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ORIGINAL RESEARCH

Prevalence, General and Periodontal Risk Factors of Gastroesophageal Reflux Disease in China

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Purpose: There is insufficient information about the prevalence and risk factors of gastroesophageal reflux disease (GERD) in the Chinese adult population. We aimed to assess the prevalence and identify the risk factors of GERD in China.

Methods: We collected data from a nationally representative sample (50,991 subjects) of Chinese adults from a large nation-wide cross-sectional survey. GERD was diagnosed by a standardized Chinese-language GERD questionnaire with a score of ≥ 8. The demographic characteristics, comorbidities and periodontal factors of all participants were collected.

Results: Fifty-thousands-one-hundred-eighty-three participants were finally included in this study. The overall prevalence of GERD was 5.6% (95% CI, 5.4–5.8%) among the general Chinese population aged 20 years or older. Women, smokers, and people with older age, BMI ≥ 25.0 kg/m^2, urban residence, lower education level or comorbidities were more prevalent with GERD ($p < 0.001$). Symptoms of severe periodontitis (OR = 1.40, 95% CI 1.28–1.52, $p < 0.001$) and lower frequency of tooth brushing (OR = 2.01, 95% CI 1.76–2.29, $p < 0.001$) were significantly associated with risk of GERD.

Conclusion: Symptom-based GERD is highly prevalent in the Chinese population. Overweight and smoking are major preventable risk factors for GERD. Periodontal factors are novel potential risk factors for GERD and should be given more attention in GERD prevention.

Keywords: gastroesophageal reflux disease, prevalence, risk factor, periodontitis, epidemiology

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common gastrointestinal disorders in the world. It is defined as a condition in which the reflux of gastric contents into the esophagus results in symptoms and/or complications in the new American College of Gastroenterology (ACG) clinical guideline.[1] Heartburn and regurgitation are typical symptoms of GERD, and patients can also have extraesophageal symptoms such as chest pain, chronic cough and laryngeal disorders.[2] A recent meta-analysis showed that the prevalence of GERD varied from 2.5% to 51.2% in different countries and regions worldwide, and the pooled prevalence was 13.3%.[3] Previously, the prevalence of GERD in China was reported to be lower than in western countries in some population-based studies.[3,4] However, to our knowledge, there is no nation-wide prevalence data of China has been reported.

The pathophysiology of GERD is multifactorial.[5] Many risk factors for GERD have been well established, including obesity or increased body mass index, smoking and genetic predisposition.[2] Several other risk factors, including older age, low socioeconomic status and low education level, were also involved in GERD.[3] The risk factors for GERD vary in different studies based on the population from different regions of China.[4,6–8] To further clarify the risk factors for GERD in the national population is important for GERD prevention and the public health in China.

The oral cavity is the beginning of the digestive tract. The oral manifestations of GERD have been concerned previously.[9,10] The most common oral manifestations include dental erosion and oral soft tissue disorders.[10] However, whether oral health affects GERD is not clear. Periodontitis is one of the most common oral diseases. It is a chronic infection and inflammatory disease that is initially caused by periodontal pathogens and eventually leads to alveolar bone resorption, tooth mobility and tooth loss.[11] Oral dysbacteriosis is a significant feature of periodontitis patients.[12] Pathogens in the oral cavity of periodontitis patients easily migrate to the esophagus by swallowing food and saliva. Studies have shown that microbes in the esophagus shift in patients with GERD or reflux disorders, which may contribute to the development of GERD.[13,14] Therefore, periodontitis may be an important potential risk factor for GERD.

We designed this study by collecting the data of representative Chinese adults (57,779 subjects) from a large national cross-sectional survey (China Lung Health Study, CPHS).[15] In this study, we aimed to assess the prevalence and identity the general and periodontal risk factors of GERD in the general Chinese population.

Methods
Study Participants
The CPHS was a cross-sectional study conducted from 2012 to 2015 in a nationally representative sample of adults aged 20–89 in China from 2012 to 2015. The study complies with the Declaration of Helsinki and was approved by the ethics review committee of Beijing Capital Medical University (No. 11-ke-42, and approved on June 24, 2011) and other participating institutes.[15] All study participants received written informed consent. Details of the study design have been published previously.[15] In brief, a multistage stratified cluster sampling procedure was adopted to recruit a nationally representative sample of adults age 20 or older from the selected communities, and a total of 57,779 adults were included from 10 provinces across the country, of whom 50,183 had natural teeth in the mouth and no missing data were included in the study. The flow diagram of selecting study participants is shown in Figure 1. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.
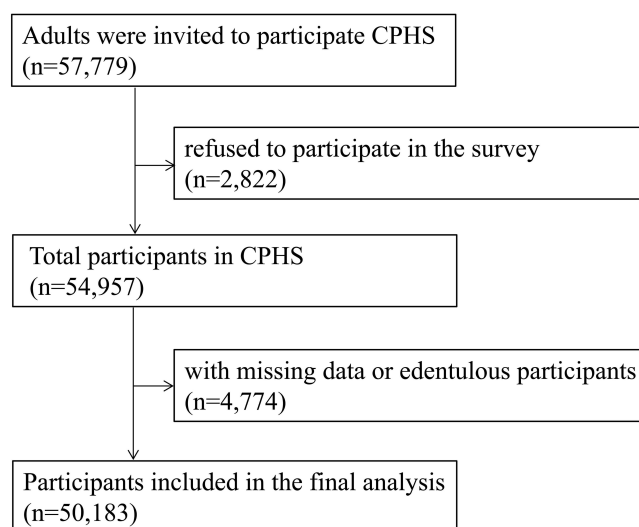
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┌─────────────────────────────────────────┐
│ Adults were invited to participate CPHS  │
│ (n=57,779)                               │
└─────────────────────────────────────────┘
              │        ┌──────────────────────────────────────┐
              ├───────▶│ refused to participate in the survey  │
              │        │ (n=2,822)                             │
              ▼        └──────────────────────────────────────┘
┌─────────────────────────────────────────┐
│ Total participants in CPHS               │
│ (n=54,957)                               │
└─────────────────────────────────────────┘
              │        ┌──────────────────────────────────────────┐
              ├───────▶│ with missing data or edentulous participants │
              │        │ (n=4,774)                                 │
              ▼        └──────────────────────────────────────────┘
┌─────────────────────────────────────────┐
│ Participants included in the final analysis │
│ (n=50,183)                               │
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Figure 1 The flow diagram of the selection of study participants.

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Data Collection

Trained interviewers administered a standardized Chinese-language GERD questionnaire (GERDQ) that has been validated for both diagnosis and follow-up of reflux disease patients (Detailed questions are in Supplementary GERD Questionnaire).[16,17] It uses a four graded scale (0–3) to score the frequency of four positive predictors of GERD, including heartburn, reflux, sleep disorders caused by reflux symptoms or the use of over-The-counter medications for reflux symptoms; and a reversed scale (3–0) for two negative predictors of GERD, including epigastric pain and nausea. Finally, the total score range of GERDQ was 0–18.[16] GERD was diagnosed in participants with a score of ≥ 8 on the evaluation of GERDQ.[16,18] All participants in the population with a score of < 8 on the evaluation of GERDQ were used as control participants in the analyses.

The trained interviewers conducted a standardized questionnaire, including information on demographic characteristics (sex, age, education level, geographic location, smoking status and residence) and comorbidities. Comorbidities included cancer, asthma, chronic obstructive pulmonary disease, hypertension, coronary heart disease, depression, diabetes mellitus, anemia and osteoporosis. A person who has smoked 100 cigarettes in his life and is still smoking is defined as current smoker.[15] Body weight and height were determined using a calibrated scale, and body mass index (BMI) was calculated as weight/height squared.

Natural tooth loss and tooth mobility are typical symptoms of severe periodontitis.[11] Trained interviewers asked all participants whether they had natural tooth loss and/or tooth mobility in the past year. The frequency of tooth brushing was also asked of all participants. Participants who had natural tooth loss and/or tooth mobility in the past year were considered to have symptoms of severe periodontitis. The tooth brushing frequency was divided into higher (≥ 1 time/day) and lower (< 1 time/day) frequency.

Statistical Analyses

The continuous variables of normal distribution were represented by the mean (standard deviation, SD). The categorical variables were presented as frequencies with percentages. SPSS statistical software (version 20.0; SPSS Inc., Chicago, IL, USA) was used for the data analyses, and statistical significance was considered at a two-sided $p < 0.05$.

The overall and prevalence of GERD and 95% confidence interval (CI) in total participants was calculated, as well as prevalence in participants grouped by geographic distribution, sex, age, education level, BMI, smoking status, several periodontitis and frequency of tooth brushing. P for difference or p for trend values among groups were also calculated.

Multiple logistic regression analyses were performed to calculate the odds ratios (ORs) and 95% CI for the associations between general and periodontal risk factors and GERD. The adjusted model 1 was adjusted for sex, age and BMI. The adjusted model 2 was additionally adjusted for education level, smoking status, comorbidities and residence.

In order to know whether the periodontal risk factors in sub-populations might exhibit differential risk of GERD, we investigated potential interaction between periodontal risk factors and age (20–39 years versus (vs) 40–59 years vs ≥60 years), sex, BMI (< 25 Kg/m^2 vs ≥ 25Kg/m^2), smoking (never smoker vs current/former smoker), education level (middle school and lower vs high school and higher), residence (urban vs rural) and comorbidities (yes vs no).

Results

The demographic characteristics of the total 50,183 participants by GERD in men and women are shown in Table 1.

Among the general Chinese population aged 20 years or older, the overall prevalence of GERD was 5.6% (95% CI, 5.4–5.8%). The prevalence in different geographic regions of China was 8.2% (95% CI, 7.7–8.8%) in the north region, 7.1% (95% CI, 6.4–7.8%) in the northeast region, 6.9% (95% CI, 6.2–7. 5%) in the northwest region, 5.1% (95% CI, 4.6–5.5%) in the southwest region, 4.3% (95% CI, 3.9–4.8%) in the east region, and 3.4% (95% CI, 3.1–3.8%) in the central south region (p for trend < 0.001). The prevalence in the northern area (north, northeast and northwest regions) was significantly higher than in the other areas ($p < 0.001$). GERD was more prevalent in urban residents (6.0%, 95% CI 5.7–6.2%) than in rural residents (5.5%, 95% CI 5.3–5.8%; $p < 0.001$) (Figure 2).

The prevalence grew with age and was 3.7% (95% CI, 3.4–4.0%) among individuals aged 20–39 years, 6.0% (95% CI, 5.7–6.3%) among individuals aged 40–59 years, and 6.9% (95% CI, 6.5–7.4%) among those aged 60 years or older

Table 1 Characteristics of the Study Population by GERD in Men and Women

Characteristics	Overall N = 50,183	Men			Women		
		Total N = 21,099	With GERD N = 1090	Without GERD N = 2009	Total N = 29,084	With GERD N = 1742	Without GERD N = 27,342
Age (%)							
20–39 y	12,619 (25.1)	5868 (27.8)	229 (21.0)	5639 (28.2)	6751 (23.2)	239 (13.7)	6512 (23.8)
40–59 y	24,916 (49.7)	9693 (45.9)	538 (49.4)	9155 (45.8)	15,223 (52.3)	948 (54.4)	14,275 (52.2)
≥ 60 y	12,648 (25.2)	5538 (26.2)	323 (29.6)	5215 (26.1)	7110 (24.4)	555 (31.9)	6555 (24.0)
Mean age (year, mean (sd))	49.4 (13.8)	49.0 (14.6)	51.1 (13.6)	48.9 (14.7)	49.7 (13.2)	53.4 (12.1)	49.5 (13.3)
BMI (%)							
< 25.0kg/m² (normal and underweight)	32,221 (64.2)	12,816 (60.7)	619 (56.8)	12,197 (61.0)	19,405 (66.7)	1061 (60.9)	18,344 (67.1)
≥ 25.0kg/m² (overweight and obese)	17,962 (35.8)	8283 (39.3)	471 (43.2)	7812 (39.0)	9679 (33.3)	681 (39.1)	8998 (32.9)
Mean BMI (kg/m²) (mean (sd))	23.99 (3.52)	24.21 (3.50)	24.56 (3.50)	24.20 (3.50)	23.84 (3.53)	24.40 (3.54)	23.80 (3.53)
Education (%)							
Middle school and lower	30,454 (60.7)	11,350 (53.8)	620 (56.9)	10,730 (53.6)	19,104 (65.7)	1227 (70.4)	17,877 (65.4)
High school and higher	19,729 (39.3)	9749 (46.2)	470 (43.1)	9279 (46.4)	9980 (34.3)	515 (29.6)	9465 (34.6)
Smoking status (%)							
Never smoker	35,853 (71.4)	7701 (36.5)	316 (29.0)	7385 (36.9)	28,152 (96.8)	1661 (95.4)	26,491 (96.9)
Current/Former smoker	14,330 (28.6)	13,398 (63.5)	774 (71.0)	12,624 (63.1)	932 (3.2)	81 (4.6)	851 (3.1)
Residence (%)							
Urban	32,393 (64.5)	13,370 (63.4)	755 (69.3)	12,615 (63.0)	19,023 (65.4)	1179 (67.7)	17,844 (65.3)
Rural	17,790 (35.5)	7729 (36.6)	335 (30.7)	7394 (37.0)	10,061 (34.6)	563 (32.3)	9498 (34.7)
Geographic region (%)							
North	9671 (19.3)	4143 (19.6)	314 (28.8)	3829 (19.1)	5528 (19.0)	480 (27.6)	5048 (18.5)
Northeast	5080 (10.1)	1529 (7.2)	110 (10.1)	1419 (7.1)	3551 (12.2)	251 (14.4)	3300 (12.1)
Northwest	5910 (11.8)	1043 (4.9)	74 (6.8)	969 (4.8)	1089 (3.7)	96 (5.5)	993 (3.6)
Southwest	9394 (18.7)	4042 (19.2)	186 (17.1)	3856 (19.3)	5352 (18.4)	290 (16.6)	5062 (18.5)
East	9424 (18.8)	3743 (17.7)	140 (12.8)	3603 (18.0)	5681 (19.5)	269 (15.4)	5412 (19.8)
Central south	9979 (19.9)	4665 (22.1)	153 (14.0)	4512 (22.5)	5314 (18.3)	189 (10.8)	5125 (18.7)
Comorbidities (%)							
Yes	5953 (11.9)	2355 (11.2)	217 (19.9)	2138 (10.7)	3598 (12.4)	389 (22.3)	3209 (11.7)
No	44,230 (88.1)	18,744 (88.8)	873 (80.1)	17,871 (89.3)	25,486 (87.6)	1353 (77.7)	24,133 (88.3)
Frequency of toothbrushing (%)							
≥1 time/day	47,445 (94.5)	19,629 (93.0)	941 (86.3)	18,688 (93.4)	27,816 (95.6)	1588 (91.2)	26,228 (95.9)
< 1 time/day	2738 (5.5)	1470 (7.0)	149 (13.7)	1321 (6.6)	1268 (4.4)	154 (8.8)	1114 (4.1)
Symptoms of severe periodontitis (%)							
Yes	11,015 (21.9)	4676 (22.2)	336 (30.8)	4340 (21.7)	6339 (21.8)	551 (31.6)	5788 (21.2)
No	39,168 (78.1)	16,423 (77.8)	754 (69.2)	15,669 (78.3)	22,745 (78.2)	1191 (68.4)	21,554 (78.8)

Notes: Comorbidities included chronic obstructive pulmonary disease, asthma, cancer, coronary heart disease, hypertension, diabetes mellitus, depression, osteoporosis and anemia. Symptoms of severe periodontitis were defined as tooth mobility and/or natural tooth loss in the past year.
Abbreviations: GERD, gastroesophageal reflux disease; BMI, body mass index.

(p for trend < 0.001). Women had a higher prevalence of 6.0% (95% CI 5.7–6.3%) than men (5.2%, 95% CI 4.9–5.5%, p < 0.001). The prevalence of GERD was higher in overweight and obese participants (BMI ≥ 25.0 kg/m²), current and former smokers and participants with lower education level (middle school and lower) (all p < 0.05) (Figure 2).

Dramatically, we found that the prevalence of GERD was much higher among participants with symptoms of severe periodontitis (8.1%, 95% CI 7.5–8.6%) and lower frequency of tooth brushing (< 1 time/day) (11.1%, 95% CI 9.9–12.2%) than those without symptoms of severe periodontitis (5.6%, 95% CI 5.4–5.8%) and with higher frequency of tooth brushing (≥ 1 time/day) (5.0%, 95% CI 4.8–5.2%, both p < 0.001) (Figure 2).

In multivariable-adjusted logistic regression analyses, older age, female sex, overweight and obesity (BMI ≥ 25.0 kg/m²), lower education level (middle school and lower), smoking, urban residents and comorbidities were significantly associated with risk of GERD in adjusted model 2 (all p < 0.05) (Table 2).
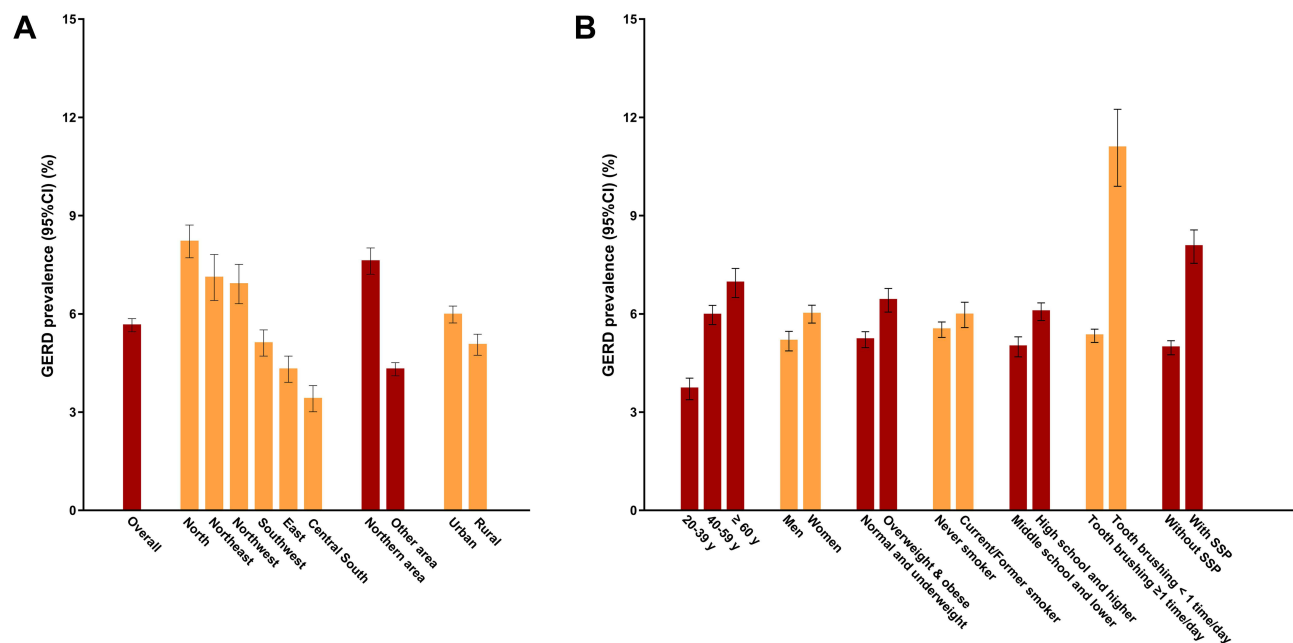
Figure 2 The prevalence of GERD in the total participants and in subgroups. (**A**) The prevalence of GERD in the total participants and in geography related subgroups. Northern area included north, northeast and northwest: Other area included southwest, east and central south. (**B**) The prevalence of GERD in non-geography related subgroups. Normal or underweight: body mass index (BMI)<25.0 kg/m2; overweight and obese: BMI≥25.0 kg/m2. Symptoms of severe periodontitis were defined as having tooth mobility and/or natural tooth loss in the past year. P<0.05.
Abbreviations: GERD, gastroesophageal reflux disease: SSP, symptoms of severe periodontitis.

For periodontal factors, symptoms of severe periodontitis were significantly associated with risk of GERD (OR = 1.40, 95% CI 1.28–1.52, $p < 0.001$) after adjusting for confounding risk factors, and lower frequency of tooth brushing (< 1 time/day) also showed higher risk of GERD (OR = 2.01, 95% CI 1.76–2.29, $p < 0.001$) in the multivariable-adjusted logistic regression analyses (Figure 3).

In the subgroup analyses, symptoms of severe periodontitis and lower frequency of tooth brushing (< 1 time/day) were still significantly associated with risk of GERD in all subgroup participants (all $p \leq 0.001$) (Figure 4).

Discussion

As far as we know, this study is the first and largest nationwide survey on GERD for the general Chinese adult population aged 20 years and older. Our data indicated that 5.6% (95% CI, 5.4–5.8%) of the general Chinese adult population had symptom-defined GERD. Overweight and obesity, low education level and smoking were major preventable risk factors of GERD in the Chinese population. Specially, we found that symptoms of severe periodontitis and lower frequency of tooth brushing were significantly associated with risk of GERD and had higher ORs compared with other general risk factors.

No gold standard is for GERD diagnosis.[1] The diagnosis of GERD is usually based on clinical symptoms, reaction to acid suppression, as well as objective testing of upper endoscopy and esophageal pH monitoring.[1,2] The diagnosis of GERD only based on symptoms has some limitations, however, it may be the most applicable method for a large general population survey because objective testing with upper endoscopy and/or esophageal pH monitoring is too expensive and complicated. Symptom-based diagnostic criteria for GERD was commonly used in large epidemiology studies previously.[3] In clinical practice of GERD, diagnosing and treating based on typical symptoms are pragmatic and recognized by societal guidelines.[1] GERDQ was widely used in clinic and its diagnostic value has been verified in several studies.[17,19–21] A recent study in China showed that the sensitivity and specificity of GERDQ were 90.30% and 92.10% for GERD diagnosis, respectively.[18]

A recent meta-analysis of 108 separate study populations containing 460,984 subjects showed that prevalence varied in accordance with country and criteria used to define gastro-esophageal reflux symptoms. Pooled

Table 2 Associations Between General Risk Factors and GERD by Logistic Regression Analyses

Risk Factors	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	OR, 95% CI	p	OR, 95% CI	p	OR, 95% CI	p
Age						
20–39 y	Ref		Ref		Ref	
40–59 y	1.65 (1.48, 1.83)	< 0.001	1.59 (1.43, 1.77)	< 0.001	1.46 (1.31, 1.63)	< 0.001
≥ 60 y	1.94 (1.73, 2.17)	< 0.001	1.88 (1.68, 2.11)	< 0.001	1.55 (1.37, 1.75)	< 0.001
P for trend	< 0.001					
Sex						
Man	Ref		Ref		Ref	
Woman	1.17 (1.08, 1.26)	< 0.001	1.16 (1.08, 1.26)	< 0.001	1.39 (1.25, 1.56)	< 0.001
BMI (kg/m^2)						
< 25.0 (normal and underweight)	Ref		Ref		Ref	
≥ 25.0 (overweight and obese)	1.25 (1.15, 1.35)	< 0.001	1.20 (1.11, 1.29)	< 0.001	1.14 (1.05, 1.23)	0.001
Education						
Middle school and lower	1.23 (1.14, 1.33)	< 0.001	1.04 (0.96, 1.13)	0.34	1.10 (1.01, 1.20)	0.03
High school and higher	Ref		Ref		Ref	
Smoking status						
Never smoker	Ref		Ref		Ref	
Current/Former smoker	1.09 (1.00, 1.18)	0.047	1.39 (1.24, 1.56)	< 0.001	1.38 (1.23, 1.55)	< 0.001
Residence						
Urban	1.19 (1.10, 1.30)	< 0.001	1.18 (1.09, 1.28)	< 0.001	1.20 (1.10, 1.31)	< 0.001
Rural	Ref		Ref		Ref	
Comorbidities						
Yes	2.14 (1.95, 2.35)	<0.001	1.93 (1.75, 2.13)	< 0.001	1.92 (1.74, 2.12)	< 0.001
No	Ref		Ref		Ref	

Notes: Adjusted model 1: multiple logistic regression analyses adjusted for age, sex and BMI; Adjusted model 2: additional adjusted for smoking status, education, residence and comorbidities. Comorbidities included chronic obstructive pulmonary disease, asthma, cancer, coronary heart disease, hypertension, diabetes mellitus, depression, osteoporosis and anemia.
Abbreviations: GERD, gastroesophageal reflux disease; BMI, body mass index.

prevalence was 13.3% (95% CI 12.0% to 14.6%) when only studies using weekly heartburn or regurgitation to define GERD were included.[3] The results of our data showed that the prevalence of symptom-defined GERD in China is 5.6% (95% CI 5.4–5.8%) that is much lower than the global prevalence and the prevalence in western
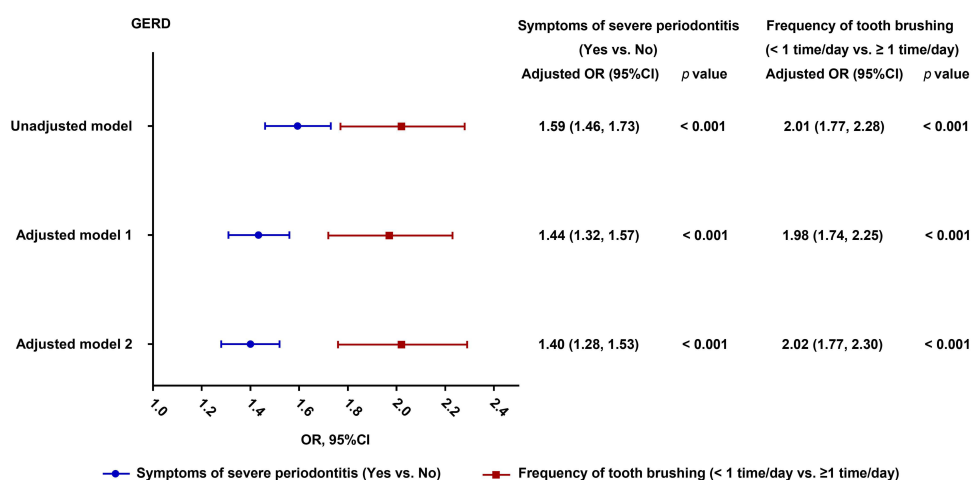

Figure 3 Associations between periodontal risk factors and GERD by multiple logistic regression analyses. Adjusted model 1: multiple logistic regression analyses adjusted for age, sex and body mass index (BMI); Adjusted model 2: additional adjusted for smoking status, education, residence and comorbidities. Symptoms of severe periodontitis were defined as having tooth mobility and/or natural tooth loss in the past year.
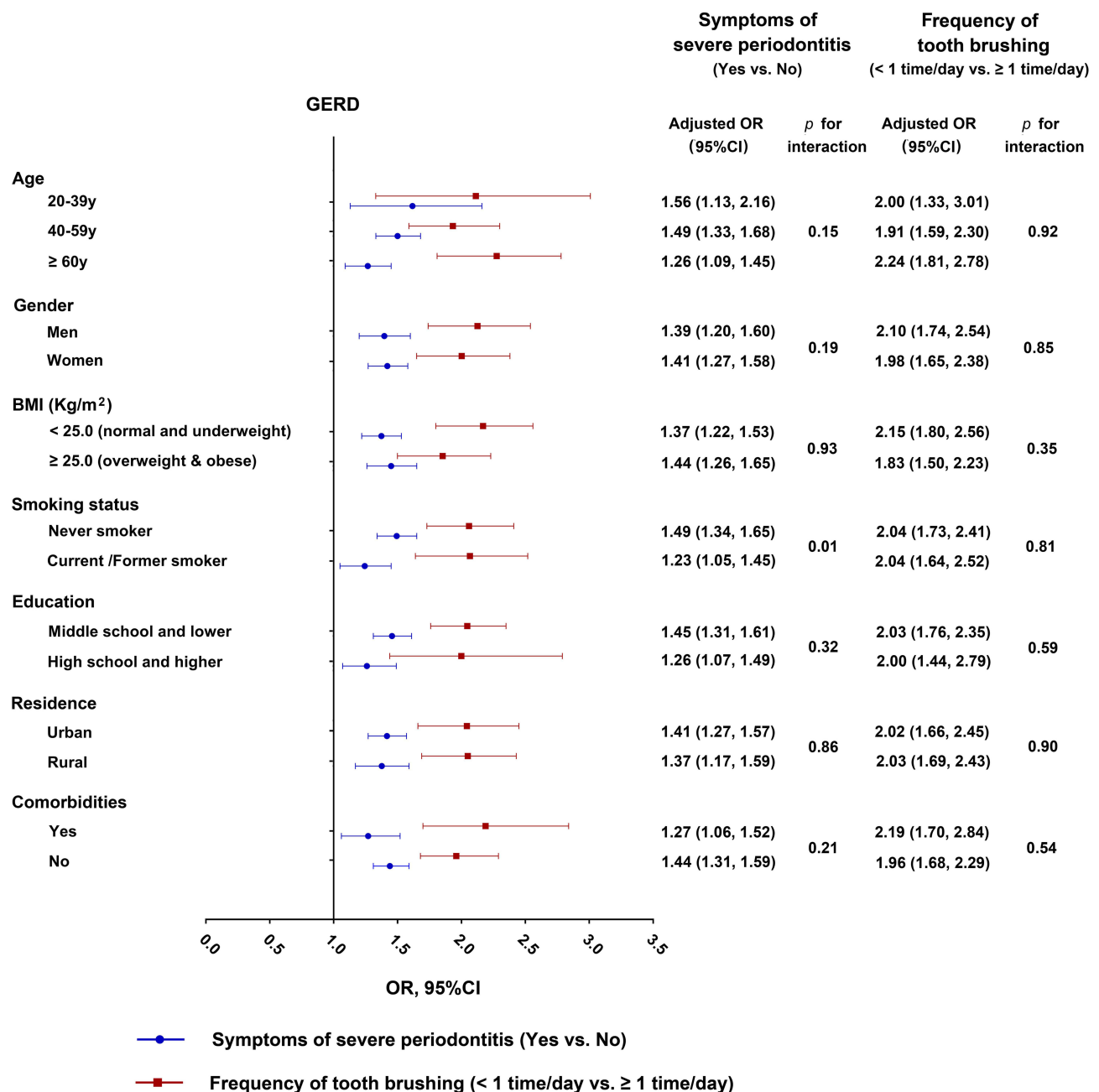**Abbreviation**: GERD gastroesophageal reflux disease.

Figure 4 Associations between periodontal risk factors and GERD in subgroups by multiple logistic regression analyses. Multiple logistic regression analyses adjusted for age, sex, BMI, smoking status, education, residence and comorbidities. Symptoms of severe periodontitis were defined as having tooth mobility and/or natural tooth loss in the past year.
Abbreviations: GERD, gastroesophageal reflux disease; BMI, body mass index.

countries. The prevalence increased with age, and women had a slightly higher prevalence than men in our study, which was consistent with previous studies.[3]

In recent decades, several studies have investigated the prevalence of GERD in China. The prevalence of GERD was 23.4% in Kashgar, Xinjiang Autonomous Region from 5080 general population participants.[6] 19.89% in Beijing from 37,442 individuals undergoing routine physical examinations in hospital.[7] 10.8% in Tibet Autonomous Region from 5, 680 general population participants,[22] 3.8% in Hong Kong SAR from 2074 subjects,[8] and 1.7% in Taizhou, Shandong province from 8831 retirees.[23] The prevalence varied strikingly among these studies, which may be due to different study populations and different diagnosis criteria of GERD. In this study, we also found that the prevalence of GERD varied

among different regions of China. The prevalence in the northern area of China was nearly two times that in other areas. Another population based study enrolled 16,078 subjects from five major cities in China from 2007 to 2008 found that the prevalence of symptom-defined GERD in China was 3.1%,[4] which is lower than the results of our study of 50,183 subjects from a rigorous sampling design of the nation-wide population in 2012 to 2015.

Increased BMI and smoking were well-documented risk factors for GERD [2]. Our study showed overweight and obesity was significantly associated with the risk of GERD compared with normal and underweight (BMI < 25.0 kg/m^2). These results were consistent with the study of Jacobson et al.[24] The relationship between obesity and GERD may be the increase of intra-abdominal pressure, the prevalence of hiatal hernia, the gradient of abdominal to thoracic pressure, the level of estrogen, and the secretion of bile and pancreatic enzymes caused by obesity.[2,25] Current/Former smokers had a higher risk of having GERD than never smokers, corresponding to an OR of 1.38 (95% CI, 1.23–1.56) in this study, and this is also consistent with the recent meta-analysis.[3] Tobacco can prolong the clearing time of the esophageal acid and reduce the pressure in the lower esophageal sphincter, which was used to explain their association.[2,25]

In this study, we found that lower education level and urban residents were also significantly associated with the risk of GERD. Urban residents usually have a better socioeconomic status than rural residents, and socioeconomic status has been demonstrated to be associated with GERD.[3] People with a lower education level in China usually have a worse socioeconomic status or older age. They were found to be more likely to suffer from GERD in this study, which was also consistent with previous studies.[3]

As far as we know, this is the first population based study to investigate periodontal risk factors for GERD. The results of our study showed that symptoms of severe periodontitis and lower frequency of tooth brushing were both significantly associated with risk of GERD, and had higher ORs (1.40, 95% CI 1.28–1.52 and 2.01, 95% CI 1.76–2.29 separately) than higher BMI and smoking after adjusting for other risk factors.

Several studies have explored the changes of microbes in the esophagus of GERD or reflux disorders. These studies showed an overall shift from gram-positive bacterial species in normal individuals to gram-negative anaerobic colonization in patients with GERD or reflux disorders.[13,14,26] Gram-negative anaerobic bacteria such as *Porphyromonas, Prevotella, Fusobacterium* and *Actinomyces* were found in the distal esophagus of GERD or reflux disorders.[26] The esophageal inflammation caused by microbes was supposed to be a possible link to GERD.[13,14,26]

Periodontitis is initially caused by periodontal pathogens infection. Periodontal pathogens are mainly gram-negative anaerobic bacteria such as *Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, aggregatibacter* and *Fusobacterium nucleatum*, which are abundant in the periodontal environment.[27] These species were consistent with the bacteria that increased in the distal esophagus of GERD.[26]

There are more than 700 different species of bacteria in the oral cavity, most of which are attached to the tooth surface and form dental plaque biofilm.[28] Most of them are anaerobic bacteria. The lower frequency of tooth brushing is associated with poor oral hygiene and more bacteria in the oral cavity. The lower frequency of tooth brushing is also an important risk factor for periodontitis.

In recent decades, there has been renewed interest in the basic principle that the oral microbiome may play an important role in overall health. Specifically, the presence of oral infections such as periodontal disease may be a pathogenic or aggravating factor for some systemic diseases.[29] Three mechanisms currently support a link between periodontitis and systemic disease: metastatic infections, dissemination of bacterial toxins and immunological injury.[30] Studies have found that *porphyromonas gingivalis*, a major cause of periodontal disease, may cause transient bacteremia during common activities such as brushing, flossing and chewing, or during dental surgery, resulting in translocation to various tissues, including brain of Alzheimer's patients, coronary arteries, tonsil and liver.[31,32] A recent study showed that 100% of patients with cardiovascular disease had *porphyromonas gingivalis* artery colonization.[33] The oral cavity is the beginning of the digestive tract, oral microbes can easily migrate into the esophagus through the swallowing of food and saliva. Therefore, we speculated that the association between periodontal risk factors and GERD may be due to the possible microbial alteration of the esophagus caused by oral dysbacteriosis.

Our study has some limitations. First, GERD was defined based on GERDQ and no objective testing and clinical examination were performed. Second, some potential risk factors for GERD, such as genetic predisposition, were not

included in this study. Third, this is a cross-sectional study, so it is impossible to establish a causal relationship between the risk factors of GERD.

Conclusion

This nationwide large-scale cross-sectional study showed that the prevalence of symptom-based GERD was 5.6% in the Chinese population, which was lower than the global average prevalence. Overweight and smoking were major preventable risk factors for GERD. Periodontal factors, including symptoms of severe periodontitis and lower frequency of tooth brushing, are novel potential risk factors for GERD and should be given more attention in GERD prevention. Long-term cohort studies are needed to confirm the associations of these periodontal risk factors in the future.

Abbreviations

GERD, gastroesophageal reflux disease; CPHS, China Pulmonary Health Study; GERDQ, GERD questionnaire; BMI, body mass index; CI, confidence interval; ORs, odds ratios; ACG, American College of Gastroenterology; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

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Author Contributions

All authors made significant contributions to the conception and design of the study, and reviewed the article critically. Zuomin Wang and Chen Wang supervised the study. Zhiqiang Liu, Lirong Liang, Xuan Zhou, Ting Yang, Kewu Huang and Yingxiang Lin contributed to the data collection. Zhiqiang Liu, Xiaoli Gao and Lirong Liang did the data analysis. Zhiqiang Liu, Xiaoli Gao, Lirong Liang, Xiaozhe Han, Shu Deng, Zuomin Wang and Chen Wang participated in data interpretation, drafting the manuscript. All authors have given final approval to the journal to which the article will be submitted, agreed on all versions of the article and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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