I^2 statistic test was used to evaluate the heterogeneity in the included literature. $I^2 > 50\%$ was considered as heterogeneity, and a random effect model was adopted; $I^2 \leqslant 50\%$, fixed effect model was used. We used Begg's test to assess publication bias and sensitivity analysis to assess the stability of the results. Meta-regression analysis was used to control the influence of interference factors.

We used ArcGIS software (version 10.6) to make the statistical map of the pooled prevalence rate in each province. ArcGIS was also used to create a trend analysis chart to evaluate the spatial changes of diseases[16]. The X-axis, Y axis, and Z axis of the chart represented longitude, latitude, and prevalence, respectively. Geoda software (version 1.12) was used for spatial autocorrelation analysis of diseases. Global Moran's I index was used to evaluate global spatial autocorrelation. Lisa cluster map and Lisa significance map were used to describing local spatial autocorrelation[17, 18]. Spearman correlation analysis was performed with R software to explore the effect of GERD on the incidence rate of upper gastrointestinal tumors. In addition, we used R software to draw a violin diagram, line charts and correlation heat diagram. A significant difference was judged by a 2-sided $P < 0.05$.

RESULTS

Literature screening results and the pooled prevalence

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The literature screening process is shown in Figure 1. A total of 70 articles were included in our study, including 52 published in Chinese and 18 published in English. Limited by the article's length, the essential characteristics of the included literature were shown in Supplementary materials 1. A total of 276,014 people from 24 provinces of the Chinese Mainland were enrolled in the study, and 27,386 people were diagnosed with GERD. The quality assessment ranged from 4 to 8, with an average of 6.01. In the 70 articles, the GERD prevalence ranged from 1.65% to 28.07%, and the pooled prevalence was 8.7% (95% CI: 7.5–9.9%). The I^2 was 99.4%, so the random effect model was adopted. The Begg's test indicated no publication bias in this study (Z= 1.11, P= 0.269). The results of sensitivity analysis showed that the pooled prevalence remained stable. To exclude the influence of research design, we conducted subgroup analyses according to the questionnaire used, random sampling, quality score, and sample size. We found that the prevalence rates estimated by different questionnaires were inconsistent (Q = 15.88, P= 0.001). The GerdQ estimated the highest GERD prevalence rate ,and the RDQ estimated the lowest. The other three indicators had no effect ondid not affect the results (P> 0.05).

The spatial, temporal, and population distribution

Figure 2A was a violin chart of theactuall prevalence, and Figure 2B was a line chart of the pooled prevalence in different periods. In the past 20 years, the prevalence of GERD in China showed an upward trend (Q=11.81, P=0.019). After controlling the influence of regions and questionnaires by meta-regression analysis, this trend still existed (t=2.37, P=0.020). Figure 3 shows the regional distribution of the prevalence of GERD. From the map, the prevalence of GERD was different in different provinces, with the highest prevalence in Xinjiang at 19.1% (95% CI: 13.5–24.7%) and the lowest prevalence in Guangdong at 3.3% (95% CI: 2.2–4.3%). Overall, the prevalence rate was high in the eastern and western regions and low in the central region (Q = 9.18, P= 0.010). Supplementary material 2 showed the geographical division. The difference was still significant after excluding the influence of times and questionnaires (t= 2.01, P=0.049). Figure 4 was a forest plot of GERD prevalence for subgroup analysis by demographic characteristics. We selected 15 indicators for demographic subgroup

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analysis. The results showed that age (Q = 48.86, P< 0.001), ethnicity (Q= 14.15, P=0.027), and BMI (Q= 5.50, P= 0.049) were statistically significant.

Spatial trend distribution and correlation analysis

The prevalence in the East-West distribution (X-axis) showed the change characteristics of ffalling andrising, and all fitted trend lines (green curve) showed a U-shape. In the North-South distribution (Y-axis), the fitting trend line (blue curve) was opposite, with low at both ends and high in the middle. See Figure 5 (A). In Figure 5 (B), Moran I value was 0.145, and Mthe onte Carlo simulation P value was 0.103, indicating no global spatial autocorrelation. However, as shown in Figure 5 (C) anFigures 5 (C) and lts of local spatial autocorrelation analysis showed that the Qinghai Tibet Plateau was a high-to-high aggregation area of GERD, and Hunan and Fujian were low-to-low aggregation areas. A total of 36 cities were involved in the meta-analysis, of which 24 cities were able to obtain tumor incidence rates and were included in the correlation analysis. The results showed that GERD was correlated with gastric (r= 0.511, P= 0.011) and esophageal tumors (r= 0.421, P= 0.041). See Figure 6.

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DISCUSSION

This is the first meta-analysis on the prevalence of GERD in the Chinese natural population. The majority of GERD in China was 8.7% (95% CI: 7.5–9.9%), which was lower than that in European and American countries, but higher than the estimated 2.5% ~5.0% GERD prevalence in previous global reviews[4-7]. This meta-analysis included 70 studies, and the distribution of effect values showed non normality (P<0.001). So we used the Begg test, a nonparametric test, to test publication bias and found that there was no bias in this study[19]. Sensitivity analysis showed that our results were stable.

In order to control the influencing factors, we also conducted subgroup analysis according to the type of study design. Our results were not related to random sampling, literature quality or sample size but were influenced by the survey instrument used. In the meta-analysis stratified by prevalence survey, the prevalence was inconsistent among different survey tools, which has been previously reported[4, 14]. This study applied the RDQ, GerdQ and other survey tools. Previous studies have shown that these questionnaires exhibited good psychometric characteristics and are suitable for application in the primary health care[11-13]. The GerdQ and RDQ were considered to have the same screening effect[12]. However, in our study, GerdQ estimated that the

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prevalence of GERD was higher than that of RDQ. When we excluded the influence of survey time and area through meta-regression, there was no difference in the prevalence between survey tools.

Our study revealed that the prevalence of GERD in China is rising. From 6.0% at the beginning of the 21st century to 10.6% at present, there was a significant difference in the prevalence among different periods (P=0.019). After controlling the survey tools and regions, the differences still existed. Chen[20] reported that during the period 2000-2007, the indications for referral endoscopy secondary to GERD increased over time. A study found that in Hong Kong, the prevalence of weekly GERD had risen by 1.3% between 2002 and 2011, which representsrepresenting an at least 50% relative increase[21]. Two studies field[7, 22] also explained that there is evidence that the global GERD prevalence has increased over the past two decades. The increase in bulk may be due to changes in people's lifestyles caused by economic development[23].

Trend analysis showed that the prevalence of GERD in China was high in eastern and western regions and low in the central areas. After controlling the survey tools and period, the prevalence rates in different parts were still separate. It has been reported that the prevalence of GERD in Central Asia is high[4]. Interestingly, this study found that the highest prevalence rate in China was Xinjiang, which is adjacent to Central Asia. Its environment and diet are similar to those in Central Asia. The dietary structure was the influencing factor of GERD[24, 25]. For example, vegetarian diets were negatively related to GERD, while meat and fat consumption were positively related to GERD. Different dietary patterns, diet styles, and eating habits in other regions, maybe the reasons for regional differences in prevalence.

We divided the papers into 15 subgroups to investigate the prevalence of GERD in different populations, and significant differences among other ethnic groups, ages, and BMIs were found. The majority of GERD was the highest in populations over 40 years old, followed by those 20-39 years old; the lowest prevalence was in those under 20 years old, consistent with an Asian meta-analysis[6]. Leonardo found through meta-analysis that compared with those aged <50 years, the OR for GERD in those aged ≥50 years was 1.32 (95% CI 1.12–1.54)[5]. A new global meta-analysis revealed that the prevalence rate was the highest in 35-60 years old and decreased slightly in those over 60 years old[4]. The current consensus is that the prevalence of GERD is different among different ethnic groups[26]. Our study proved that the prevalence of GERD in the Uygur population is significantly higher than that of other ethnic groups. This was also

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consistent with our regional distribution, as the Uygur people mainly live in Xinjiang Province, which is in western China. The prevalence, frequency and severity of GERD were reported to increase with BMI, which was consistent with our findings[26]. The results of a large-scale prospective study also suggested that a decrease in BMI can improve GERD-related symptoms, while an increase in BMI may aggravate GERD symptoms[27]. In addition, some studies believed that the decline of Helicobacter pylori infection will lead to a healthier stomach and increased gastric acid secretion, leading to reflux disease[28]. Our research did not support this statement. The other 11 factors evaluated had no effects on the prevalence of GERD, and their impact on GERD remains controversial.

We found that GERD did not have global spatial autocorrelation, but has local spatial autocorrelation. In addition, the local spatial autocorrelation analysis results demonstrated that the area with the high incidence of GERD was different from the high spatial autocorrelation area of GERD. The Tibet and Qinghai were high-to-high aggregation areas, and Hunan and Fujian were low-to-low aggregation areas. This unstable result may be related to the fact that we have many missing values. There were 7 provinces without data. More studies may be needed to explore the spatial autocorrelation of GERD in China. Our study found that GERD was positively correlated with esophageal cancer and gastric cancer in spatial distribution. The association of GERD and esophageal cancer has been reported[29], and we confirmed this conclusion from the perspective of the spatial distribution of the disease. The correlation between GERD and gastric cancer may be due to the increase of gastric acid secretion in some gastric cancers, which leads to the occurrence of GERD. A meta-analysis suggests that GERD may be a significant risk factor for laryngeal cancer[30]. But future prospective controlled studies are needed. There was no correlation between GERD and oral cancer and esophageal cancer, and no similar literature report has been found.

In our study, all respondents were healthy people, not patients or a specific group of people, and the study covers most provinces in China, all of which suggested that the research sample was satisfactory and representative. We conducted a number of subgroup analyses to explore the prevalence of different populations. In addition, we evaluated the temporal and spatial distribution of GERD in Chinese Mainland for the first time, and analyzed the spatial correlation between GERD and upper respiratory tract tumors. However, this meta-analysis has several limitations. First, there was

considerable heterogeneity in the calculation of crude prevalence and subgroup analysis. Second, although we included a lot of literature, the literature of some regions and subgroups was still insufficient. Finally, the lack of data in seven provinces may affect our spatial correlation analysis results.

In conclusion, in this systematic review, the summary estimate of the prevalence of GERD in Chinese people was 8.7%, indicating a trend of higher prevalence in the West and East than in the Center, and an increasing prevalence over time. The prevalence rate of GERD was higher in people who were over 40 years old, obese and Uygur. The prevalence of GERD was positively correlated with that of esophageal cancer in spatial distribution. Considering the population of China, further studies are needed to identify effective strategies to reduce the incidence of GERD in China.

Authors Contributions

Study design: LTL, CCW; Data collection: LTL, ZJM, LSR, CCW; Analysis and interpretation of data: LTL, LSR; Drafting of the manuscript: LTL, CCW; Critical revision of the manuscript: ZJM, LSR; Approval of the final version for publication: all the authors.

Competing Interests

The authors declare no conflict of interest.

Funding

There was no funding for this study.

Ethics and consent to participate

This was a meta-analysis and did not require ethical review.

Acknowledgments

The author thanks Mr. Ri-Hui Liu for his great support and help in the statistical analysis and writing of this paper.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Abbreviations

GERD: Gastroesophageal reflux disease; **EE:** Erosive esophagitis; **NERD:** Nonerosive reflux disease; **GerdQ:** Gastroesophageal reflux disease questionnaire; **RDQ:** Reflux disease questionnaire; **CNKI:** Chinese ethnicityal Knowledge Infrastructure; **BMI:** Body mass index

Figure legends:

Figure 1. Flowchart of the selection of studies

Figure 2. Violin diagram of the original prevalence and line chart of the pooled prevalence of GERD in different periods

Figure 3. Prevalence of GERD in different provinces of China

Figure 4. Forest plot for subgroup analysis by demographic data

Figure 5. Spatial trend distribution of GERD

Figure 6. Correlation heat map of the relationship between GERD and upper gastrointestinal tumors

Supplementary materials 1. Characteristics of the included studies

Supplementary materials 2. Three geographical divisions of China

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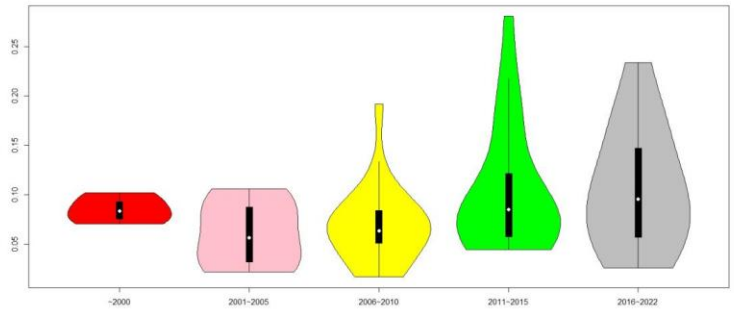
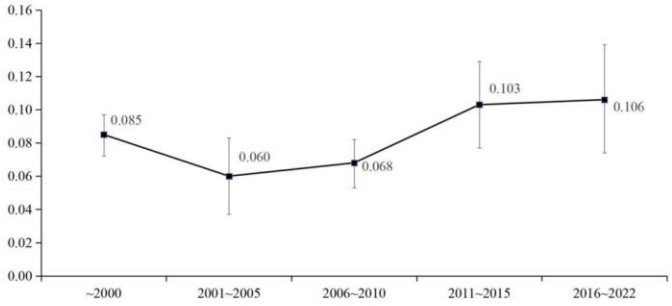
Figure 1. Flowchart of the selection of studies

Figure 2. Violin diagram of the original prevalence and line chart of the pooled prevalence of GERD in different periods



(A) Violin diagram of the original prevalence



(B) Line chart of the pooled prevalence

Figure 3. Prevalence of GERD in different provinces of China

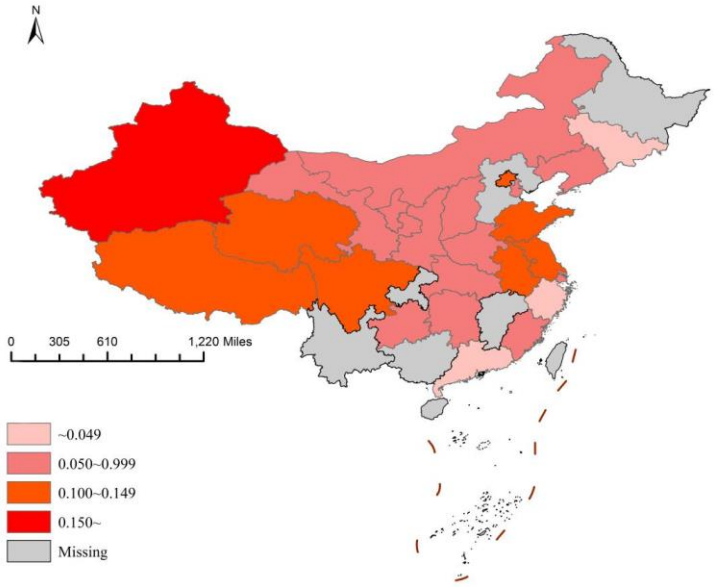


Figure 4. Forest plot for subgroup analysis by demographic data

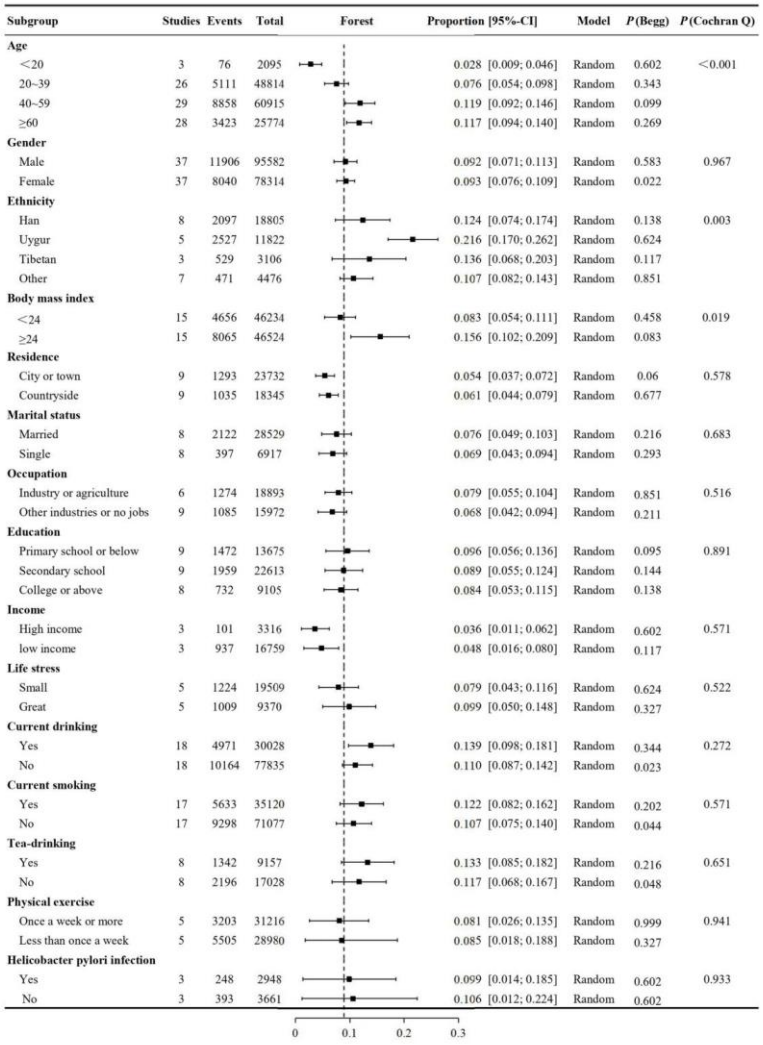


Figure 5. Spatial trend distribution of GERD

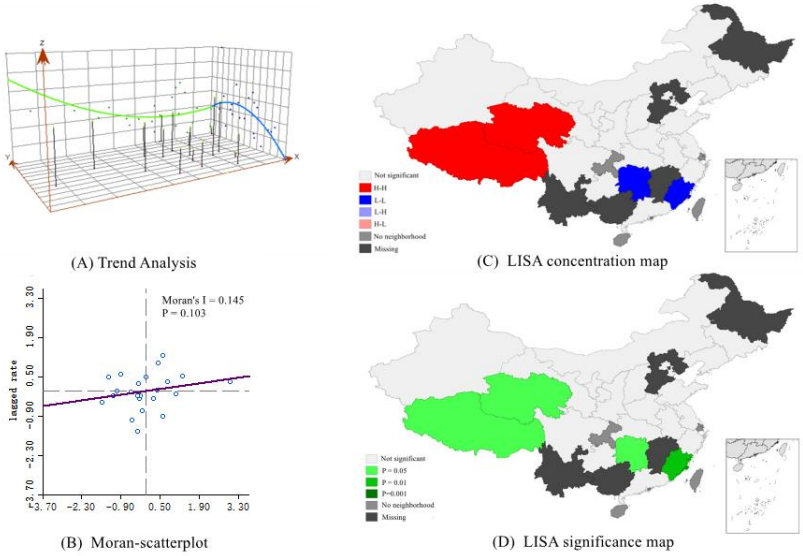
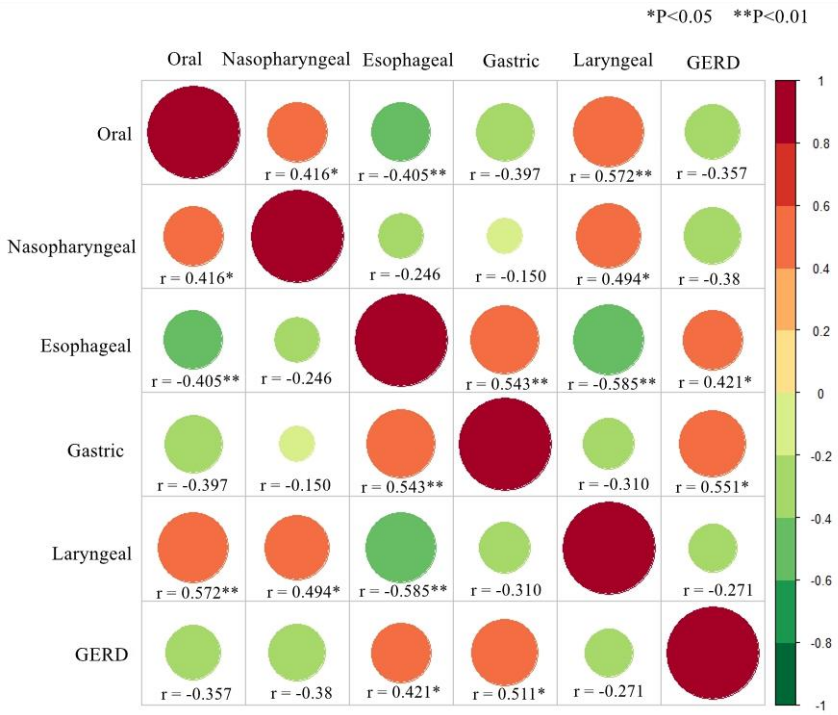


Figure 6. Correlation heat map of the relationship between GERD and upper gastrointestinal tumors



Supplementary materials 1. Characteristics of the included studies

ID	Study	Investigation time	Province	Questionnaire	Random sample	Quality score	Sample size	Number of cases	Subgroup
1	Zhang et al, 2020[1]	2014~2019	Jiangsu	GerdQ	No	6	4785	858	①②③④⑥⑦⑩⑪⑫⑮
2	Guo et al,1997[2]	1996	Beijing	Others	Yes	6	2500	176	—
3	Wu et al,2004[3]	2000~2003	Beijing	Others	Yes	6	1936	167	③
4	Pan et al,1999[4]	1999	Beijing,Shanghai	Others	Yes	7	4992	448	②③⑤⑨
5	Jiang et al,2010[5]	2008	Beijing	RDQ	Yes	7	2615	220	②③④⑤⑦⑩⑪⑬⑮
6	Ming et al,2017[6]	2015	Sichuan	GerdQ	Yes	7	787	116	①③④
7	Xiong et al,2006[7]	2003	Guangdong	RDQ	Yes	7	3338	83	②③⑤
8	Rong et al,2013[8]	2013	Xinjiang	GerdQ	Yes	7	2980	468	①
9	Li et al,2015[9]	2013	Shanghai	RDQ	Yes	6	3126	266	②③⑩⑪
10	Jiang et al,2016[10]	2014	Fujian	GerdQ	Yes	7	936	89	①②③④⑩⑪⑫
11	Peng,2008[11]	2007	Guangdong	RDQ	Yes	6	3210	53	①②⑤⑥⑦⑧⑨⑩⑪⑬⑮
12	Yao et al,2018[12]	2014~2015	Qinghai	RDQ	Yes	8	3015	284	①②③④
13	Cai et al,2012[13]	2010	Guangdong	RDQ	Yes	5	1834	43	—

14	Shen et al,2010[14]	2009	Fujian	RDQ	Yes	7	1347	118	②③⑨
15	Zhang et al,2013[15]	2009~2011	Shaanxi	RDQ	Yes	7	2879	259	②
16	Xiang et al,2012[16]	2011	Jilin	RDQ	No	4	2069	96	②③
17	Wei et al,2013[17]	2010	Fujian	GerdQ	Yes	7	203	10	②③
18	Zhan et al,2013[18]	2009	Fujian	RDQ	Yes	6	1982	134	②
19	Zhu et al,2009[19]	2006	Guizhou	RDQ	Yes	6	1692	116	②③
20	Li et al,2014[20]	2012	Henan	RDQ	Yes	7	508	28	②
21	Hu et al,2018[21]	2016	Shanghai	RDQ	Yes	7	2007	99	②③
22	Zhang et al,2005[22]	2004	Xinjiang	Others	Yes	8	4980	528	①②③⑨
23	Shen et al,2010[23]	2008	Beijing	Others	Yes	6	2502	207	②③④⑤⑪⑮
24	Zhang et al,2013[24]	2012	Shanxi	GerdQ	No	5	1210	116	②
25	Cai,2008[25]	2005	Hubei	RDQ	Yes	7	3563	77	②③⑤
26	Lin et al,2019[26]	2017	Hubei	GerdQ	Yes	7	3352	137	②③④⑦⑩⑪⑫⑭
27	Li et al,2019[27]	2017	Xinjiang	GerdQ	No	6	4987	887	①②③④⑩⑪⑫
28	Li et al,1997[28]	1997	Shanghai	Others	Yes	8	2500	192	②③⑨⑩⑪⑫

29	He et al,2010[29]	2007~2008	Beijing,Guangdong,Hubei, Shaanxi,Shanghai	RDQ	Yes	8	16078	933	②③④⑤⑥⑦⑧⑨⑩⑪⑬⑮
30	Chen,2016[30]	2013~2014	Henan	RDQ	Yes	5	4856	345	②③⑤
31	Ji,2018[31]	2013	Gansu	Others	Yes	6	23297	1786	②
32	Wang,2019[32]	2017~2018	Shandong	GerdQ	Yes	8	5149	570	②③⑥⑦⑩⑪⑫
33	Lin et al,2018[33]	2010~2012	Eight provinces(not grouped by province)	Others	Yes	5	24208	1074	—
34	Yin et al,2013[34]	2008~2009	Gansu,Shaanxi,Qinghai,Ningxia	RDQ	No	6	12265	1246	—
35	Wang et al,2004[35]	2004	Shaanxi	Others	Yes	6	2532	98	—
36	Wang et al,2019[36]	2012	Henan	GerdQ	Yes	8	2844	492	②③⑥⑩⑪⑭
37	Fang et al,2019[37]	1996, 2008	Beijing	Others	Yes	7	2378	211	—
38	Gong et al,2019[38]	2009~2016	Beijing	GerdQ	No	8	37442	7449	②③④⑩⑪⑬
39	Cai et al,2015[39]	2010~2011	Henan	GerdQ	Yes	6	2950	141	—
40	Zhang et al,2019[40]	2016~2017	Tibet	GerdQ	Yes	6	5680	614	①②③⑦⑩⑪
41	Zou et al,2009[41]	2009	Shanghai	Others	Yes	6	3135	84	—
42	Yan et al,2009[42]	2005~2006	Shanghai	RDQ	Yes	5	919	57	—
43	Li et al,2019[43]	2017~2018	Guangdong	GerdQ	No	5	1522	61	—

44	Chen et al,2012[44]	2007	Zhejiang	Others	No	6	8831	150	④
45	Peng et al,2009[45]	2006~2007	Guangdong	Others	No	5	2580	150	—
46	Li et al,2018[46]	2017~2018	Shaanxi	Others	No	5	887	23	—
47	Liu et al,2019[47]	2018	Liaoning	RDQ	Yes	7	986	82	—
48	Ma et al,2009[48]	2005~2006	Shanghai	RDQ	Yes	7	919	57	②③④⑤⑥⑦⑧⑨⑩⑪⑬
49	Niu et al,2012[49]	2011~2012	Xinjiang	GerdQ	No	6	1995	560	①
50	Ma et al,2014[50]	2014	Shanghai	RDQ	Yes	6	1021	48	—
51	Gao and Shi,2017[51]	2013	Beijing	Others	Yes	5	3410	751	②③⑦⑩⑪⑫
52	Qiao et al,2014[52]	2013	Jiangsu	RDQ	No	4	249	17	—
53	Zhong et al,2012[53]	2012	Sichuan	Others	No	4	360	20	—
54	Li et al,2007[54]	2007	Henan	RDQ	Yes	5	508	28	②
55	Mei et al,2008[55]	2008	Zhejiang	RDQ	Yes	5	3347	105	②③⑥
56	Jia,2017[56]	2015	Jiangsu	RDQ	No	4	221	20	—
57	Gansu Cancer Hospital, 2014[57]	2013~2013	Gansu	Others	Yes	4	4000	345	—
58	Chen et al,2011[58]	2009~2011	Four provinces(not grouped by province)	Others	No	4	2253	432	—
59	Liu et al, 2017[59]	2015~2016	Shaanxi	Others	No	4	2483	205	—

60	Tang ,2011[60]	2009~2010	Anhui	GerdQ	No	5	347	43	—
61	Lu et al,2020[61]	2016	Shandong	Others	No	4	2925	452	—
62	Ying et al,2006[62]	2006	Henan	RDQ	Yes	6	327	21	—
63	Chen et al,2004[63]	2002~2003	Tianjin	Others	Yes	5	7220	406	—
64	Yu, 2009[64]	2008	Zhejiang	RDQ	No	7	1369	109	②④⑥
65	Guo, 2002[65]	1996	Beijing	Others	Yes	5	2486	254	—
66	Xiang, 2014[66]	2012	Hunan	RDQ	No	5	200	14	—
67	Yang, 2021[67]	2019	Shaanxi	Others	Yes	7	2423	302	—
68	Chen,et al,2021[68]	2018	Inner Mongolia	GerdQ	Yes	6	1069	84	②③④⑩⑪⑫⑭
69	He,et al, 2013[69]	2011	Shanghai	GerdQ	Yes	5	1428	85	—
70	Kahaer, 2021[70]	2020	Xinjiang	GerdQ	Yes	7	5080	1187	①②③④⑨⑩⑪

①Nation ②Sex ③Gender ④Body mass index (BMI) ⑤Residence ⑥Marital status ⑦Education ⑧Income ⑨Occupation ⑩Smoking ⑪Alcohol consumption ⑫Teadrinking ⑬Physical exercise ⑭Helicobacter pylori(HP) ⑮Life stress.

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Supplementary materials 2. Three geographical divisions of China