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The prevalence and severity of periodontal disease in Mainland China: Data from the Fourth National Oral Health Survey (2015–2016)

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Abstract

Aim: To evaluate periodontal conditions in adults in mainland China based on data from the 4th National Oral Health Survey.

Materials and methods: Data of adult subjects (35- to 44-year-old group [N = 4409], 55- to 64-year-old group [N = 4622], and 65- to 74-year-old group [N = 4428]) were analysed. Demographic, socio-economic, personal habit, dental history, and health attitude data were obtained using a questionnaire. Periodontal condition was assessed using the standardized case definitions of the 2018 classification scheme. A multivariate analysis was performed to investigate the relationship between periodontitis severity and age, smoking status, gender, and region using generalized additive models after adjusting for confounders.

Results: The frequency of subjects with periodontitis was 52.8%, 69.3%, and 64.6% in the three age groups, respectively. The frequency of subjects with severe periodontitis (stage III or IV) was 10.6%, 37.3%, and 43.5% in the three age groups, respectively. The severity of periodontal disease was positively associated with age. Current and former smokers exhibited significantly greater disease severity than non-smokers after adjustment for confounders. No significant difference of severity was found between males and females.

Jian Jiao and Wudi Jing contributed equally to this work.

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Conclusion: Within the limitations of the study, the prevalence of periodontitis is very high among adults in mainland China. Periodontal status is associated with age and smoking status.

KEYWORDS

Chinese adults, mainland China, periodontal condition, the 4th National Oral Health Survey

1 | INTRODUCTION

Periodontal disease is common among adults worldwide. The prevalence of periodontitis ranges from 4% to 76.0% in developed countries (Aimetti et al., 2015; Akinkugbe et al., 2018; Baelum & Lopez, 2012; Eke et al., 2018; Holde et al., 2017; Holtfreter et al., 2009, 2010; Kassebaum et al., 2014a; Van der Velden, 2009) and from over 50% to nearly 90% in developing countries (Baelum & Scheutz, 2002; Gjermo et al., 2002; Shaju et al., 2011; Yang et al., 2017). The burden of periodontitis, especially severe periodontitis, is increasing due to increasing life expectancy and decreasing prevalence of tooth loss worldwide (Kassebaum et al., 2014a, 2014b). It has been estimated that severe periodontitis affects 11% of the global population. The prevalence of severe periodontitis is 3% to 18% in developed countries (Aimetti et al., 2015; Akinkugbe et al., 2018; Baelum & Lopez, 2012; Eke et al., 2018; Holde et al., 2017; Holtfreter et al., 2009, 2010; Kassebaum et al., 2014a; Van der Velden, 2009) and from 8% to 46% in developing countries (Baelum & Scheutz, 2002; Figueiredo et al., 2013; Gjermo et al., 2002; Kassebaum et al., 2014a; Shaju et al., 2011; van der Velden et al., 2015; Yang et al., 2017).

The differences in the prevalence of periodontitis and severe periodontitis are a result of variation in socio-economic status, ethnicity, and exposure to other risk factors. Also, the situation is complicated by the use of different definitions of periodontitis severity (Aimetti et al., 2015; Baelum & Lopez, 2012; Caton et al., 2018; Eke et al., 2015; Holde et al., 2017; Page & Eke, 2007; Tonetti et al., 2018). In 2018, a classification scheme for periodontal disease was proposed at the World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions. The scheme enables not only diagnosis and treatment but also comparison of periodontal disease distributions between populations (Caton et al., 2018).

Periodontal disease is classified as a major dental disease by the World Health Organization (WHO) and is a public health problem that impacts oral and systemic health worldwide (Chen et al., 2018). Therefore, reliable epidemiological data are needed to assess the oral health status and disease burden and to formulate prevention policies (Holde et al., 2017; Kassebaum et al., 2014a, 2014b).

Information on the prevalence of periodontal disease in China, the most populous country in the world, was lacking until the Fourth National Oral Health Survey in 2017 (Lu et al., 2018). The survey was conducted according to the procedures and criteria of the WHO and yielded accurate and reliable data. We evaluated periodontal conditions in Chinese adults using the 2018 classification of periodontal disease (Tonetti et al., 2018) based on the data of the Fourth

Clinical Relevance

Scientific rationale for study: Reliable epidemiological data are needed to assess periodontal condition, oral health status, and disease burden, as well as to formulate prevention policies. However, information on periodontal disease in China is lacking, particularly data based on the most recent clinical classification scheme.

Principal findings: The prevalence of periodontitis and severe periodontitis was very high among adults in mainland China. High prevalence and severity of periodontitis was found in smokers and the elderly.

Practical implications: The findings highlight the importance of early prevention and treatment of periodontal disease in Chinese adults. Policies and measures should be implemented to improve awareness of periodontal health and facilitate timely and effective periodontal treatment.

National Oral Health Survey of China and explored the effect of age on periodontitis severity.

2 | MATERIALS AND METHODS

2.1 | Study design and sample

Data were obtained from the Fourth National Oral Health Survey of China, a cross-sectional survey supported by the Scientific Research Fund of the National Health Commission of the People's Republic of China and organized by the Chinese Stomatological Association (CSA), with cooperation from the Chinese Center for Disease Control and Prevention, stomatological/dental schools or hospitals nationwide, and the Centers for Disease Control in the administrative areas involved. The survey began in 2015 and gathered data on the oral health status and behaviour of residents in mainland China. Data collection was carried out in 2015 and 2016. The protocols for the Fourth National Oral Health Survey were reported in the *Chinese Journal of Dental Research*, the official journal of the CSA (Lu et al., 2018).

The size of sample was calculated to have a prevalence rate 86% of periodontal diseases of 2005, a 10% acceptable margin of error, and an anticipated response rate of 80%. The planned sample size was 4230 each for the 35–44, 55–64, and 65–74 years age groups.

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The final sample size was 4409, 4622, and 4428 for each group, respectively. Data of three subjects were excluded due to data missing.

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (Approval no. 2014-003).

2.2 | Clinical periodontal examinations and interviews

Periodontal examinations were performed using a community periodontal index probe, and the following four periodontal parameters were assessed: bleeding on probing (BOP), presence of calculus, periodontal probing depth (PPD), and clinical attachment loss (CAL). A full-mouth examination was performed, during which the probe was walked along gingival crevices with a force of ≤ 20 g to assess BOP, calculus presence, PPD, and CAL. For each parameter, each tooth was scored according to the severity of the most severe site. Prior to the survey, calibration training programmers were launched to ensure reliability of the results. Examiners with both inter- and intraexaminer kappa values higher than .6 for periodontal pocket depths were qualified. In the survey, 5% of the random participants were also selected to test the inter-examiner reproducibility. The kappa values for the three age groups ranged from .76 to .8.

Data on demographics (age, gender, and region), socio-economic status (level of education and income), and personal habits (smoking status) were collected using a questionnaire during face-to-face interviews.

2.3 | Data extraction

The following demographic and clinical data were extracted for analysis. *Periodontal examination data included* (a) Calculus (defined by visual examination for supragingival calculus and by probing for subgingival calculus, 0 = absence, 1 = presence, 9 = tooth excluded, and X = tooth not present), (b) PPD (0 = 1–3 mm, 1 = 4–5 mm, 2 = ≥6 mm, 9 = tooth excluded, and X = tooth not present), (c) BOP (0 = absence, 1 = presence, 9 = tooth excluded, and X = tooth not present), and (d) CAL (measured by the distance from the cementoenamel junction to the bottom of the periodontal pocket, 0 = 0–3 mm, 1 = 4–5 mm, 2 = 6–8 mm, 3 = 9–11 mm, 4 = ≥12 mm, 9 = tooth excluded, and X = tooth not present). Interview data from the questionnaire included age, gender, smoking status, region, level of education, and annual family income. Data of the third molars were excluded for analysis.

Periodontal disease was diagnosed according to the classification scheme proposed at the 2018 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions as follows: periodontally healthy: <10% BOP-positive teeth and PPD \leq 3 mm; gingivitis: \geq 10% BOP-positive teeth and PPD \leq 3 mm; and Periodontitis was staged using the algorithm developed by Graetz et al. (2019). For each tooth, CAL of the most severe sites was recorded, and a CAL of 1–2 mm was defined as stage I, 3–4 mm as stage II, and \geq 5 mm as stage III. Next, the number of missing teeth was considered (stages I and II, no tooth missing; stage III, \leq 4 teeth missing; and stage IV, \geq 5 teeth missing, it should be noted that reasons for tooth missing were not considered here). We also evaluated the complexity of management. Stage II patients were reclassified as stage III if the maximum PPD was \geq 6 mm. Stage III patients were reclassified as stage IV if there were less than 20 remaining teeth or 10 opposing pairs.

The extent of periodontitis was described as localized (<30% of teeth involved) or generalized (\geq 30% of teeth involved).

2.4 | Data analysis

The data were analysed using IBM SPSS Statistics 20 software (IBM Corp.), and graphs were generated with R (http://www.R-project.org). The primary outcome was periodontal status according to the 2018 classification. The secondary outcomes were presence of BOP, presence of calculus, PPD, and CAL. The parameters mentioned above of each tooth were determined by the score of the most severe site. We reported the percentage of teeth with, at the subject level, BOP, calculus, CAL ≥4 mm, CAL ≥6 mm, CAL ≥9 mm, CAL ≥12 mm, PPD ≥4 mm, and PPD ≥6 mm. The percentages of subjects with different periodontal diagnoses in the full sample and according to gender, smoking status, and regional subgroups were computed. The mean frequencies of the above-mentioned periodontal parameters in the full sample and in subjects with periodontitis (stages I-IV) were also computed. The prevalence of periodontitis, severe periodontitis (stages III and IV), and edentulous subjects stratified by provincial administrative unit in mainland China are shown as red, blue, and purple, respectively, in colourcoded maps. The original map was downloaded from Sinomap press (http://bzdt.ch.mnr.gov.cn/browse.html?picId=%224o28b0625501 ad13015501ad2bfc0294%22).

Periodontal data for the Hong Kong Special Administrative Region, Macao Special Administrative Region, and Taiwan Province were not available, and so the corresponding colours from the original map were retained. In addition, a multivariate analysis was performed. The diagnosis was encoded as an ordinal variable according to periodontitis severity (1 = periodontally healthy, 2 = gingivitis, 3 = periodontitis stage I, 4 = stage II, 5 = stage III, and 6 = stage IV). In addition, generalized additive models were used to explore the relationship between periodontal status (dependent variable) and age (independent variable) after adjusting for confounders (gender, smoking status, region, years of education, and annual family income). The differences of the relation between/among subgroups (by gender, smoking status, and region) were also analysed and illustrated. The results are displayed as smoothing plots for the full sample and subgroups. The level of significance was set at $p \le .05$.

3 | RESULTS

The demographic data of the participants are shown in Table 1. The subjects were randomly selected from 31 provinces, autonomous

TABLE 1 Characteristics of subjects included in the study

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			35–44 years (N = 4409)		55-64 years (N = 4622)		65–74 years (N = 4428)		Total (N = 13,459)	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)			40.03	3.06	59.92	2.92	69.11	2.84	56.43	12.40
Education level (years)			10.15	4.48	7.02	4.56	6.05	4.48	7.76	4.83
Number of missing teeth			0.72	1.60	3.60	5.50	6.96	7.96	3.76	6.20
Number of missing teeth in dentates			0.72	1.60	3.31	4.84	5.91	6.59	3.28	5.22
	N	%	N		%	N	%		N	%
Male	2196	49.8%	2292		49.6%	2221	50.2%	6	6709	49.8%
Female	2213	50.2%	2330		50.4%	2207	49.8%	6	6750	50.2%
Current smoker	1231	27.9%	1271		27.5%	1045	23.69	6	3547	26.4%
Non-smoker	2954	67.0%	2839		61.5%	2761	62.4%	6	8554	63.6%
Former smoker	226	5.1%	510		11.0%	622	14.0%	6	1358	10.1%
Urban	2235	50.7%	2338		50.6%	2247	50.7%	6	6820	50.7%
Rural	2174	49.3%	2284		49.4%	2181	49.3%	6	6639	49.3%
Edentulism	0	0.0%	51		1.1%	203	4.6%		254	1.9%

 TABLE 2
 Distribution of subjects according to the 2018 classification in total and by age groups

	35-45		55-65		65-75		Total	
	N	%	N	%	N	%	N	%
Healthy	698	15.8%	463	10.0%	530	12.0%	1691	12.6%
Gingivitis	1385	31.4%	900	19.5%	828	18.7%	3113	23.1%
Stage I	1203	27.3%	577	12.5%	301	6.8%	2081	15.5%
Stage II	656	14.9%	905	19.6%	635	14.3%	2196	16.3%
Stage III	400	9.1%	932	20.2%	779	17.6%	2111	15.7%
Stage IV	67	1.5%	791	17.1%	1145	25.9%	2003	14.9%
Edentulous	0	0.0%	54	1.2%	210	4.7%	264	2.0%

regions, and municipalities of mainland China. In total, data from 13,459 subjects were included in the analysis; invalid data from five subjects were excluded. The mean age of the subjects was 54 years (56.43 ± 12.40 years). The sample consisted of 6709 males (49.8%) and 6750 females (50.2%). For smoking status, 3547 (26.4%) of the subjects were current smokers, 8554 were non-smokers (63.6%), and 1358 were former smokers (10.1%). There were 6820 subjects from urban regions (50.7%) and 6639 from rural regions (49.3%).

Periodontal conditions in the subjects according to age group are shown in Table 2. The frequency of subjects with periodontitis was 52.8%, 69.3%, and 64.6% in the three age groups, respectively. The frequency of subjects with severe periodontitis (stage III or IV) was 10.6%, 37.3%, and 43.5% in the three age groups, respectively. There were 54 edentulous persons in the 55- to 64-year-old group and 210 edentulous persons in the 65- to 75-year-old group. The severity of periodontal disease was greater in the elderly, males, current smokers, and former smokers. The severity of periodontal disease was similar between urban and rural areas, but the latter had a higher frequency of edentulous persons.

The periodontal parameters measured for the subjects are summarized in Figure 1. The mean frequencies at the subject level of BOP, calculus, CAL \geq 4 mm, and PPD \geq 4 mm were 49.9%, 70.3%, 18.7%, and 15.9%, respectively, and those of CAL \geq 9 mm and PPD \geq 6 mm were 1.0% and 1.2%, respectively. Distributions of the extent of patients with stage of periodontitis were shown in Table S1. The number of missing teeth was 3.76 ± 6.20 for all subjects (Table S3).

Smoothing plots were generated to represent the relationship between periodontitis severity and age, after adjusting for gender, smoking status, region, years of education, and annual family income (Figure 2). The severity of periodontal disease was positively associated with age. The tends were similar in all age groups (Figure 2a). Current and former smokers exhibited significantly greater disease severity than non-smokers (Figure 2b). Also, males seemed to exhibit greater disease severity than females, but the difference was not significant (Figure 2c). The difference of severity of periodontal disease between persons lived in urban and rural region was not significant (Figure 2d).

The prevalence of periodontitis, severe periodontitis (stages III and IV), and edentulous subjects stratified by province is mapped in Figures 3–5. Periodontal conditions differed markedly according to geographic region.

4 | DISCUSSION

There is a lack of epidemiological data on periodontal diseases based on the 2018 classification scheme. However, Page and Eke (2007) proposed case definitions for use in population-based surveillance of periodontitis and updated them in 2015 (CDC/AAP classification) (Eke et al., 2015). The similarities of the 2018 and CDC/AAP classification schemes enable comparison of prevalence data obtained using the two schemes (Caton et al., 2018; Eke et al., 2015; Page & Eke, 2007; Tonetti et al., 2018).

Our data showed that almost 90% of Chinese adults suffered from periodontal disease of various severities; >30% had severe periodontitis (the percentage was 10.6% in 35–44 age group, 37.3% in 55–64 age group, and 43.5% in 65–74 age group, respectively). The rates are much higher than those reported by studies from some developed countries based on the CDC/AAP classification. Data from a population-based study (the Study of Health in Pomerania) showed that crude prevalence of severe periodontitis was 11.8% (7.3% in 30–39 age group, 21.2% in 40–49 age group, 31.3% in 50–59 age group, 32.8% in 60–69 age group, and 29.2% in 70–81 age group) (Holtfreter et al., 2009). Another population-based studies (the Oral Infections and Vascular Disease Epidemiology Study, subjects aged 55–81 years) in USA reported that prevalence of severe periodontitis was 32.2% (Holtfreter et al., 2012).

In a sample of US population (2011–2012 National Health and Nutrition Examination Survey), the overall prevalence of severe periodontitis was 13.2% (4.8% in 30–39 age group, 12.7% in 40–49 age group, 19.1% in 50–59 age group, 20.3% in 60–69 age group, and 9.9% in 70–80 age group) (Montero et al., 2019).

The mean number of missing tooth was 3.76 (0.72 for 35–44 age group, 3.60 for 55–64 age group, and 6.96 for 65–74 age group), which is similar to that of a sample in USA (4.0) (Eke et al., 2018) but much higher than that in a sample in German (2.9 for adults) (Holtfreter et al., 2010). The large number of missing tooth shows, to a certain extent, the severe situation of periodontal health of China (although caries or trauma is also important causes of tooth missing).

The poor periodontal condition in China may be due to poor oral hygiene (calculus presence, 70.3%) or to genetic and environmental factors. The higher frequency of calculus is likely due to lack of awareness of oral health and limited access to dental care in the past (Jiao et al., 2017; Wang et al., 2018). In the participants of the present study, the percentage of subjects who received tooth cleaning within the past year ranged from 2.2% to 7.9% for the three age groups; the percentage of subjects who had never seen a dentist in the past ranged from 30.9% to 43.1%; and the percentage of subjects who brushes their teeth \geq twice per day ranged from 30.1% to 47.8% and nearly 94.8% to 98.3% of them rarely or never used a dental floss (The fourth national oral health epidemiological survey report, 2018).

Comparing with the data 10 years ago (the 4th National Oral Health Survey in 2005), individuals' periodontal condition did not improve (Liu et al., 2016). Instead, some parameters are worse than they were 10 years ago. In 35-44 age group, prevalence of BOP and PPD ≥4 mm increased by 10.1% and 11.8%, respectively, and prevalence of calculus and CAL \geq 4 mm increased by 0.6% and 5.7%. In 65–74 age group, prevalence of calculus, BOP, PPD ≥4 and CAL ≥4 mm increased by 1.6%, 14.6%, 12.4%, and 2.9%, respectively. The poor periodontal condition and potential deterioration trend calls for an effective mechanism for oral health care, especially for periodontal health care in China. National oral health policy should emphasize periodontal health education, such as the importance of periodontal health and the harm of periodontal diseases, and periodontal health promotion, such as promoting good habits such as daily floss using and regular oral examination. To reverse the serious periodontal condition, workforce of dental service, such as dentists, periodontists and hygienists, is also in urgent need.

The severity of periodontal disease was positively associated with age for subjects aged 35–45 years to those aged 55–65 years (Table 2 and Figure 2a). This should be brought to the attention of health policy makers and clinicians because of its serious implications for oral and systemic health and the financial burden imposed on society (Holde et al., 2017). The severity of periodontitis remained stable after 65 years of age (Table 2 and Figure 2a). However, periodontal conditions at this age were very serious. Over 30% of elderly people had lost at least five teeth (excluding the third molars), and almost 5% were edentulous. China is an ageing society, and ageing affects oral function and quality of life (Yang et al., 2017). Severe periodontitis can damage the health of elderly patients, and tooth loss caused by periodontal disease affects their mastication ability and quality of life.

Smoking affects periodontal health and the outcomes of periodontal treatments (Du et al., 2018; Eke et al., 2016; Graetz et al., 2019; Leite et al., 2018; Nociti et al., 2015). In this study, periodontitis in current and former smokers was more severe than in non-smokers. However, the severity of periodontitis between males and females was not significant.

In the previous study using the same database (Sun et al., 2018), the number of teeth with CAL \geq 4 mm was significantly different between subjects lived in urban and rural areas. However, there were no significant differences in periodontal conditions between urban and rural areas in the present study. The inconsistence between the two studies was due to the varied outcomes for analysis and sample composition (only data from subjects in the 35-44 age group was used for analysis in the previous study). The social and economic gaps between urban and rural areas did not influence periodontitis severity. This was due to the time required for policy implementation, training of dentists, and improvement of public health awareness. Indeed, only 756





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35-44 yrs

55-64 yrs

65-74 yrs

FIGURE 1 Periodontal parameters at tooth level of subject with different stages of periodontitis according to the 2018 classification. (a-d) Periodontal parameters (percentages of teeth affected) at tooth level according to age and gender. (e, f) Number of missing teeth according to age and gender. (g) Number of missing teeth according to the stages. Means and 95% confidential intervals were shown the figures. *Including missing teeth for non-periodontal reasons



FIGURE 2 Smoothing plots of the relationships between severity of periodontitis and age analysed using generalized additive models with adjustment for gender, smoking status, region, years of education, and annual family income. (a) The relationship between periodontitis severity and age. (b) Periodontitis severity differed significantly between non-smokers and current/former smokers. (c) No significant difference of periodontitis severity was detected between males and females. (d) No significant difference of periodontitis severity was detected between persons residing in urban and rural regions

in 2004; moreover, some of them performed only supragingival scaling. Also, the mean annual number of dental visits by citizens in Beijing was 0.34 at the beginning of the twenty-first century (Meng, 2008). The number of dentists engaged in periodontal prevention and treatment has increased; however, improvement of public periodontal health lags behind economic development and the implementation of preventive policies. According to the

and edentulous jaws in the administrative regions, the severity of periodontitis was not associated with economic development (the correlation coefficient between severity of periodontal status and annual family income was -0.14, p = .143). Instead, the prevalence of periodontitis may be related to genetic, environmental, and social factors (Buchwald et al., 2013; Kassebaum et al., 2014a, 2014b; Norderyd et al., 1999; Tonetti et al., 2017).

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FIGURE 3 Frequency of persons diagnosed with periodontitis (according to the 2018 new classification) in mainland China

China is a developing country whose population accounts for onefifth of the global population. However, over 10 years have passed since the last national epidemiological survey was conducted, and reliable data on periodontal conditions are lacking (Sun et al., 2018). In addition, the oral diseases suffered by the Chinese population are expected to change over time due to the ageing of the population as well as economic development and lifestyle changes. The Fourth National Oral Health Survey, performed in 2015–2016 in mainland China, provided valuable information for policymakers, clinicians (Lu et al., 2018), and the general population. Also, converting clinical



FIGURE 4 Frequency of persons diagnosed with severe periodontitis (according to the 2018 new classification, stage III or IV) in mainland China

examination parameters such as BOP, calculus presence, PPD, and CAL to severity of the disease would enhance our understanding of periodontal status in mainland China.

This study has several limitations. First, only the most severe site of periodontitis was recorded during the examination although all sites were examined carefully. This may result in an overestimation



FIGURE 5 Frequency of edentulous persons in mainland China

of the frequency of bleeding and the misclassification of good periodontal health as gingivitis. In addition, CAL at the most severe site, instead of the inter-dental CAL at the severe inter-dental site and in most cases they are at the same site, was used to evaluate the periodontal condition. This may overestimate the severity of periodontitis. Second, furcation involvement, tooth mobility, and malocclusion were not evaluated, and the complexity of disease management could not be calculated. This may have resulted in an underestimation of the frequency of stages III and IV periodontitis. Third, the reason of tooth missing was not available for analysis. Therefore, prevalence of stage

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IV periodontitis was possibly overrated due to tooth missing in other reasons. Therefore, the corresponding explanation was also added in the discussion to report one of the limitations of the present study. Fourth, periodontal status may be influenced by a great number of factors. Only some main risk factors widely reported were taken into consideration in the present study. Following study is needed to analyse the effect of potential influential factors of severity of periodontitis. Fifth, the evaluation of periodontitis grade provides information on the biological features of the disease, including the rate of progression, risk of further progression, treatment outcomes, and the risk of the disease or its treatment affecting general health. However, it was not possible to evaluate periodontitis grade in this study due to the lack of longitudinal or radiographic data. Epidemiological and clinical data need to be converted to facilitate comparison among studies of different designs.

5 | CONCLUSION

Within the limitations of the present study, the prevalence of periodontitis and severe periodontitis was very high among adults in mainland China. Periodontal status is associated with age and smoking status.

CONFLICT OF INTEREST

The authors declared that they had no conflict of interests.

DATA AVAILABILITY

The raw data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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