

# The Historical Views on the Disease Name, Etiology and Pathogenesis for Gastroesophageal Reflux Disease in Traditional Chinese Medicine with Combined Knowledge Graph and Qualitative analysis

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## Research

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# Abstract

## Background

To clarify the historical views on disease name, etiology and pathogenesis for Gastroesophageal reflux disease (GERD) in ancient Traditional Chinese Medicine (TCM).

## Methods

A comprehensive literature search was performed in < Zhong Hua Yi Dian > database with keywords 'Acid regurgitation', 'Epigastric upset' and 'Bilious vomiting'. All the information about disease names, etiology and pathogenesis were included and extracted by two independent reviewers. The Citespace software was used for data analysis. After data importing and purging, the analysis was performed in two steps with 1000 years interval. This study mainly used descriptive statistics, co-occurrence analysis, and cluster analysis, accompanied with qualitative analysis.

## Results

A total of 187 disease name, 286 etiology and 429 pathogenesis records related to GERD were final identified. The authors and bibliographies co-occurrence analysis showed there were 13 main nodes and 6 lines before 1000 A.D., 151 nodes and 65 lines after 1000 A.D.. As for disease name, 'Ou Ku' and 'Ou Dan', the earliest names related to GERD in TCM appeared in the Han and Jin dynasties. In disease etiology analysis, 8 nodes appeared during 1-1000 A.D. and increased rapidly until 1900 A.D.; the cluster analysis identified 9 research hotspots which contains Internal injury diet, Pathogenic factor of gallbladder, Internal injury due to emotional disorder, Food retention, Heat stagnation of body fluid, Incoordination between the spleen and stomach, Damp-heat syndrome of stomach, Phlegm-fire, Cold evil invading the stomach. As for disease pathogenesis, the earliest explanation 'the evil in gallbladder and ascendant rising of stomach qi' was appeared in the 3rd century; the cluster analysis identified 8 research hotspots which contains Spleen qi deficiency and adverse rising of phlegm and fluid retention, Pathogenic factor invading upper-jiao, Heat stagnation of body fluid at lung and stomach, Insufficiency-cold of middle qi, Phlegm moving due to fire, Phlegm and fluid retention in upper-jiao and cold food retention of stomach, Sufficient wood and insufficient soil, Food retention of middle-jiao.

## Conclusions

There are many treatises focused on GERD related symptoms and signs in TCM. This study clarified its name, etiology and pathogenesis, which provides a good reference for further theoretical and clinical research.

# Background

Gastroesophageal reflux disease (GERD) refers to a clinical status of gastric and duodenal contents flowing back into the esophagus causing discomfort and/or pathological changes in the esophageal mucosa [1]. At present, its incidence rate in global population is about 20%, which China is about 5–10%, and increasing year by year [2–3]. The common symptoms contain heartburn, acid reflux, stomach pain, and epigastric upset, etc., which usually bring negative effects on patients' physiology, psychology and quality of life. In severe cases, the hurts on extraesophageal tissues in throat and airway maybe occurred, such as esophageal erosion, ulcers, stenosis, etc., which needs more medication or more difficult endoscopic surgery and bring heavier medical burden, furthermore, the uncontrolled condition has risks of carcinogenesis. Western medicine treatment on this disease has fast effect and clear mechanism. However, the refractory GERD and poor improvement on quality of life in the clinic are still commonly [4]. Now, many studies have shown that Traditional Chinese Medicine (TCM) treatment in GERD has advantages of good efficacy and low relapse rate [5]. Therefore, reviewing and evaluating the historical cognitions on GERD in ancient TCM have great values on enriching and improving the diagnosis and treatment technologies for GERD.

Knowledge graph (KG) is a method that uses mathematical methods to simplify the structure of knowledge units to achieve visual knowledge structure with the development of computer technology [6]. The application of KG in TCM research is becoming more and more popular now [7]. And, it has already used in the syndrome diagnosis [8–10], data mining on classics [11], surgeries [12], Daoyin therapy [13] and so on. This study aims to mine the historical cognitions on GERD in ancient TCM with KG and qualitative analysis.

## Methods

### Search Strategy

The search source of this study is the fifth edition of < Zhong Hua Yi Dian >, which contains 1,156 ancient Chinese medical books and covers various fields of TCM. It is by far the largest series TCM e-book, and can easily export the search results in text form.

GERD hasn't corresponding disease name in ancient TCM books. Many modern research guidelines and consensus classify it as 'Acid regurgitation' (酸/反), 'Epigastric upset' (胃), 'Bilious vomiting' (呕), and 'Shiguan dan' (食管炎), etc.. Of those, some researches considered 'Shiguan dan' (食管炎) as the most suitable name because it reflects GERD's disease location, etiology, pathogenesis and main symptoms much better [5]. However, 'Shiguan dan' (食管炎) has not been widely used in clinical researches and practices. So, we still adopt 'Acid regurgitation' (酸/反), 'Epigastric upset' (胃), 'Bilious vomiting' (呕) as search keywords in this study.

All the information about disease names, etiology and pathogenesis relating with search keywords were included. As for the duplicated content appeared in different bibliographies and periods, only the earliest

information were included. However, if the information only contains search keywords and symptoms without specific explanations or not main complains, or no reliable reference resource, or unclear book index, will be excluded.

## Data Management

Firstly, we extracted and preliminary classified the disease names, etiology and pathogenesis presented in the search results. Secondly, enriched the bibliographic details of the involved ancient TCM books, including their authors, writing time and dynasty, etc., with book name search in the Reference Book Database of China National Knowledge Infrastructure (CNKI) and Duxiu Databases. The books with unknown author name were marked by 'Anonymous Author', and were excluded if they do not have clear writing timing or authors' birth and death year. These information mainly extracted from the < Dictionary of Traditional Chinese Medicine Literature Philology> [14], <The Dictionary of Traditional Chinese Medicine Literature> [15], <The Dictionary of Chinese Medical Books> [16], <The Collection of Traditional Chinese Medicine Terms> [17], <The Great Dictionary of Chinese Ancient Literature> [18], <The Chinese Medicine Ci Hai> [19], and < Traditional Chinese Medical Records> [20].

## Data Analysis

The Citespace software was used for data analysis. Firstly, we entered the disease name, etiology, pathogenesis, book title, author and writing time in the software's compatible 'refworks' format. Because Citespace's optional time range is 1000 A.D. to now, so for books written between 1 A.D. and 1000 A.D. were recoded as "actual writing time + 1000". The < Huang Di nei jing>, which was compiled during the Warring States period (475 - 221 B.C.), was only involved in qualitative explanation.

Regarding different mapping characters in different software version, we adopted Citespace III for book title and author analysis, and CitespaceⅣ for keyword analysis. After data importing, the analysis were performed in two steps with 1000 years interval. The key parameters setting are listed as following: Time Slicing: 1000–2000, Year Per Slice: 100, Term Type: burst term, Node Type: author/institution/keyword, Selection Criteria: top N per slice, Pruning: pathfinder (pruning sliced network, pruning the merged network). The visualization for Tree Ring History and Timezone were performed with author, institution, and keywords nodes. This study mainly used descriptive statistics, co-occurrence analysis, and cluster analysis, accompanied with word frequency analysis.

## Results

### General results

A total of 1,294, 827, 180, and 1814 records related to 'Tu Suan' (acid regurgitation), 'Cao Za' (epigastric upset), 'Ou Ku' (bilious vomiting) and 'Tun Suan' (acid regurgitation) were obtained correspondingly. Abiding by the predefined inclusion and exclusion criteria, 188, 188, 154, and 549 records were excluded. Then, we integrated these records and classified them into three categories, disease name, etiology, and pathogenesis. Finally, 187, 286, and 429 records were identified respectively.

# Knowledge Graph and Qualitative Literature Analysis for Authors and Bibliographies

## Co-occurrence Analysis for Authors and Bibliographies

The co-occurrence analysis showed that there were 13 main nodes and 6 lines before 1000 A.D., and 151 nodes and 65 lines after 1000 A.D. (Fig. 1, when time lapse from ancient to present, color changes from blue to red). However, no obvious center was formed. The GERD related symptoms and signs were first described in the <Huang Di nei jing> which compiled during the Warring States period (475 – 221 B.C.) and recorded by 7 doctors from the Eastern Han Dynasty to the Northern Song Dynasty (1-1000 A.D.). In the Song, Jin and Yuan dynasties (1000–1300 A.D.), the records increased gradually. Liu Wansu, Ma Zongsu, and Yang Shizhen were more concerned about it than other doctors in the same period. During the Ming and Qing dynasties (1300–1900 A.D.), related records increased rapidly. The top 5 informative books are <Zhang Shi Yi Tong> (Qing Dynasty), <Zheng Zhi Hui Bu> (Qing), <Yi Jian Neng Yi> (Ming and Qing Dynasties), <Nei Jing Bo Yi> (Qing), <Feng Shi Jin Nang Mi Lu> (Qing); the top 10 authors are Gong Tingxian (Ming Dynasty), Wang Kentang (Ming), Zhang Lu (Qing), Luo Mei (Qing), Zhang Jiebin (Ming), Zhou Xuehai (Qing), Shen Jin'ao (Qing), Sun Yikui (Ming), Wan Quan (Ming), Fu Shan (Qing). But, the information decreased significantly since 1900 (Fig. 1).

## Co-occurrence Analysis for Disease Names

During the Han and Jin dynasties (200 to 300 A.D.), 'Ou Ku' and 'Ou Dan', the earliest names of GERD in TCM appeared and were described later in <Huang Di Nei Jing Tai Su> which written by Yang Shangshan to comment the <Huang Di nei jing> in the Sui Dynasty [21]. During the Sui and Tang dynasties (600 to 700 A.D.), there were five disease names related to GERD, 'Yi Cu', 'She Tu Suan Lu', 'Tun Suan', 'Tu Suan Shui', and 'Cu Yan'. During the Song and Yuan dynasties (1200 to 1300 A.D.), 'Tun Suan', the most widely used disease name was proposed, accompanied with other 6 names, 'Tu Suan', 'Cao Za', 'Zhong Suan', 'Cu Xin', 'Xin Cao', and 'Xue Cao'. During the Ming Dynasty (1400 to 1600 A.D.), 4 disease names included 'Ou Dan', 'Dan Dan', 'Yan Suan', and 'Xin Cao Za' were putted forward. In the Qing Dynasty (1600 to 1900 A.D.), the ancient TCM doctors proposed other 8 disease names which included 'Cu Xin', 'Cu Suan', 'Tan Cao', 'Huo Cao', 'Cu Yan', 'Yi Suan', 'Cu Tun', and 'Zuo Suan' (Fig. 2).

## Qualitative Literature Analysis for Disease Names

The disease name 'Ou ku', 'Tu Suan' and related symptoms were first proposed in the <Huang Di nei jing> and described as 'When Yang Ming qi recovery, purification qi prevail, the trees are old and dry, and the animals suffer many blight. The diseases of the people are lateral thorax and dryness are to the left. They often sigh, even heartburn, painful abdominal mass, vomiting (Ou Ku), cough, hiccups, and upset', and 'vomiting and acid vomiting (Tu Suan) of various kinds, sudden and severe diarrhea, which all caused by heat' in *Comprehensive Discourse on the essentials of the Most reliable (Chap. 74)* in *Su Wen*.

Simultaneously, the *Ling Shu* stated 'often vomiting bitter liquid, sighing, being afraid of being caught, this is due to the evil in gallbladder and reversed flow of evil at stomach, and gallbladder fluid caused bitter mouth (Ou Ku), stomach qi on the reverse cause vomiting, so which called Ou Dan' in *The Four Seasonal Qi (Chap. 19)*. Chao Yuanfang, a famous TCM doctor and scientist in the Sui Dynasty, first identified the 'Tu Suan' as an independent disease and defined it as 'Stomach acid rises up the throat but have no time to spit out or swallow'. 'Cao Za', another disease name of GERD, was first recognized as concurrent symptom in the Jin and Yuan dynasties, and later identified as an independent disease in the < Danxi's experiential therapy > which written by Zhu Danxi in the Yuan Dynasty.

## Knowledge Graph and Qualitative Literature Analysis for Etiology

### Co-occurrence Analysis for Disease Etiology Analysis

A total of 8 etiology nodes appeared during 1-1000 A.D. and the largest were 'accumulated cold' and 'phlegm stagnation'. After 1000 A.D., more and more nodes appeared until 1900 A.D., and the outbreak periods is 1400 to 1500 A.D. (Ming Dynasty). It should be note that there were 4 nodes appeared from 1100 to 1200 A.D., including 'internal injury raw and cold', 'internal injury diet', 'invasion of wind-cold' and 'food retention', which mainly represent the disease etiology of GERD (Fig. 3).

### Cluster Analysis for Disease Etiology

The cluster analysis identified 9 research hotspots for GERD etiology (Fig. 4):

☒) *Internal injury diet*. It is the earliest appeared etiology and has received continuous attention which accompanied with fluid retention and internal injury by raw and cold food. The high-frequency words mainly contain internal injury diet, insufficiency of natural endowment, hunger and fullness, hot nature diet, exogenous wind-cold, spleen deficiency, misuse of spicy, more impatience and anger, seven emotions stimulating, internal injury food and drink, internal injury milk, fire phlegm, excessive stomach Qi, injury to spleen and stomach by erroneous purgation, stomach cold, ascendant rising of stomach fire/stomach fire rising, deficient cold of spleen and stomach, typhoid fever malaria and Yin of stomach injury, injury to spleen by stagnant wood, liver Qi stagnation, exogenous summer-heat and damp, improper diet and overstrain, hot phlegm, exterior syndrome of febrile disease accompanying dyspepsia, extreme cold, stagnation of qi activity and food retention.

☒) *Pathogenic factor of gallbladder*. It was appeared in the 11th century (Northern Song Dynasty) and disappeared in the mid-16th century (Ming Dynasty). The high-frequency words are recovery of YangMing qi, dry evil pathogenic features, think of emotion, reversed flow of YangMing qi, dryness of climate affecting gallbladder, preponderance of YangMing qi, pathogenic factor of gallbladder.

☒) *Internal injury due to emotional disorder*. It was appeared in the 12th century (Southern Song Dynasty). The high-frequency keywords contain weakness of spleen qi, internal injury due to emotional disorder,

worries affecting qi, spleen-stomach deficiency, thinking, external infection of four seasons, sufficiency of natural endowment, phlegm-dampness, thinking resulting disorder of blood.

☒) *Food retention*. It was appeared in the 13th century (Yuan Dynasty) and faded out in the mid-18th century (Qing Dynasty). The high-frequency keywords are improper diet, liver-qi depression, the spleen wet not shipped, heat stagnation, food retention, stomach heat, dampness-heat with cold food, fondness of liquor, moodiness, excessive deliberation, heat stagnation of spleen and stomach, deficiency of qi and blood, qi stagnation.

☒) *Heat stagnation of body fluid*. It was appeared in the 13th century (Yuan Dynasty). The high-frequency keywords are internal injuries of cold content, heat stagnation of body fluid, phlegm and retained fluid, internal injury diet and digestive disorders, dampness-heat of spleen and stomach and invasion of wind-cold, weakness of middle qi and heat stagnation of phlegm and retained fluid, phlegm-fire, fire stagnation, preponderance of ShaoYang qi, macronosia generating insufficiency of the spleen, qi deficiency due to oldness, phlegm stagnation generating acid, external cold and interior heat, external, heat stagnation of food.

☒) *Incoordination between the spleen and stomach*. It was also appeared in the 13th century (Yuan Dynasty). The high-frequency keywords are food retention, cold pathogenic disease with food retention, incoordination between the spleen and the stomach, stomach fire, heat stagnation of body fluid at lung and stomach, food stagnation and phlegm, hot origin cold end, internal heat stagnation and outside wind-cold, cold in upper-jiao, spleen deficiency generating cold, stomach cold, internal cold, gastric disorder with wind-damp.

☒) *Damp-heat syndrome of stomach*. It was appeared in the 15th century (early Ming Dynasty). The high-frequency keywords contain damp-heat syndrome of stomach, damp-heat, liver-fire, dyspepsia caused by excessive eating or improper diet, weakness of stomach qi, weakness and cold of stomach qi, insufficiency of qi and blood and deficiency of spleen-stomach after parturition, deficiency of spleen Yang, stagnation of liver qi, phlegm-fire confusing heart stagnate at stomach, accumulation of dry feces.

☒) *Phlegm-fire*. It was appeared in the 16th century (mid-Ming Dynasty). The high frequency key words contain phlegm-fire, deficiency of heart blood, mistreatment injuring spleen, insufficiency of middle qi, phlegm-dampness and qi constraint, consumptive disease, deficiency of spleen yin, blood-insufficiency and stomach heat, deficiency of spleen yin and heart yin, food retention, essence derived from food stagnation, Qi stagnation, phlegm stagnation, indigestion due to intestinal worm.

☒) *Cold evil invading the stomach*. It was also appeared in the 16th century (mid-Ming Dynasty), accompanied with stomach deficiency. The high-frequency keywords contain food retention, lodged rheum generating heat stagnation, cold evil invading the stomach, excessive acid, deficiency of both spleen and kidney, internal injury diet, phlegm stagnation of middle-jiao, after cold pathogenic disease, indigestion-induced heat stagnation, deficiency-cold, fire deficiency generating reduction of soil productivity.

# Qualitative Literature Analysis for Disease Etiology

The < Huang Di nei jing > first proposed the disease etiology is 'the evil in gallbladder and reversed flow of evil at stomach' or 'the recovery of Yang Ming Year'. In the Sui and Tang dynasties, the etiology was classified as 'Phlegm and fluid retention' which includes phlegm, cold phlegm, stomach deficiency phlegm stagnation, retained fluid, and 'Diet' which includes food of internal injury, food retention, alcohol addiction with food retention.

From the Song Dynasty, the etiological studies enriched significantly and mainly proposed the following six categories: *a) Five evolution stages and six climatic factors.* It is similar to 'theory of circulatory phases' in < Huang Di nei jing >. The < Su Wen Yao Zhi Lun > stated 'When dryness recovery, purification qi prevail, ..., vomiting, cough, hiccups, and upset, disease in the diaphragm', 'When Yang Ming qi recovery, purification qi prevail, ..., vomiting, cough, hiccups, and upset', written by Ma Zongsu in the Yuan Dynasty. In the Ming Dynasty, Lou Ying and Xu Chunfu believed that 'the recovery of YangMing, often sigh and vomiting.' *b) Diet.* The < The Three for Extremely-Disease and Syndrome Party Theory > stated 'When there is retained fluid, it makes epigastric upset; when there is lodging food, which cause acid regurgitation', written by Chen Yan in the Song Dynasty. Yan Yonghe explained more exactly in his book < Yan's Ji Sheng Fang > as 'If you are insufficiency of natural endowment, when you are hungry or lose your appetite, or after a meal with five flavors, fishy fish, cheese, raw and cold fruits and vegetables, those will stop storing the stomach, and then you will suffer from stagnation, acid regurgitation and vomit.' *c) Mistreatment injuring spleen.* In the Ming Dynasty, Zhang Jingyue putted forward that the spleen and stomach can be injured by misusing of digestive or attack medicines which results in epigastric upset. In The Ming Dynasty, <Concise Medicine Sufficient > stated 'there are also misuse of medicines such as helping digestion and removing accumulation, deficiency of spleen and stomach, less blood and epigastric upset, deficiency of middle-jiao and upset accompanying not hungry', written by Sun Zhihong. *d) Internal injury due to emotional disorder and liver-qi depression.* Zhu Danxi putted forward that phlegm accumulation caused by qi disease is the cause of acid regurgitation, because too much worry could result in stagnation of qi activity, then the liver depression restrict spleen and touch off acid regurgitation. *e) Exposure to exogenous cold.* The < Zheng Zhi Hui Bu > stated that 'normally stagnant body fluid caused dampness-heat; when the wind-cold, internal heat stagnation and outside wind-cold, the epigastric upset it will be and the sour taste will sting the heart' which refers to the external wind-cold; and 'if the cold evil invading the stomach, suddenly into acid, heat transformed from cold, the acid belongs to the cold also' which refers to the cold evil invading the stomach, written by Li Yongcui in the Qing Dynasty. *f) Spleen-stomach deficiency.* The < Hua Tuo Shen Fang > proposed the disease of Spleen Deficiency which is characterized by sallow of complexion due to spleen disorders; stiff tongue, poor appetite, vomiting, weakness of limbs due to superabundance; and frequent disorders, acid regurgitation, uncured dysentery due to deficiency.

## Knowledge Graph and Qualitative Literature Analysis for Pathogenesis

# Co-occurrence Analysis for Disease Pathogenesis

The earliest explanation of GERD pathogenesis, 'the evil in gallbladder and ascendant rising of stomach qi', appeared in the 3rd century A.D.. Three hundred years later, the discussions on disease pathogenesis increased obviously between 600 A.D. and 700 A.D. (Tang Dynasty), conversely, decreased from 1100 A.D. to 1200 A.D. (Song Dynasty). However, it was exploded again from 1200 A.D. to 1300 A.D. (Jin and Yuan dynasties). Among them, the highest frequency point 'heat stagnation of body fluid at lung and stomach' was appeared in this period, accompanied with 'internal heat stagnation and invasion of wind-cold', 'phlegm due to fire', 'hot origin cold end', and so on. After 1500 A.D. (Ming Dynasty), the node connections number and node area decreased significantly and continuously (Fig. 5).

## Cluster Analysis for Disease Pathogenesis

The cluster analysis identified 8 research hotspots for GERD pathogenesis (Fig. 6):

①) *Spleen qi deficiency and adverse rising of phlegm and fluid retention.* It is the earliest declared pathogenesis which appeared in the 11th century (Northern Song Dynasty) and faded out in the 13th century (Yuan Dynasty). So, it was only used as a research hotspot in the early period. The high frequency keywords contain zangfu organs weakness and stagnant cold of both spleen and stomach, stagnation of food at diaphragm, spleen qi deficiency and adverse rising of phlegm and fluid retention, deficiency of spleen generating cold and digestive disorders.

②) *Pathogenic factor invading upper-jiao.* It was appeared in the 11th century (Northern Song Dynasty) and faded out in the 15th century (Ming Dynasty). The high frequency keywords contain stagnated heat over qi of stomach and midriff, exuberance of lung metal, pathogenic factor invading upper-jiao, preponderance of ShaoYang qi, heat illness due to internal cold injury, foul smell ascending may causing abdominal flatulence, metal not calming wood, stomach cold, excess of stomach qi.

③) *Heat stagnation of body fluid at lung and stomach.* It was appeared in the 12th century (Southern Song Dynasty) and faded out in the 15th century (early Ming Dynasty). The high frequency keywords contain true heat disease with false cold manifestation, internal heat stagnation and invasion of wind-cold, heat stagnation of body fluid at lung and stomach, abdominal mass with stagnation causing retained fluid, lung fire flaming respiratory, abdominal mass with stagnation causing phlegm, dampness-heat of stomach and indigestion, internal fire flaming upward, stagnant dampness-heat of liver and lurk at lung and stomach, spleen weakness causing phlegm retention of middle-jiao.

④) *Insufficiency-cold of middle qi.* It is the longest researched pathogenesis, lasted for more than 700 years, which appeared in the 12th century (southern Song Dynasty) and faded out around the 18th century (Qing Dynasty). The high frequency keywords contain fire arouse phlegm, phlegm moving due to fire, phlegm-fire, food stagnation and internal heat flaming upward, food stagnation, phlegm and retained fluid stagnation of middle-jiao, deficiency of heart blood, wet phlegm and qi stagnation, heat phlegm, stagnant essence of food at stomach.

☒) *Phlegm moving due to fire*. It was appeared in the 13th century (Yuan Dynasty) and faded out in the 17th century (early Qing Dynasty), accompanied with stomach deficiency, high frequency keywords are dyspepsia, lodged rheum generating heat stagnation, after cold pathogenic disease, indigestion-induced heat stagnation, insufficiency-cold, fire deficiency generating reduction of soil productivity.

☒) *Phlegm and fluid retention in upper-jiao and cold food retention of stomach*. It was appeared in the 14th century (Yuan Dynasty) and faded out in the 17th century (early Qing Dynasty). The high frequency keywords contain middle-jiao not transportation and transformation, disorder of upper-jiao, phlegm and fluid retention, dampness-heat of stomach, liver fire, dyspepsia caused by excessive eating or improper diet, weakness of stomach qi, heat stagnation of body fluid, cold enveloping heat.

☒) *Sufficient wood and insufficient soil*. It was appeared around the 15th century (Ming Dynasty) and faded out around the 18th century (Qing Dynasty). The high frequency keywords contain damp-heat, food stagnation and phlegm, food retention with heat, deficiency-fire, fire stagnation, deficiency-cold, sufficient wood and insufficient soil, deficiency-cold stagnation.

☒) *Food retention of middle-jiao*. It was the latest appeared pathogenesis which was proposed in the 16th century (Ming Dynasty) and lasted till now. The high frequency keywords contain dyspepsia, TaiYang channel accompanying stomach syndrome, phlegm stagnation, food retention of middle-jiao, exogenous cold disease accompanying dyspepsia.

## Qualitative Literature Analysis for Disease Pathogenesis

As for 'Ou Ku', the earliest presented pathogenesis is 'the evil in gallbladder and ascendent rising of stomach qi', which was written in < Huang Di nei jing > and high recognized and praised by historical doctors. In the Jin Dynasty, Zhang Zihe stated 'sanjiao's blockage is bad for throat and it's gallbladder disease and bilious vomiting (Ou Ku)' in < Ru Men Shi Qin > and concluded that the disease's location is sanjiao. Qin Changyu, a doctor in the Ming Dynasty, proposed that 'gallbladder fever' can also result in it. Tang Rongchuan believed that bilious vomiting could be caused by the transformed fire from the combination of excessive fetal qi and Yang Ming's qi, documented in < Theory of Blood Syndrome > in the Qing Dynasty.

There were many discussions on the pathogenesis of acid regurgitation (Tun Suan) and acid vomiting (Tu Suan). For example, 'vomiting and acid vomiting of various kinds, sudden and severe diarrhea, which all caused by heat', recorded in < Huang Di nei jing >; spleen-stomach deficiency, retention of food, phlegm and fluid retention of diaphragm is the main pathogenesis, considered by Chao Yuanfang in Sui Dynasty; 'Blazing fire can make gold, but can't calm wood', written by Liu Wansu in Jin Dynasty who praised highly on < Huang Di nei jing > and believed that acid vomiting was caused by heat; Li Dongyuan, on the other hand, believed that the disease's pathogenesis is cold and 'the pungent and hot medicine could cure it', and proposed the principle of the treatment is 'pour lung with heat medicine'; Zhu Danxi innovatively put forward the idea of 'hot origin and cold end' for the disease which caused by dampness-heat internal stagnation, body fluid internal stagnation, heat generating acid and crouching in the lung and stomach;

Zhang Jingyue thought the pathogenesis was the liver qi crusading the weak spleen and stomach qi and unborn spleen Yang; Li Yongzhi, a famous doctor in the Ming Dynasty, believed the damp-heat is the basis of the disease and acid regurgitation and acid vomiting are differently, which demonstrated by the record 'there is dampness and heat in the stomach towards mouth, the food suppressed by dampness and heat goes into stomach, and the food cannot be digested, so the clear air does not rise and the turbid air does not fall which further confronting and result in the qi reversing. Therefore, the vomiting reverse to swallowing, which called acid regurgitation (Tun Suan)', and 'there is dampness and heat which caused by the outside wind-cold or raw and cold diet, then the more stagnation of internal heat, acid stab heart, intention to vomit, upset in the chest, or spit out acid water, making upper and lower teeth sour and astringent and not closure, which reduce acid vomiting (Tu Suan)', written in his Book < Zheng Zhi Hui Bu >.

Cao Za, another disease name of GERD, was first discussed in < Danxi Xinfu > as 'The water in the Middle Part of Gastric Cavity is cold, and the epigastric upset (Cao Za) below the heart', which was written by Zhu Danxi in Yuan Dynasty. Zhang Jingyue proposed that it was mostly caused by 'disorder of spleen qi' or 'injured spleen deficiency', and could be divided into deficient cold epigastric upset and phlegm-fire epigastric upset from the perspective of deficiency and sufficiency, or fire epigastric upset and phlegm-fire epigastric upset from the perspective of disease causes. Xu Chunfu believed that phlegm-fire was the main cause, and pointed out that phlegm and fluid-retention was the key pathogenesis of epigastric upset and acid regurgitation in his < Gu Jin Yi Tong Da Quan >.

## Discussion

There are many treatises focused on GERD related symptoms and signs in TCM, which have been on the rise over time and reached its peak in Ming and Qing dynasties. This trend is roughly consistent with the development of whole TCM, and it is known that this disease is common and frequent in clinic since ancient time.

## Cognition on the disease name

This study pre-defined the GERD's name in TCM as Ou ku (bilious vomiting), Tu Suan (acid vomiting), Tun Suan (acid regurgitation), and Cao Za (epigastric upset), and performed the literature search and data analysis. However, we found more derived names for GERD, even for same disease name in TCM. For example, bilious vomiting was also called 'gallbladder vomiting' and 'gallbladder disease'; Acid vomiting and Acid regurgitation were also known as 'Yan Suan', 'Yi Cu', 'Zhong Suan', 'Cu Xin', 'Cu Yan', 'Yi Suan', 'Zuo Tun', 'Zuo Suan', 'Cu Tun' and so on. Besides, Acid vomiting and Acid regurgitation are differently, which the former one refers to spitting out acid water like vinegar, the later one refer to acid water flooding into throat but swallowing down, though both of them have the acid flooding. However, the difference is so tiny that doctors often omit it in clinic. The epigastric upset was also called 'Xin Cao', 'Xin Cao Za', 'Tan Cao', or 'Huo Cao'.

It is important to note that there is no disease name exact cover the GERD in TCM because of its complicated clinical manifestations. Most of the disease names in TCM only present one or more typical symptoms of GERD, for example, the gastrointestinal symptoms but not extra-esophageal reflux symptoms.

## Cognition on the disease etiology and pathogenesis

The TCM doctors in the past dynasties have comprehensively discussed the etiology of GERD from many aspects, such as external factors, internal injury, emotion, and so on, and formed different research themes in different periods. The main etiologies contain food of internal injury, damp-heat syndrome of stomach, cold evil invading the stomach, phlegm-fire, heat stagnation of body fluid, food retention, incoordination between the spleen and the stomach, internal injury due to emotional disorder, and the evil in gallbladder.

In terms of pathogenesis, the earliest view is liver-gallbladder heat and stomach qi inversion for bilious vomiting, reported in < Huang Di nei jing >. The epigastric upset was close related to phlegm and fire, considered by Zhu Danxi from the Yuan Dynasty. The views on the pathogenesis of acid regurgitation and acid vomiting are differently in different periods and different doctors, but they can be mainly classified into four categories: cold, heat, deficiency of spleen and stomach, and hot origin cold end. For example, Li Dongyuan thought it was cold, Zhu Danxi thought it was hot origin cold end, Zhang Jingyue thought it was weakness of spleen and stomach, Li Yongzi thought acid regurgitation was dampness-heat of stomach and acid vomiting was wind-cold outside and dampness-heat inside.

## Limitation

Firstly, the data retrieval is only carried out in < Zhong Hua Yi Dian > which does not include all the ancient TCM books though it is the largest electronic database of series TCM books so far. Secondly, some book without clear author and written time was not included in the data collation stage. Thirdly, only common gastrointestinal symptoms of GERD were included but not extra-esophageal reflux symptoms, as predefined search strategy. Therefore, the results may be not present comprehensive cognition on GERD in TCM. However, all the ancient TCM books included in < Zhong Hua Yi Dian > are very important medical works in the TCM history and represent the core context of Chinese Medicine to a large extent. Secondly, this study focus on the historical origins of GERD in TCM, the missing information on some authors and written time do not affect the main results and conclusions. And, the extra-esophageal reflux symptoms are not the common and core diagnostic criteria of GERD. So the research group believe that the results and conclusions of this study are high scientific and reliable on the whole.

## Conclusions

This study performed a comprehensive retrospect on the historical views for GERD in ancient TCM, with text information extraction, knowledge mapping and qualitative analysis, and clarified the disease name, etiology, and pathogenesis, which provides a good reference for further improving and developing theoretical cognition of this disease and treatment based on syndrome differentiation.

# Abbreviations

Gastroesophageal reflux disease, GERD

Traditional Chinese Medicine, TCM

Knowledge graph, KG

China National Knowledge Infrastructure, CNKI

Anno Domini, A.D.

Before Christ, B.C.

# Declarations

## **Ethics approval and consent to participate**

There is no people or animals involved in this study, so there is no Ethics approval and Consent to participate for this study.

## **Consent for publication**

All authors read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

## **Availability of data and material**

All data generated or analyzed during this study are included in this published article. The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

## **Competing interests**

Non-financial associations that may be relevant or seen as relevant to the submitted manuscript. All authors declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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## Authors' contributions

Prof. Hou ZK are the guarantor of integrity of the entire study and were responsible for the conception and design of the study. Prof. Liu FB, Prof. Tao SY and Prof. Chen B are the advisers for the study. Pu SQ, Ph.D. is responsible for the acquisition, analysis and interpretation of data, and manuscript writing. Liu ZX, Ph.D., Li SY, Ph.D. and Zhang M Ph.D. had aided the data collection. Prof. Hou ZK and Xin YJ, Ph.D. are co-responsible for the manuscript editing and polishing.

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## Figures

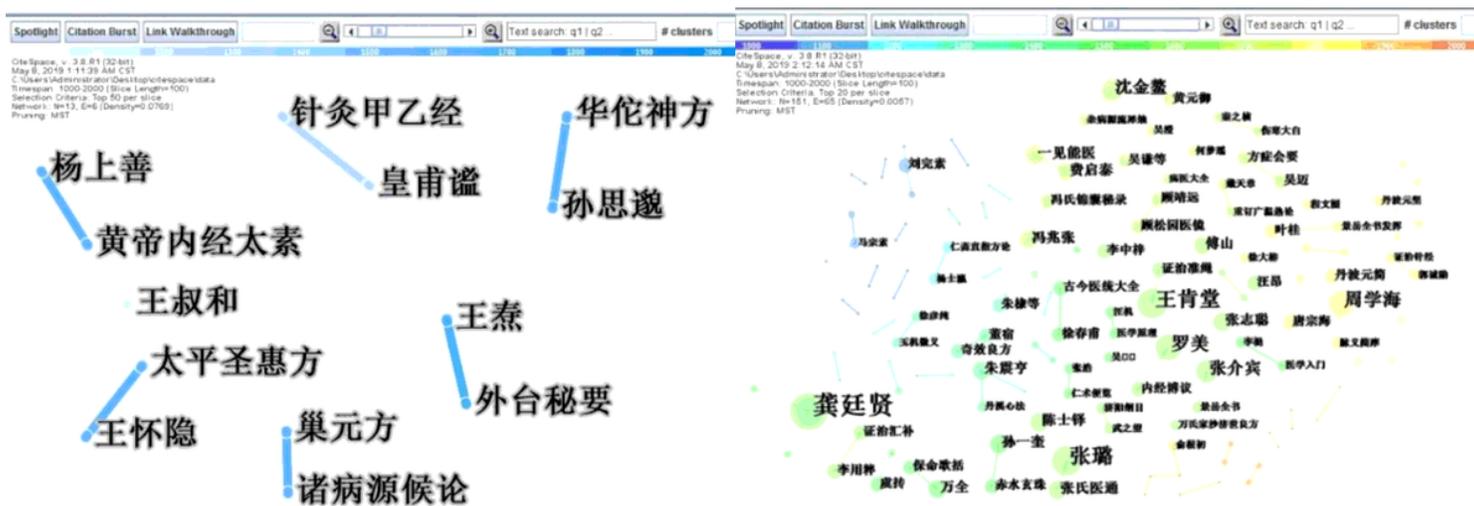


Figure 1

Co-occurring analysis for authors and bibliographies of TCM ancient books for GERD (1-1000 A.D. [left], 1000-2000 A.D. [right])

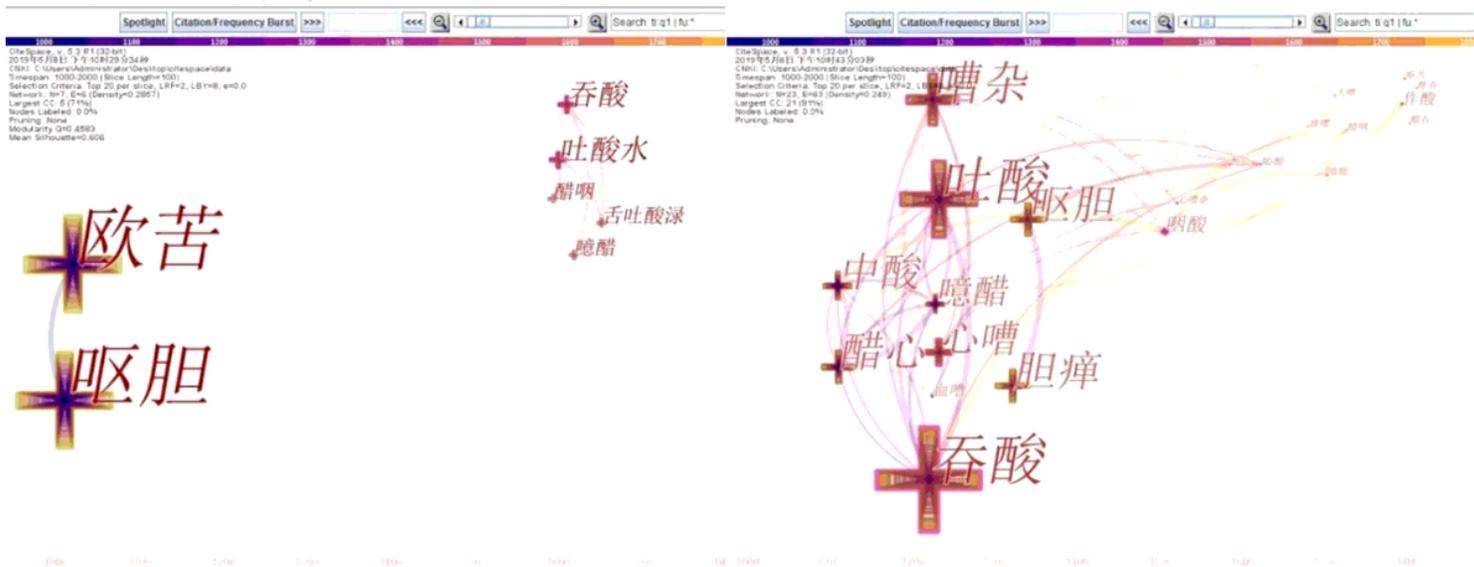


Figure 2

Co-occurring analysis for disease names of GERD in ancient TCM books (1-1000 A.D. [left], 1000-2000 A.D. [right])



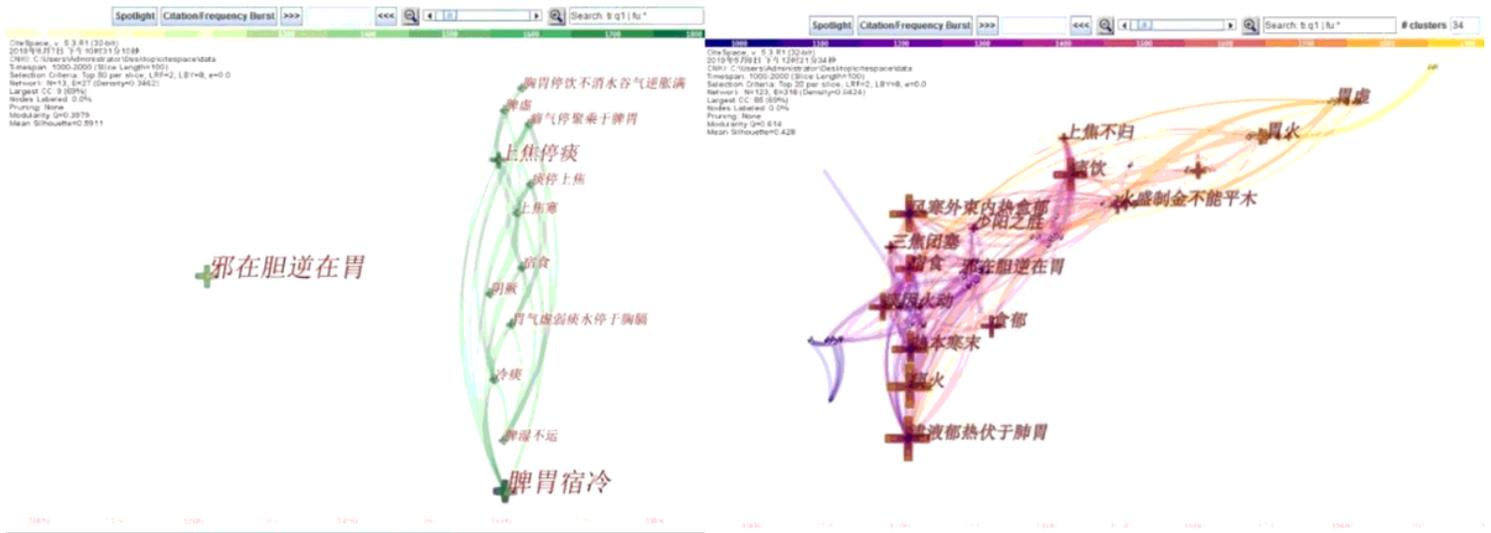


Figure 5

Co-occurring time zone analysis for disease pathogenesis of GERD in ancient TCM books (1-1000 A.D. [left], 1000-2000 A.D. [right])

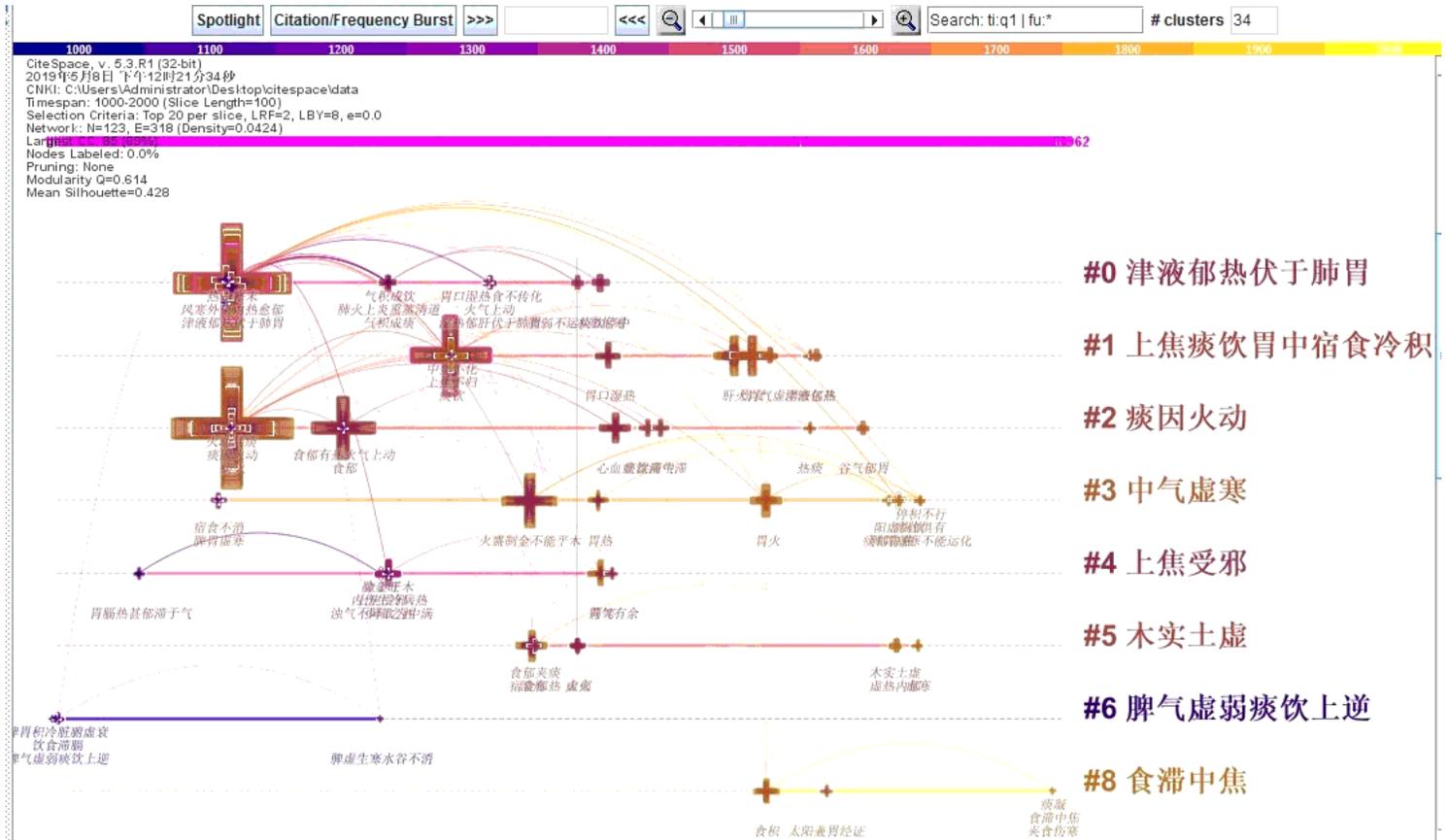


Figure 6

The time zone pictures of cluster analysis for disease Pathogenesis of GERD in ancient TCM books