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Association Between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey in China (2015-2016)

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Association Between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey in China (2015-2016)

Running title: Association between periodontitis and hypertension

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ABSTRACT

Objectives To evaluate the association between periodontitis severity and hypertension based on Chinese epidemiological data.

Design This cross-sectional survey enrolled adults from the Fourth National Oral Health Survey of China (2015-2016).

Setting The study data were obtained from the Fourth National Oral Health Survey of China (2015-2016).

Participants The study included dentate individuals aged 35-44 years (n = 4,409), 55-64 years (n = 4,568), and 65-74 years (n = 4,218).

Primary and secondary outcome measures Periodontal status, defined on the basis of the 2018 classification scheme, and periodontal parameters (e.g., bleeding on probing [BOP], probing depth [PD], and attachment loss [AL]) were compared between hypertensive and normotensive individuals. Smoothed scatterplots were constructed to demonstrate the associations of periodontal parameters and periodontal status with hypertension.

Results Severe periodontitis (stages III and IV) was present in 41.34% and 27.99% of hypertensive and normotensive individuals, respectively ($p < 0.001$). The prevalence of severe periodontitis was higher in hypertensive individuals than that in normotensive individuals among participants aged 35-44 years (18.12% and 10.09%, $p < 0.001$) and 55-64 years (40.12% and 36.77%, $p = 0.035$), but not in participants aged 65-74 years (46.40% and 45.14%, $p = 0.429$). Therefore, the difference in periodontal status between hypertensive and normotensive individulas decreased with age. There were higher prevalences of BOP, PD ≥ 4 mm, and PD ≥ 6 mm in hypertensive individuals than in normotensive individuals (57.71% vs 53.12%, 22.11% vs 16.29%, and 2.07% vs 1.22%, respectively). Periodontitis severity and the proportion of teeth with PD ≥ 4 or ≥ 6 mm were positively associated with hypertension.

Conclusion Based on the data of the Fourth National Oral Health Survey of China, hypertensive individuals were more likely than normotensive individuals to have periodontitis. Periodontal severity is associated with hypertension.

Key Words: Hypertension, oral medicine, epidemiology, public health.

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Strengths and limitations of this study

The study included data from a large-scale national survey in which participants were representative of the Chinese population. The periodontitis classification proposed at the 2017 World Workshop was used to determine the association between periodontitis and hypertension. Hypertension was self-reported and blood pressure was not measured.

INTRODUCTION

Hypertension, which affects 45% of the global population, is the most common cardiovascular disease (CVDs) worldwide [1,2]. It is defined as systolic or diastolic blood pressure (BP) of ≥140 or ≥90 mmHg, respectively. Hypertension is frequently poorly controlled and untreated [3]. It ia a complex disease with multiple causes and a major risk factor for CVDs [4]. Oxidative stress, endothelial dysfunction, and inflammation are associated with the development of hypertension [5]. The results of experimental and clinical studies suggest that inflammation has a major role in the development of hypertension [6]. Chronic inflammation predisposes to the development of pro-hypertensive inflammation.

Periodontal disease, an immune-inflammatory reaction to plaque biofilms [7], has received substantial attention because of its association with CVDs. The Global Burden of Disease Study revealed that periodontitis was the sixth most prevalent disease worldwide. Periodontitis affects 743 million people worldwide (11.2% of the global population); the prevalence is higher in China than in other countries. The Fourth National Oral Health Survey of China showed that 90.9% individuals aged 35-44 years

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had periodontal disease [8, 9]. The low-grade inflammation associated with periodontitis has harmful effects on the endothelial function, which may result in hypertension [10]. A recent study revealed that individuals with periodontitis have increased risks of hypertension and antihypertensive treatment failure [11,12]. Previous studies have suggested that dental treatment can improve blood pressure, although the findings have been inconclusive and further studies are needed [13-16].

Periodontitis and hypertension are major health problems, and their association received considerable public health attention. Therefore, we evaluated the relationship between periodontitis and hypertension based on the data from the Fourth National Oral Health Survey of China. We sought to determine whether individuals with periodontitis are more likely to have hypertension compared with individuals who do not have periodontitis; we also sought to determine whether periodontitis severity is associated with hypertension.

MATERIALS AND METHODS

Study design and sample

This cross-sectional study obtained data from adult participants of the Fourth National Oral Health Survey of China (2015-2016) [8]. The planned sample size was 4,230 each for the age groups 35-44, 55-64 and 65-74 years. We excluded data from edentulous participants and from participants without complete information. Finally, 13,195 individuals were included (4,409, 4,568, and 4,218 individuals aged 35-44, 55-64, and 65-74 years, respectively).

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Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

Data collection

We collected data related to oral examination findings and questionnaire answers.

1. *Periodontal examination*

Periodontal examinations were performed using a community periodontal index probe. A full-mouth examination was performed, during which the probe was walked along the gingival crevices using a force of ≤ 20 g to assess bleeding on probing (BOP), the presence of calculus, probing depth (PD), and attachment loss (AL). For each parameter, each tooth was scored according to the condition of the most severely affected site. Training programs were conducted for examiner calibration before the survey. The reliability of the results was assessed using kappa values; kappa values for periodontal pocket depth were ≥ 0.6. Additionally, 5% of the participants were randomly selected for assessment of inter-examiner reproducibility. The kappa values for all age-groups were 0.76-0.80.

Patient and public involvement

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The study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Study parameters

Supragingival and subgingival calculus were identified by visual examination and probing, respectively (0 = absent, 1 = present, 9 = tooth excluded, and X = tooth not present). PD was recorded as 0 (1–3 mm), 1 (4–5 mm), 2 (≥6 mm), 9 (tooth excluded), or X (tooth not present). BOP was recorded as 0 (absent), 1 (present), 9 (tooth excluded), or X (tooth not present). AL was measured as the distance from the cementoenamel junction to the bottom of the periodontal pocket; it was recorded as 0 (0–3 mm), 1 (4–5 mm), 2 (6–8 mm), 3 (9–11 mm), 4 (≥12 mm), 9 (tooth excluded), or X (tooth not present).

The classification scheme proposed at the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions was used to classify the periodontal status as periodontally healthy (< 10% BOP-positive sites and PD ≤ 3 mm) or gingivitis (≥ 10% BOP-positive sites and PD ≤ 3 mm). Periodontitis was staged using the algorithm developed by Graetz *et al* [17]. For each tooth, stages I-III periodontitis were defined as AL of 1–2 mm, 3–4 mm, and ≥ 5 mm, respectively. We also considered the number of teeth lost when classifying periodontitis: stages I and II, no tooth loss; stage III, ≤ 4 teeth lost; and stage IV, ≥ 5 teeth lost. The cause of tooth loss was not considered. Finally, we evaluated the complexity of patient management. Stage II patients were reclassified as stage III if the maximum PD was ≥ 6 mm. Stage

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III patients were reclassified as stage IV if there were < 10 opposing pairs of teeth).

2. *Interview data from the questionnaire*

Questionaires were administered during in-person interviews to collect data regarding demographics, socioeconomic status, habits, dental history, and health attitudes. The following information was collected for analysis: age (years), annual family income (in increments of 10,000 yuan), sex (male or female), duration of education (years), self-reported hypertension (yes or no), smoking status (current smoker, former smoker, or non-smoker), and region (urban or rural).

Statistical analyses

Statistical analyses were performed using SPSS (version 19; IBM Corp., Armonk, NY, USA) or R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The primary outcome was periodontal status (healthy, gingivitis, and stages I-IV periodontitis). The secondary outcomes were the proportions of BOP-positive teeth, teeth with PD ≥ 4 and ≥ 6 mm, teeth with AL ≥ 4, ≥ 6, and ≥ 9 mm; and missing teeth. First, descriptive analysis was performed. Quantitative data were reported as means and standard deviations; categorical data were reported as numbers and percentages. Periodontal parameters were compared between hypertensive and normotensive individuals; subgroup analyses were conducted according to age group and smoking status. Periodontal status and parameters were analysed using the chi-square test. Additionally, smoothed scatterplots based on generalised additive models

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were constructed, with adjustment for confounders (sex, smoking status, region, duration of education, and annual family income), to evaluate the relationships of hypertension prevalence with periodontal status or parameters. The level of statistical significance was set at $p < 0.05$.

RESULTS

The participants were randomly selected from 31 provinces, autonomous regions, and municipalities in mainland China. In total, data from 13,195 individuals were included in the analysis; invalid data from five participants and data from 264 edentulous patients were excluded. The mean individual age was 56.43 ± 12.40 years. The sample consisted of 6,575 men (49.83%) and 6,620 women (50.17%). There were 3,470 non-smokers (26.30%), 8,405 current smokers (63.71%), and 1,318 former smokers (9.99%). Hypertension was present and absent in 3,154 (23.90%) and 10,041 (76.10%) participants, respectively.

Differences in periodontal status between hypertensive and normotensive participants decreased with age

Table 1 and S1 present the distributions of periodontal status according to age in participants with and without hypertension.

Significantly greater proportions of hypertensive participants had stages I-IV periodontitis (70.23% vs. 61.51%, p < 0.001) and severe periodontitis (stages III-IV, 41.34% vs. 27.99%, p < 0.001), compared with normotensive participants. Stratified

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analysis according to age showed that the prevalence of periodontitis (stage I-IV) was significantly greater in hypertensive participants than in normotensive participants among individuals aged 35-44 years (52.33% vs. 59.06%, p = 0.030), 55-64 years (72.61% vs. 69.19%, p = 0.023), and 65-74 years (70.23% vs. 66.35%, p = 0.009). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants among individuals aged 35-44 years (18.12% vs. 10.09%, p < 0.001) and 55-64 years (40.12% vs. 36.77%, p = 0.035), but not among individuals aged 65-74 years (46.40% vs. 45.14%, p = 0.429). Therefore, differences in periodontal status between hypertensive and normotensive participants decreased with age (Table 1).

Table 1. Comparison of distribution of periodontal status according to the 2018 classification by age groups between hypertensive and normotensive subjects.

		NT			HT		
		N	%	95% CI	N	%	95% CI
35-45 years	Health	658	15.9	14.8~17.1	40	14.5	10.7~19.0
	Gingivitis	1312	31.7	30.3~33.2	73	26.4	21.5~31.9
	Stage I	1134	27.4	26.1~28.8	69	25.0	20.2~30.4
	Stage II	612	14.8	13.7~15.9	44	15.9	12.0~20.6
	Stage III	360	8.7	7.9~9.6	40	14.5	10.7~19.0
	Stage IV	57	1.4	1.1~1.8	10	3.6	1.9~6.3
55-65 years	Health	347	10.6	9.6~11.7	116	9.0	7.5~10.6
	Gingivitis	661	20.2	18.9~21.6	239	18.4	16.4~20.6
	Stage I	403	12.3	11.2~13.5	174	13.4	11.7~15.4
	Stage II	658	20.1	18.8~21.5	247	19.1	17.0~21.3
	Stage III	659	20.1	18.8~21.5	273	21.1	18.9~23.3
	Stage IV	544	16.6	15.4~17.9	247	19.1	17.0~21.3
65-75 years	Health	348	13.2	12.0~14.5	182	11.5	10.0~13.1

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	Gingivitis	539	20.4	18.9~22.0	289	18.3	16.4~20.2
	Stage I	175	6.6	5.7~7.6	126	8.0	6.7~9.4
	Stage II	384	14.6	13.3~16.0	251	15.9	14.1~17.7
	Stage III	475	18.0	16.6~19.5	304	19.2	17.3~21.2
	Stage IV	715	27.1	25.5~28.8	430	27.2	25.0~29.4
Total	Health	1353	13.5	12.8~14.2	338	10.7	9.7~11.8
	Gingivitis	2512	25.0	24.2~25.9	601	19.1	17.7~20.5
	Stage I	1712	17.1	16.3~17.8	369	11.7	10.6~12.9
	Stage II	1654	16.5	15.8~17.2	542	17.2	15.9~18.5
	Stage III	1494	14.9	14.2~15.6	617	19.6	18.2~21.0
	Stage IV	1316	13.1	12.5~13.8	687	21.8	20.4~23.2

HT = Hypertension; NT = Normotension.

Table S1 showed the distribution of periodontal status stratified according to smoking status. Periodontitis (stage I-IV) was more common in hypertensive participants than in normotensive participants among current smokers (76.16% vs. 68.15%, $p < 0.001$) and non-smokers (67.25% vs. 57.41%, $p < 0.001$), but not among former smokers (73.59% vs. 70.58%, $p = 0.270$). Severe periodontitis (stage III and stage IV) was significantly more common in hypertensive participants than in normotensive participants among non-somkers (48.45% vs. 34.67%, $p < 0.001$), current smokers (36.82% vs. 23.75%, $p < 0.001$), and former smokers (50.26% vs 37.93%, $p < 0.001$).

Periodontal status was significantly worse in hypertensive participants than in normotensive participants

Tables 2 and 3 present comparisons of periodontal parameters between hypertensive and normotensive participants. Compared with normotensive participants, hypertensive participants had significantly greater proportions of teeth with BOP (57.71% vs. 53.12%), PD ≥ 4 mm (22.11% vs. 16.29%), PD ≥ 6 mm (2.07% vs. 1.22%), AL ≥

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4 mm (28.86% vs. 20.56%), AL ≥ 6 mm (8.44% vs. 5.54%), and AL ≥ 9 mm (1.72% vs. 1.18%). Differences in periodontal parameters between hypertensive and normotensive participants decreased with age. The differences in periodontal parameters between hypertensive and normotensive participants were similar among current smokers, former smokers, and non-smokers. Difference in the mean prevalence of periodontal pocket (PD ≥ 4 mm) were consistent in the stratified analysis.

Compared with normotensive participants, hypertensive participants had significantly greater proportions of teeth with PD ≥ 4 mm (4.45 vs. 3.46), PD ≥ 6 mm (0.37 vs. 0.22), AL ≥ 4 mm (1.18 vs. 0.81), and AL ≥ 6 mm (0.2 vs. 0.12). The mean number of BOP-positive teeth did not significant differ between hypertensive and normotensive participants (12.43 vs. 12.33). The mean number of teeth showed a distribution pattern similar to the distribution patterns of various periodontal parameters. The difference in the mean number of teeth between hypertensive and normotensive participants decreased with age. Furthermore, differences in the prevalences of teeth with PD ≥ 4 mm and deep PD sites were consistent in the stratified analysis.

Table 2. Comparison of percentage of teeth affected by age groups and smoking status.

		NT		HT		
	PTA	Mean	95% CI	Mean	95% CI	p*
35-45 years	BOP+	46.5	45.41~47.55.	50.32	45.92~54.72	0.096
	PD≥ 4mm	10.5	9.90~11.05	15.83	12.86~18.80	0.001
	PD≥ 6mm	0.5	0.40~0.59	1.09	0.56~1.63	0.031
	AL≥ 4mm	6	5.55~6.41	10.14	7.85~12.43	0.001
	AL≥ 6mm	0.8	0.69~0.95	1.62	0.82~2.42	0.052
55-65 years	BOP+	52.5	51.30~53.72	54.03	52.11~55.96	0.188
	PD≥ 4mm	17.9	17.11~18.76	20.3	18.92~21.68	0.004

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	PD≥ 6mm	1.4	1.21~1.65	1.9	1.55~2.24	0.024
	AL≥ 4mm	22.1	21.16~22.95	21.53	20.15~22.92	0.543
	AL≥ 6mm	5.3	4.90~5.78	5.49	4.79~6.18	0.722
65-75 years	BOP+	49.3	47.91~50.59	50.84	49.09~52.58	0.157
	PD≥ 4mm	17.4	16.45~18.28	19.6	18.39~20.81	0.004
	PD≥ 6mm	1.5	1.29~1.81	1.84	1.49~2.19	0.185
	AL≥ 4mm	28.7	27.59~29.78	27.62	26.25~28.99	0.240
	AL≥ 6mm	8.9	8.28~9.61	8.29	7.47~9.11	0.226
Current smoker	BOP+	49.6	46.77~52.42	49.89	45.99~53.79	0.311
	PD≥ 4mm	21.4	19.36~23.52	22.94	20.16~25.72	0.000
	PD≥ 6mm	2.2	1.53~2.80	2.09	1.34~2.84	0.006
	AL≥ 4mm	36.3	33.86~38.78	33.54	30.24~36.84	0.000
	AL≥ 6mm	13.1	11.38~14.75	11.38	9.26~13.50	0.001
Non-smoker	BOP+	48.9	47.22~50.57	51.56	49.42~53.69	0.000
	PD≥ 4mm	15.4	14.30~16.47	17.91	16.49~19.33	0.000
	PD≥ 6mm	1.1	0.89~1.40	1.66	1.27~2.05	0.000
	AL≥ 4mm	25.1	23.79~26.41	24.67	23.10~26.23	0.000
	AL≥ 6mm	7.2	6.44~7.92	6.60	5.71~7.50	0.000
Former smoker	BOP+	50.2	46.54~53.82	48.84	44.03~53.65	0.603
	PD≥ 4mm	18.7	16.23~21.21	22.62	18.90~26.34	0.000
	PD≥ 6mm	2.2	1.32~3.13	2.31	1.07~3.56	0.126
	AL≥ 4mm	30.7	27.81~33.60	32.77	28.63~36.92	0.001
	AL≥ 6mm	9.3	7.63~10.97	11.66	9.01~14.30	0.002
Total	BOP+	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	PD≥ 4mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	PD≥ 6mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	AL≥ 4mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	AL≥ 6mm	0.0	0.00~0.00	0.00	0.00~0.00	0.001

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; PD = probing depth; PTA = Percentage of teeth affected;

* significant difference by Student's t test.

Table 3. Number of percentage of teeth affected by age groups and smoking status.

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			NT		HT	
	NTA	Mean	95% CI	Mean	95% CI	p*
35-45 years	BOP+	12.69	12.40~12.99	13.61	12.42~14.80	0.143
	PD≥ 4mm	2.83	2.68~2.99	4.19	3.40~4.98	0.001
	PD≥ 6mm	0.13	0.10~0.15	0.27	0.14~0.40	0.036
	AL≥ 4mm	1.58	1.47~1.70	2.58	2.00~3.16	0.001
	AL≥ 6mm	0.20	0.17~0.24	0.38	0.21~0.55	0.049
55-65 years	BOP+	13.01	12.69~13.33	13.37	12.86~13.88	0.241
	PD≥ 4mm	4.21	4.02~4.40	4.76	4.43~5.08	0.005
	PD≥ 6mm	0.28	0.24~0.32	0.41	0.34~0.49	0.003
	AL≥ 4mm	5.03	4.82~5.23	4.80	4.49~5.11	0.222
	AL≥ 6mm	1.07	0.99~1.15	1.08	0.95~1.21	0.914
65-75 years	BOP+	10.92	10.59~11.26	11.47	11.03~11.91	0.051
	PD≥ 4mm	3.52	3.33~3.72	4.25	3.98~4.52	0.000
	PD≥ 6mm	0.27	0.23~0.31	0.36	0.29~0.42	0.042
	AL≥ 4mm	5.65	5.43~5.88	5.60	5.31~5.88	0.752
	AL≥ 6mm	1.46	1.36~1.56	1.40	1.27~1.53	0.508
Current smoker	BOP+	12.30	11.93~12.67	12.09	0.33~0.42	0.583
	PD≥ 4mm	4.59	4.36~4.82	5.49	594.42~0.00	0.001
	PD≥ 6mm	0.31	0.27~0.35	0.50	61.18~0.00	0.001
	AL≥ 4mm	4.86	4.62~5.09	6.13	658.63~0.00	0.000
	AL≥ 6mm	1.19	1.09~1.29	1.59	179.14~0.00	0.001
Non-smoker	BOP+	12.29	12.06~12.51	12.62	12.22~13.02	0.159
	PD≥ 4mm	2.89	2.78~3.01	3.91	3.68~4.15	0.000
	PD≥ 6mm	0.16	0.14~0.18	0.29	0.24~0.34	0.000
	AL≥ 4mm	3.10	2.98~3.22	4.38	4.15~4.61	0.000
	AL≥ 6mm	0.60	0.56~0.64	0.92	0.83~1.01	0.000
Former smoker	BOP+	12.72	12.13~13.32	12.21	11.28~13.14	0.359
	PD≥ 4mm	4.12	3.76~4.48	5.14	4.50~5.78	0.006
	PD≥ 6mm	0.36	0.27~0.44	0.53	0.37~0.69	0.069
	AL≥ 4mm	5.29	4.90~5.68	5.94	5.32~6.55	0.081
	AL≥ 6mm	1.18	1.02~1.33	1.66	1.36~1.96	0.005
Total	BOP+	12.33	12.15~12.51	12.44	12.42~14.80	0.574
	PD≥ 4mm	3.46	3.36~3.57	4.45	3.40~4.98	0.000
	PD≥ 6mm	0.22	0.20~0.24	0.37	0.14~0.40	0.000
	AL≥ 4mm	3.77	3.67~3.88	5.00	2.00~3.16	0.000

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	AL≥ 6mm	0.81	0.77~0.85	1.18	0.21~0.55	0.000

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; NTA = Number of teeth affected; PD = probing depth;

* significant difference by Student's t test.

Hypertension prevalence increased with periodontitis severity

Multivariate regression analysis was performed to evaluate the relationship between hypertension and age stratified according to periodontal status, after adjustments for sex, smoking status, region, duration of education, and annual family income (Table 4). Compared with participants who did not have periodontitis, participants with stages III and IV periodontitis had a significant greater risk of hypertension (odds ratio [OR] = 1.698, 95% confidence interval [CI] = 1.45-1.99, $p < 0.000$). However, the difference between participants with stages I and II periodontitis and participants without periodontitis was not statistically significant (OR = 1.028, 95% CI = 0.88-1.20, $p = 0.717$). Therefore, hypertension prevalence increased with periodontitis severity. Notably, the OR for participants with stages III and IV periodontitis decreased with age; it was not statistically significant in participants aged 65-74 years (Table 4).

Table 4. Relationships between hypertension and periodontal status (compared with non-periodontitis) according to the 2018 classification analyzed by logistic regressions with adjustment for gender, smoking status, region, years of education, and annual family income

Age group	Periodontal stauts	OR	95% CI	p

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35-45 years	Periodontitis (stage III & IV)#	1.617	1.00~2.61	0.050
	Periodontitis (stage I & II)#	0.966	0.65~1.43	0.863
55-65 years	Periodontitis (stage III & IV)#	1.402	1.07~1.84	0.015
	Periodontitis (stage I & II)#	1.301	1.00~1.69	0.051
65-75 years	Periodontitis (stage III & IV)#	1.205	0.96~1.42	0.113
	Periodontitis (stage I & II)#	1.121	0.96~1.42	0.336
Total	Periodontitis (stage III & IV)#	1.698	1.45~1.99	0.000
	Periodontitis (stage I & II)#	1.028	0.88~1.20	0.717

Relationships of hypertension with periodontal parameters

Table 5 and Table 6 present the multivariate regression analyses of the relationships of hypertension with periodontal parameters, after adjustments for sex, smoking status, region, duration of education, and annual family income. Hypertension prevalence increased with increases in the proportions of teeth with BOP (OR = 1.204, 95% CI = 1.05-1.38 , p = 0.006), PD ≥ 4 mm (OR = 1.733, 95% CI = 1.43-2.10, p < 0.001), and PD ≥ 6 mm (OR = 2.443, 95% CI = 1.19-5.03, p = 0.015), but it decreased with increases in the proportions of teeth with AL ≥ 4 mm (OR = 0.874, 95% CI = 0.73-1.05, p = 0.155) and AL ≥ 6 mm (OR = 0.743, 95% CI = 0.53-1.04, p = 0.083). There were significant positive associations of hypertension with the number of teeth with BOP (OR = 1.008, 95% CI = 1.00-1.01, p = 0.001), PD ≥ 4 mm (OR = 1.029, 95% CI = 1.02-1.04, p = 0.000), and PD ≥ 6mm (OR = 1.071, 95% CI = 1.03-1.11, p < 0.001). There were statistically insignificant negative associations of the presence of hypertension with the proportions of teeth with AL ≥ 4 mm and AL ≥ 6 mm (Table

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6).

Table 5. Relationships between probability of hypertension and percentage of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

PTA	OR	95% CI	p
BOP+	1.204	1.05~1.38	0.006
PD≥ 4mm	1.733	1.43~2.10	0.000
PD≥ 6mm	2.443	1.19~5.03	0.015
AL≥ 4mm	0.874	0.73~1.05	0.155
AL≥ 6mm	0.743	0.53~1.04	0.083

AL= attachment loss; BOP = bleeding on probing; PD = probing depth; PTA = percentage of teeth affected.

Table 6. Relationships between probability of hypertension and percentage of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

NTA	OR	95% CI	p
BOP+	1.008	1.00~1.01	0.001
PD≥ 4mm	1.029	1.02~1.04	0.000
PD≥ 6mm	1.071	1.03~1.11	0.000
AL≥ 4mm	0.997	0.99~1.01	0.507
AL≥ 6mm	0.987	0.97~1.01	0.217

AL= attachment loss; BOP = bleeding on probing; NTA = number of teeth affected; PD = probing depth.

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Significantly more teeth were missing in hypertensive participants than in normotensive participants

Table S1 presents a comparison of the number of missing teeth between participants with and without hypertension. Significantly more teeth were missing in hypertensive participants than in normotensive participants (4.36 vs. 2.94 teeth). The difference in the number of missing teeth between hypertensive and normotensive participants decreased with age. Analysis of the relationship according to smoking status showed that hypertension prevalence increased and then decreased with increases in the number of missing teeth.

DISCUSSION

Based on data from the Fourth National Oral Health Survey of China, periodontitis is significantly and strongly associated with hypertension among Chinese adults, independent of the effects of age, sex, and smoking. This association between periodontitis and hypertension has considerable importance [18].

In this study, we used data from a large-scale national survey in which participants were representative of the Chinese population. Periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop. The association of hypertension with periodontitis was assessed according to age and smoking status to minimize errors and the effects of confounding factors. Periodontitis was associated with a higher prevalence of hypertension among Chinese adults, independent of known confounders.

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Hypertension prevalence increased with periodontitis severity, particularly among young participants (35-44 years). Therefore, participants with risk factors, particularly young adults, should engage in healthy lifestyle habits to improve their oral health. Accordingly, there is a need to improve the education and awareness of dental treatment and preventive management among individuals at risk for hypertension, particularly in younger population. Periodontitis and hypertension are chronic diseases; therefore, substantial exposure time may be necessary for their development. The exposure time to risk factors may be considerably shorter in younger individuals than that in older individuals. The influence of the longer exposure time to the common risk factors for periodontitis and hypertension in older individuals may mask the effects of periodontitis on the development of hypertension. When the confounding effects of the risk factors were removed, a link between periodontitis and hypertension was identified. Therefore, severe periodontitis may have a greater role in the development of hypertension among younger individuals than among older individuals. The association of periodontitis with hypertension was also present in never smokers and former smokers, who had less exposure to common risk factors. The greater susceptibility to hypertension among young individuals with severe periodontitis may be attributed to periodontal inflammation.

This study evaluated the association between periodontal status and hypertension risk among young and older adults. Hypertension prevalence increased with periodontitis severity, which was most prominent in individuals aged 35-44 years. Adult aged < 65 years with hypertension had significantly greater risks of stages III and IV periodontitis,

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compared with individuals who did not have hypertension. Therefore, healthcare providers should carefully monitor oral health status in their patients to prevent hypertension, particularly among adults; they should conduct regular oral examinations and engage in periodontal disease management.

The association between periodontitis and hypertension was also present in participants who had a greater proportion of teeth with BOP or deep periodontal pockets. The findings suggest that severe periodontal inflammation, as evidenced by the depth of the inflamed periodontal pocket and the number of bleeding sites, is associated with hypertension. In particular, the presence of BOP indicates acute inflammation, which may lead to systemic effects and subsequent hypertension. The association of chronic inflammation (i.e., PD) with hypertension suggests that persistent, long-term inflammation may also underlie this relationship. Our study adds to the existing literature concerning oral health parameters associated with systemic outcomes [19, 20]. BOP and PD are the most appropriate clinical measures when the outcome of interest is an acute disease, whereas AL is more strongly correlated with chronic systemic conditions [19]. Our findings of an association between hypertension and the severity of periodontal inflammation (BOP and PD) are consistent with the results of previous studies [12, 21]. Although the causality of the observed association remains unclear, several hypotheses have been proposed, including endothelial dysfunction, oxidative stress, worsening of systemic inflammation in response to bacteraemia, and dissemination of inflammatory mediators from periodontal pockets, particularly BOP [22]. This association is further supported by the results of a randomised clinical trial that showed short-term

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benefits of periodontal therapy on hypertension [23]. Additionally, a recent study identified oral pathogens associated with high or uncontrolled BP, which supports our findings [24].

Our finding of an association between the number of missing teeth and hypertension is consistent with the results reported by Taguchi et al [25]. Missing teeth are indicative of poor oral health; they presumably were lost because of caries and periodontal disease. Thus, the absence of several teeth suggests the presence of severe periodontal disease, caries, or other oral health problems; these may have contributed to the increased risk of hypertension. This association was strongest in younger adults. There were no residual confounding effects of age that may have affected our study results. Because of the high prevalence of hypertension in Chinese adults, further studies are needed to clarify the association between periodontitis and hypertension. Moreover, attention is needed concerning the prevention and treatment of periodontitis in the general population.

There is minimal knowledge concerning the natural history of the association between periodontal disease and hypertension [26-30]. A significant linear trend was observed between the severity of periodontal disease and hypertension in a cross-sectional study of 3,352 patients with periodontal disease and 902 controls [28]. A recent prospective cohort study of Japanese individuals demonstrated an increased incidence of hypertension among participants with periodontal pockets ≥ 4 mm at baseline [29]. Our findings are consistent with the results in a similar study of 6,617 men and 7,377 women who underwent dental examinations as part of the NHANES III in the USA [31]. In the

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present study, after multivariate adjustment, gingival bleeding (BOP) was associated with an increased risk of hypertension, whereas periodontitis severity (defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions) and PD were positively associated with hypertension. Participants with severe periodontal disease (stages III and IV periodontitis) had a greater risk of hypertension compared with participants who had mild or no periodontal disease. Furthermore, there was a threshold relationship between severe periodontal disease and hypertension.

To our knowledge, the present study is one of few concerning the association between periodontal disease and hypertension in a large sample of Chinese adults, after adjustments for potential confounders. We evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.

The main limitation of the present study was that hypertension was self-report and not based on blood pressure measurements, which is inherent to any epidemiological cohort study. However, field measurements of blood pressure are regarded as validated tools, have been used in previous studies [19, 22], and are considered useful for the analysis of large samples. Furthermore, although recall and reporting bias could not be excluded, the results largely reflect real-world clinical practice. First, the self-reported diagnosis

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was based on a face-to-face interview to ensure the validity and accuracy of the information. Second, the reliability of the study results is supported by data from the China Hypertension Survey (2012-2015) [32], which showed an overall hypertension prevalence of 23.2% in the Chinese adult population; this prevalence is similar to the prevalence observed in our study (23.9%).

In summary, our epidemiological analysis revealed an association between periodontitis and hypertension. We collected high-quality, large-scale clinical data related to periodontal disease and hypertension. We also collected detailed information regarding potential confounders, including variables that reflect health behavior (e.g., flossing). However, there was no strong evidence of a causal relationship. Future studies should be conducted to improve the understanding of the underlying mechanisms and interactions between periodontitis and hypertension, which will further strengthen collaborations between the dental and medical communities. Preventive measures for periodontal disease in oral health promotion programs should be emphasised to improve systemic health outcomes.

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Contributorship statement

YZ is the major contributor in writing the manuscript and participates in data analysis and collation. JJ participates in data analysis and collation. WJ participates in writing the manuscript. XF, BT, DH, HL, BW, CW, SZ, XL, WR, WW, XW, and YS conceive the study design and draft the protocol. HM conceives the study design, drafts the protocol, and revise the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interests.

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Data sharing statement

Dataset available from the Fourth National Oral Health Survey of China (2015-2016).

Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

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Table s1. Number of missing teeth by age groups and smoking status

	NT		HT		
	Mean	95% CI	Mean	95% CI	p*
35-44	0.70	0.65~0.75	1.01	0.74~1.28	0.024
55-64	3.26	3.10~3.43	3.42	3.15~3.69	0.305
65-74	6.04	5.79~6.30	5.70	5.39~6.01	0.104
Non-smoker	3.30	3.10~3.50	4.27	3.87~4.67	0.000
Current smoker	2.70	2.58~2.81	3.42	3.95~4.44	0.000
Former smoker	3.55	3.21~3.89	5.70	4.68~5.98	0.000
Total	2.94	2.84~3.04	4.35	4.15~4.55	0.000

HT = Hypertension; NT = Normotension;

* significant difference by Student's t test.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	10-13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Secondary Subject Heading:	Infectious diseases, Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, ORAL MEDICINE, Epidemiology < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES

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Association Between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey in China (2015-2016)

Running title: Association between periodontitis and hypertension

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ABSTRACT

Objectives To evaluate the association between periodontitis severity and hypertension based on Chinese epidemiological data.

Design This cross-sectional survey enrolled adults from the Fourth National Oral Health Survey of China (2015-2016).

Setting The study data were obtained from the Fourth National Oral Health Survey of China (2015-2016).

Participants The study included dentate individuals aged 35-44 years (n = 4,409), 55-64 years (n = 4,568), and 65-74 years (n = 4,218).

Primary and secondary outcome measures Periodontal status, defined on the basis of the 2018 classification scheme, and periodontal parameters (e.g., bleeding on probing [BOP], probing depth [PD], and attachment loss [AL]) were compared between hypertensive and normotensive individuals. Smoothed scatterplots were constructed to demonstrate the associations of periodontal parameters and periodontal status with hypertension.

Results Severe periodontitis (stages III and IV) was present in 41.34% and 27.99% of hypertensive and normotensive individuals, respectively ($p < 0.001$). The prevalence of severe periodontitis was increase in hypertensive individuals than that in normotensive individuals among participants aged 35-44 years (18.12% and 10.09%, $p < 0.001$) and 55-64 years (40.12% and 36.77%, $p = 0.035$), but not in participants aged 65-74 years (46.40% and 45.14%, $p = 0.429$). Therefore, the difference in periodontal status between hypertensive and normotensive individulas decreased with age. There were increased prevalences of BOP, PD ≥ 4 mm, and PD ≥ 6 mm in hypertensive individuals than in normotensive individuals (57.71% vs 53.12%, 22.11% vs 16.29%, and 2.07% vs 1.22%, respectively). Periodontitis severity and the proportion of teeth with PD ≥ 4 or ≥ 6 mm were positively associated with hypertension.

Conclusion Based on the data of the Fourth National Oral Health Survey of China, periodontitis is significantly and strongly associated with hypertension among Chinese adults, independent of the effects of age, sex, and smoking.

Key Words: Hypertension, oral medicine, epidemiology, public health.

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Strengths and limitations of this study

- The subject group was based on a large-scale national survey in China, and the sample size of the study was relatively large.
- Periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop.
- Hypertension was self-report and not based on blood pressure measurements.

INTRODUCTION

Hypertension, which affects 45% of the global population, is the most common cardiovascular disease (CVDs) worldwide [1,2]. It is defined as systolic or diastolic blood pressure (BP) of ≥140 or ≥90 mmHg, respectively. Hypertension is frequently poorly controlled and untreated [3]. It ia a complex disease with multiple causes and a major risk factor for CVDs [4]. Oxidative stress, endothelial dysfunction, and inflammation are associated with the development of hypertension [5]. The results of experimental and clinical studies suggest that inflammation has a major role in the development of hypertension [6]. Chronic inflammation predisposes to the development of pro-hypertensive inflammation.

Periodontal disease, an immune-inflammatory reaction to plaque biofilms [7], has received substantial attention because of its association with CVDs. The Global Burden of Disease Study revealed that periodontitis was the sixth most prevalent disease worldwide. Periodontitis affects 743 million people worldwide (11.2% of the global population); the prevalence is higher in China than in other countries. The Fourth

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National Oral Health Survey of China showed that 90.9% individuals aged 35-44 years had periodontal disease [8, 9]. The low-grade inflammation associated with periodontitis has harmful effects on the endothelial function, which may result in hypertension [10]. A recent study revealed that individuals with periodontitis have increased risks of hypertension and antihypertensive treatment failure [11,12]. Previous studies have suggested that dental treatment can improve blood pressure, although the findings have been inconclusive and further studies are needed [13-16].

Periodontitis and hypertension are major health problems, and their association received considerable public health attention. Therefore, we evaluated the relationship between periodontitis and hypertension based on the data from the Fourth National Oral Health Survey of China. We sought to determine whether individuals with periodontitis are more likely to have hypertension compared with individuals who do not have periodontitis; we also sought to determine whether periodontitis severity is associated with hypertension.

MATERIALS AND METHODS

Study design and sample

This cross-sectional study obtained data from adult participants of the Fourth National Oral Health Survey of China (2015-2016) [8]. The planned sample size was 4,230 each for the age groups 35-44, 55-64 and 65-74 years. We excluded data from edentulous participants and from participants without complete information. Finally, 13,195 individuals were included (4,409, 4,568, and 4,218 individuals aged 35-44, 55-64, and

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65-74 years, respectively).

Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

Data collection

We collected data related to oral examination findings and questionnaire answers.

1. *Periodontal examination*

Periodontal examinations were performed using a community periodontal index probe. A full-mouth examination was performed, during which the probe was walked along the gingival crevices using a force of ≤ 20 g to assess bleeding on probing (BOP), the presence of calculus, probing depth (PD), and attachment loss (AL). For each parameter, each tooth was scored according to the condition of the most severely affected site. Training programs were conducted for examiner calibration before the survey. The reliability of the results was assessed using kappa values; kappa values for periodontal pocket depth were ≥ 0.6. Additionally, 5% of the participants were randomly selected for assessment of inter-examiner reproducibility. The kappa values for all age-groups were 0.76-0.80.

Patient and public involvement

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The study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Study parameters

Supragingival and subgingival calculus were identified by visual examination and probing, respectively (0 = absent, 1 = present, 9 = tooth excluded, and X = tooth not present). PD was recorded as 0 (1–3 mm), 1 (4–5 mm), 2 (≥6 mm), 9 (tooth excluded), or X (tooth not present). BOP was recorded as 0 (absent), 1 (present), 9 (tooth excluded), or X (tooth not present). AL was measured as the distance from the cementoenamel junction to the bottom of the periodontal pocket; it was recorded as 0 (0–3 mm), 1 (4–5 mm), 2 (6–8 mm), 3 (9–11 mm), 4 (≥12 mm), 9 (tooth excluded), or X (tooth not present).

The classification scheme proposed at the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions was used to classify the periodontal status as periodontally healthy (< 10% BOP-positive sites and PD ≤ 3 mm) or gingivitis (≥ 10% BOP-positive sites and PD ≤ 3 mm). Periodontitis was staged using the algorithm developed by Tonetti *et al* [17]. For each tooth, stages I-III periodontitis were defined as AL of 1–2 mm, 3–4 mm, and ≥ 5 mm, respectively. We also considered the number of teeth lost when classifying periodontitis: stages I and II, no tooth loss; stage III, ≤ 4 teeth lost; and stage IV, ≥ 5 teeth lost. The cause of tooth loss was not considered. Finally, we evaluated the complexity of patient management. Stage II patients were reclassified as stage III if the maximum PD was ≥ 6 mm. Stage

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III patients were reclassified as stage IV if there were < 10 opposing pairs of teeth). Stages of periodontitis reflects the severity and complexity of managing the individual patient.

2. *Interview data from the questionnaire*

Questionaires were administered during in-person interviews to collect data regarding demographics, socioeconomic status, habits, dental history, and health attitudes. The following information was collected for analysis: age (years), annual family income (in increments of 10,000 yuan), sex (male or female), duration of education (years), self-reported hypertension (yes or no), smoking status (current smoker, former smoker, or non-smoker), and region (urban or rural).

Statistical analyses

Statistical analyses were performed using SPSS (version 19; IBM Corp., Armonk, NY, USA) or R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The primary outcome was periodontal status (healthy, gingivitis, and stages I-IV periodontitis). The secondary outcomes were the proportions of BOP-positive teeth, teeth with PD ≥ 4 and ≥ 6 mm, teeth with AL ≥ 4, ≥ 6, and ≥ 9 mm; and missing teeth. First, descriptive analysis was performed. Quantitative data were reported as means and standard deviations; categorical data were reported as numbers and percentages. Periodontal parameters were compared between hypertensive and normotensive individuals; subgroup analyses were conducted according to age group

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and smoking status. Periodontal status and parameters were analysed using the chi-square test. Additionally, smoothed scatterplots based on generalised additive models were constructed, with adjustment for confounders (sex, smoking status, region, duration of education, and annual family income), to evaluate the relationships of hypertension prevalence with periodontal status or parameters. The level of statistical significance was set at $p < 0.05$.

RESULTS

The participants were randomly selected from 31 provinces, autonomous regions, and municipalities in mainland China. In total, data from 13,195 individuals were included in the analysis; invalid data from five participants and data from 264 edentulous patients were excluded. The mean individual age was 56.43 ± 12.40 years. The sample consisted of 6,575 men (49.83%) and 6,620 women (50.17%). There were 3,470 non-smokers (26.30%), 8,405 current smokers (63.71%), and 1,318 former smokers (9.99%). Hypertension was present and absent in 3,154 (23.90%) and 10,041 (76.10%) participants, respectively.

Differences in periodontal status between hypertensive and normotensive participants decreased with age

Table 1 and S1 present the distributions of periodontal status according to age and gender in participants with and without hypertension.

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Significantly greater proportions of hypertensive participants had stages I-IV periodontitis (70.23% vs. 61.51%, p < 0.001) and severe periodontitis (stages III-IV, 41.34% vs. 27.99%, p < 0.001), compared with normotensive participants. Stratified analysis by gender showed that the prevalence of periodontitis (stage I-IV) was significantly greater in hypertensive participants than in normotensive participants in females (66.48 % vs. 55.92 %, p <0.001) but not in males (74.09 % vs. 67.10%, p = 0.057). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants both in males (46.13% vs. 32.64%, p < 0.001) and females (36.60 % vs. 23.35 %, p < 0.001). Stratified analysis according to age showed that the prevalence of periodontitis (stage I-IV) was significantly greater in hypertensive participants than in normotensive participants among individuals aged 35-44 years (52.33% vs. 59.06%, p = 0.030), 55-64 years (72.61% vs. 69.19%, p = 0.023), and 65-74 years (70.23% vs. 66.35%, p = 0.009). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants among individuals aged 35-44 years (18.12% vs. 10.09%, p < 0.001) and 55-64 years (40.12% vs. 36.77%, p = 0.035), but not among individuals aged 65-74 years (46.40% vs. 45.14%, p = 0.429). Therefore, differences in periodontal status between hypertensive and normotensive participants decreased with age (Table 1).

Table 1. Comparison of distribution of periodontal status according to the 2017 classification by age/gender groups between hypertensive and normotensive subjects.

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		NT			HT		
		N	%	95% CI	N	%	95% CI
Male	Health	598	11.9	11.1~12.9	159	10.2	8.7~11.7
	Gingivitis	1051	21.0	19.9~22.1	246	15.7	14.0~17.6
	Stage I	844	16.8	15.8~17.9	171	10.9	9.5~12.6
	Stage II	883	17.6	16.6~18.7	266	17.0	15.2~18.9
	Stage III	906	18.1	17.0~19.2	357	22.8	20.8~25.0
	Stage IV	730	14.6	13.6~15.6	364	23.3	21.2~25.4
Female	Health	755	15.0	14.1~16.0	179	11.2	9.8~12.9
	Gingivitis	1461	29.1	27.8~30.3	355	22.3	20.3~24.4
	Stage I	867	17.2	16.2~18.3	199	12.5	10.9~14.2
	Stage II	770	15.3	14.3~16.3	277	17.4	15.6~19.3
	Stage III	588	11.7	10.8~12.6	260	16.3	14.6~18.2
	Stage IV	586	11.7	10.8~12.6	323	20.3	18.4~22.3
35-45 yrs	Health	658	15.9	14.8~17.1	40	14.5	10.7~19.0
	Gingivitis	1312	31.7	30.3~33.2	73	26.4	21.5~31.9
	Stage I	1134	27.4	26.1~28.8	69	25.0	20.2~30.4
	Stage II	612	14.8	13.7~15.9	44	15.9	12.0~20.6
	Stage III	360	8.7	7.9~9.6	40	14.5	10.7~19.0
	Stage IV	57	1.4	1.1~1.8	10	3.6	1.9~6.3
55-65 yrs	Health	347	10.6	9.6~11.7	116	9.0	7.5~10.6
	Gingivitis	661	20.2	18.9~21.6	239	18.4	16.4~20.6
	Stage I	403	12.3	11.2~13.5	174	13.4	11.7~15.4
	Stage II	658	20.1	18.8~21.5	247	19.1	17.0~21.3
	Stage III	659	20.1	18.8~21.5	273	21.1	18.9~23.3
	Stage IV	544	16.6	15.4~17.9	247	19.1	17.0~21.3
65-75 yrs	Health	348	13.2	12.0~14.5	182	11.5	10.0~13.1
	Gingivitis	539	20.4	18.9~22.0	289	18.3	16.4~20.2
	Stage I	175	6.6	5.7~7.6	126	8.0	6.7~9.4
	Stage II	384	14.6	13.3~16.0	251	15.9	14.1~17.7
	Stage III	475	18.0	16.6~19.5	304	19.2	17.3~21.2
	Stage IV	715	27.1	25.5~28.8	430	27.2	25.0~29.4
Total	Health	1353	13.5	12.8~14.2	338	10.7	9.7~11.8
	Gingivitis	2512	25.0	24.2~25.9	601	19.1	17.7~20.5
	Stage I	1712	17.1	16.3~17.8	369	11.7	10.6~12.9
	Stage II	1654	16.5	15.8~17.2	542	17.2	15.9~18.5

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Stage III	1494	14.9	14.2~15.6	617	19.6	18.2~21.0
Stage IV	1316	13.1	12.5~13.8	687	21.8	20.4~23.2

HT = Hypertension; NT = Normotension.

Table S1 showed the distribution of periodontal status stratified according to smoking status. Periodontitis (stage I-IV) was more common in hypertensive participants than in normotensive participants among current smokers (76.16% vs. 68.15%, $p < 0.001$) and non-smokers (67.25% vs. 57.41%, $p < 0.001$), but not among former smokers (73.59% vs. 70.58%, $p = 0.270$). Severe periodontitis (stage III and stage IV) was significantly more common in hypertensive participants than in normotensive participants among non-somkers (48.45% vs. 34.67%, $p < 0.001$), current smokers (36.82% vs. 23.75%, $p < 0.001$), and former smokers (50.26% vs 37.93%, $p < 0.001$).

Periodontal status was significantly worse in hypertensive participants than in normotensive participants

Tables 2 and 3 present comparisons of periodontal parameters between hypertensive and normotensive participants. Compared with normotensive participants, hypertensive participants had significantly greater proportions of teeth with BOP (57.71% vs. 53.12%), PD ≥ 4 mm (22.11% vs. 16.29%), PD ≥ 6 mm (2.07% vs. 1.22%), AL ≥ 4 mm (28.86% vs. 20.56%), AL ≥ 6 mm (8.44% vs. 5.54%), and AL ≥ 9 mm (1.72% vs. 1.18%). Differences in periodontal parameters between hypertensive and normotensive participants decreased with age. The differences in periodontal parameters between hypertensive and normotensive participants were similar among

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current smokers, former smokers, and non-smokers. Difference in the mean prevalence of periodontal pocket (PD ≥ 4 mm) were consistent in the stratified analysis.

Compared with normotensive participants, hypertensive participants had significantly greater proportions of teeth with PD ≥ 4 mm (4.45 vs. 3.46), PD ≥ 6 mm (0.37 vs. 0.22), AL ≥ 4 mm (1.18 vs. 0.81), and AL ≥ 6 mm (0.2 vs. 0.12). The mean number of BOP-positive teeth did not significant differ between hypertensive and normotensive participants (12.43 vs. 12.33). The mean number of teeth showed a distribution pattern similar to the distribution patterns of various periodontal parameters. The difference in the mean number of teeth between hypertensive and normotensive participants decreased with age. Furthermore, differences in the prevalences of teeth with PD ≥ 4 mm and deep PD sites were consistent in the stratified analysis.

Table 2. Comparison of percentage of teeth affected by age groups and smoking status.

	PTA	NT		HT		
		Mean	95% CI	Mean	95% CI	p*
35-45 years	BOP+	46.5	45.41~47.55.	50.32	45.92~54.72	0.096
	PD≥ 4mm	10.5	9.90~11.05	15.83	12.86~18.80	0.001
	PD≥ 6mm	0.5	0.40~0.59	1.09	0.56~1.63	0.031
	AL≥ 4mm	6	5.55~6.41	10.14	7.85~12.43	0.001
	AL≥ 6mm	0.8	0.69~0.95	1.62	0.82~2.42	0.052
55-65 years	BOP+	52.5	51.30~53.72	54.03	52.11~55.96	0.188
	PD≥ 4mm	17.9	17.11~18.76	20.3	18.92~21.68	0.004
	PD≥ 6mm	1.4	1.21~1.65	1.9	1.55~2.24	0.024
	AL≥ 4mm	22.1	21.16~22.95	21.53	20.15~22.92	0.543
	AL≥ 6mm	5.3	4.90~5.78	5.49	4.79~6.18	0.722
65-75 years	BOP+	49.3	47.91~50.59	50.84	49.09~52.58	0.157
	PD≥ 4mm	17.4	16.45~18.28	19.6	18.39~20.81	0.004
	PD≥ 6mm	1.5	1.29~1.81	1.84	1.49~2.19	0.185
	AL≥ 4mm	28.7	27.59~29.78	27.62	26.25~28.99	0.240

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	AL≥ 6mm	8.9	8.28~9.61	8.29	7.47~9.11	0.226
Current smoker	BOP+	49.6	46.77~52.42	49.89	45.99~53.79	0.311
	PD≥ 4mm	21.4	19.36~23.52	22.94	20.16~25.72	0.000
	PD≥ 6mm	2.2	1.53~2.80	2.09	1.34~2.84	0.006
	AL≥ 4mm	36.3	33.86~38.78	33.54	30.24~36.84	0.000
	AL≥ 6mm	13.1	11.38~14.75	11.38	9.26~13.50	0.001
Non-smoker	BOP+	48.9	47.22~50.57	51.56	49.42~53.69	0.000
	PD≥ 4mm	15.4	14.30~16.47	17.91	16.49~19.33	0.000
	PD≥ 6mm	1.1	0.89~1.40	1.66	1.27~2.05	0.000
	AL≥ 4mm	25.1	23.79~26.41	24.67	23.10~26.23	0.000
	AL≥ 6mm	7.2	6.44~7.92	6.60	5.71~7.50	0.000
Former smoker	BOP+	50.2	46.54~53.82	48.84	44.03~53.65	0.603
	PD≥ 4mm	18.7	16.23~21.21	22.62	18.90~26.34	0.000
	PD≥ 6mm	2.2	1.32~3.13	2.31	1.07~3.56	0.126
	AL≥ 4mm	30.7	27.81~33.60	32.77	28.63~36.92	0.001
	AL≥ 6mm	9.3	7.63~10.97	11.66	9.01~14.30	0.002
Total	BOP+	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	PD≥ 4mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	PD≥ 6mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	AL≥ 4mm	0.0	0.00~0.00	0.00	0.00~0.00	0.000
	AL≥ 6mm	0.0	0.00~0.00	0.00	0.00~0.00	0.001

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; PD = probing depth; PTA = Percentage of teeth affected;

* significant difference by Student's t test.

Table 3. Number of teeth affected by age groups and smoking status.

	NTA	NT		HT		
		Mean	95% CI	Mean	95% CI	p*
35-45 years	BOP+	12.69	12.40~12.99	13.61	12.42~14.80	0.143
	PD≥ 4mm	2.83	2.68~2.99	4.19	3.40~4.98	0.001
	PD≥ 6mm	0.13	0.10~0.15	0.27	0.14~0.40	0.036
	AL≥ 4mm	1.58	1.47~1.70	2.58	2.00~3.16	0.001

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	AL≥ 6mm	0.20	0.17~0.24	0.38	0.21~0.55	0.049
55-65 years	BOP+	13.01	12.69~13.33	13.37	12.86~13.88	0.241
	PD≥ 4mm	4.21	4.02~4.40	4.76	4.43~5.08	0.005
	PD≥ 6mm	0.28	0.24~0.32	0.41	0.34~0.49	0.003
	AL≥ 4mm	5.03	4.82~5.23	4.80	4.49~5.11	0.222
	AL≥ 6mm	1.07	0.99~1.15	1.08	0.95~1.21	0.914
65-75 years	BOP+	10.92	10.59~11.26	11.47	11.03~11.91	0.051
	PD≥ 4mm	3.52	3.33~3.72	4.25	3.98~4.52	0.000
	PD≥ 6mm	0.27	0.23~0.31	0.36	0.29~0.42	0.042
	AL≥ 4mm	5.65	5.43~5.88	5.60	5.31~5.88	0.752
	AL≥ 6mm	1.46	1.36~1.56	1.40	1.27~1.53	0.508
Current smoker	BOP+	12.30	11.93~12.67	12.09	0.33~0.42	0.583
	PD≥ 4mm	4.59	4.36~4.82	5.49	594.42~0.00	0.001
	PD≥ 6mm	0.31	0.27~0.35	0.50	61.18~0.00	0.001
	AL≥ 4mm	4.86	4.62~5.09	6.13	658.63~0.00	0.000
	AL≥ 6mm	1.19	1.09~1.29	1.59	179.14~0.00	0.001
Non-smoker	BOP+	12.29	12.06~12.51	12.62	12.22~13.02	0.159
	PD≥ 4mm	2.89	2.78~3.01	3.91	3.68~4.15	0.000
	PD≥ 6mm	0.16	0.14~0.18	0.29	0.24~0.34	0.000
	AL≥ 4mm	3.10	2.98~3.22	4.38	4.15~4.61	0.000
	AL≥ 6mm	0.60	0.56~0.64	0.92	0.83~1.01	0.000
Former smoker	BOP+	12.72	12.13~13.32	12.21	11.28~13.14	0.359
	PD≥ 4mm	4.12	3.76~4.48	5.14	4.50~5.78	0.006
	PD≥ 6mm	0.36	0.27~0.44	0.53	0.37~0.69	0.069
	AL≥ 4mm	5.29	4.90~5.68	5.94	5.32~6.55	0.081
	AL≥ 6mm	1.18	1.02~1.33	1.66	1.36~1.96	0.005
Total	BOP+	12.33	12.15~12.51	12.44	12.42~14.80	0.574
	PD≥ 4mm	3.46	3.36~3.57	4.45	3.40~4.98	0.000
	PD≥ 6mm	0.22	0.20~0.24	0.37	0.14~0.40	0.000
	AL≥ 4mm	3.77	3.67~3.88	5.00	2.00~3.16	0.000
	AL≥ 6mm	0.81	0.77~0.85	1.18	0.21~0.55	0.000

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; NTA = Number of teeth affected; PD = probing depth;

* significant difference by Student's t test.

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Hypertension prevalence increased with periodontitis severity

Multivariate regression analysis was performed to evaluate the relationship between hypertension and age stratified according to periodontal status, after adjustments for sex, smoking status, region, duration of education, and annual family income (Table 4). Compared with participants who did not have periodontitis, participants with stages III and IV periodontitis had a significant greater risk of hypertension (odds ratio [OR] = 1.698, 95% confidence interval [CI] = 1.45-1.99, $p < 0.000$). However, the difference between participants with stages I and II periodontitis and participants without periodontitis was not statistically significant (OR = 1.028, 95% CI = 0.88-1.20, $p = 0.717$). Therefore, hypertension prevalence increased with periodontitis severity. Notably, the OR for participants with stages III and IV periodontitis decreased with age; it was not statistically significant in participants aged 65-74 years (Table 4).

Table 4. Relationships between blood pressure (hypertension vs. normotension) and periodontal status (compared with non-periodontitis) according to the 2017 classification analyzed by logistic regressions with adjustment for gender, smoking status, region, years of education, and annual family income

Age group	Periodontal stauts*	OR	95% CI	p
35-45 years	Periodontitis (stage III & IV)#	1.617	1.00~2.61	0.050
	Periodontitis (stage I & II)#	0.966	0.65~1.43	0.863
55-65 years	Periodontitis (stage III & IV)#	1.402	1.07~1.84	0.015
	Periodontitis (stage I & II)#	1.301	1.00~1.69	0.051

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65-75 years	Periodontitis (stage III & IV)[#]	1.205	0.96~1.42	0.113
	Periodontitis (stage I & II)[#]	1.121	0.96~1.42	0.336
Total	Periodontitis (stage III & IV)[#]	1.698	1.45~1.99	0.000
	Periodontitis (stage I & II)[#]	1.028	0.88~1.20	0.717

[*] According to the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions [17].

Relationships of hypertension with periodontal parameters

Table 5 and Table 6 present the multivariate regression analyses of the relationships of hypertension with periodontal parameters, after adjustments for sex, smoking status, region, duration of education, and annual family income. Hypertension prevalence increased with increases in the proportions of teeth with BOP (OR = 1.204, 95% CI = 1.05-1.38 , p = 0.006), PD ≥ 4 mm (OR = 1.733, 95% CI = 1.43-2.10, p < 0.001), and PD ≥ 6 mm (OR = 2.443, 95% CI = 1.19-5.03, p = 0.015), but it decreased with increases in the proportions of teeth with AL ≥ 4 mm (OR = 0.874, 95% CI = 0.73-1.05, p = 0.155) and AL ≥ 6 mm (OR = 0.743, 95% CI = 0.53-1.04, p = 0.083). There were significant positive associations of hypertension with the number of teeth with BOP (OR = 1.008, 95% CI = 1.00-1.01, p = 0.001), PD ≥ 4 mm (OR = 1.029, 95% CI = 1.02-1.04, p < 0.000), and PD ≥ 6mm (OR = 1.071, 95% CI = 1.03-1.11, p < 0.001). There were statistically insignificant negative associations of the presence of hypertension with the proportions of teeth with AL ≥ 4 mm and AL ≥ 6 mm (Table 6).

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Table 5. Relationships between blood pressure (hypertension vs. normotension) and percentage of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

PTA	OR	95% CI	p
BOP+	1.204	1.05~1.38	0.006
PD≥ 4mm	1.733	1.43~2.10	0.000
PD≥ 6mm	2.443	1.19~5.03	0.015
AL≥ 4mm	0.874	0.73~1.05	0.155
AL≥ 6mm	0.743	0.53~1.04	0.083

AL= attachment loss; BOP = bleeding on probing; PD = probing depth; PTA = mean percentage of teeth affected per individual.

Table 6. Relationships between blood pressur (hypertension vs. normotension) and percentage of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

NTA	OR	95% CI	p
BOP+	1.008	1.00~1.01	0.001
PD≥ 4mm	1.029	1.02~1.04	0.000
PD≥ 6mm	1.071	1.03~1.11	0.000
AL≥ 4mm	0.997	0.99~1.01	0.507
AL≥ 6mm	0.987	0.97~1.01	0.217

AL= attachment loss; BOP = bleeding on probing; NTA = mean number of teeth affected per individual; PD = probing depth.

Significantly more teeth were missing in hypertensive participants than in normotensive participants

Table S1 presents a comparison of the number of missing teeth between participants

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with and without hypertension. Significantly more teeth were missing in hypertensive participants than in normotensive participants (4.36 vs. 2.94 teeth). The difference in the number of missing teeth between hypertensive and normotensive participants decreased with age. Analysis of the relationship according to smoking status showed that hypertension prevalence increased and then decreased with increases in the number of missing teeth.

DISCUSSION

Based on data from the Fourth National Oral Health Survey of China, periodontitis is significantly and strongly associated with hypertension among Chinese adults, independent of the effects of age, sex, and smoking. The association between periodontitis and hypertension reported in this study is in agreement with that recently reported reviews [18,19]. This association between periodontitis and hypertension has considerable importance [20].

In recent systemic reviews analyzing the association between periodontitis and hypertension, the included studies had been conducted in different countries across Asia, Europe, America, and Africa, lacking the large-scale data from China [18,19]. In this study, we used data from a large-scale national survey in which participants were representative of the Chinese population. Besides, the lack of consistent measures of case definition and severity of periodontitis in the retrieved studies did not allow for a relevant analysis of extent and severity of periodontitis with hypertension. In the present study, periodontitis was diagnosed in accordance with the classification

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proposed at the 2017 World Workshop. The association of hypertension with periodontitis was assessed according to age and smoking status to minimize errors and the effects of confounding factors. Periodontitis was associated with a increase prevalence of hypertension among Chinese adults, independent of known confounders. In most of the studies, periodontal status was clinically evaluated through PD and/or clinical attachment level measurement [18,19]. Nevertheless, several definitions of periodontal diseases have been used across studies and only a few have distinguished severe forms of periodontitis. In the present study, periodontitis severity was defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Participants with severe periodontal disease (stages III and IV periodontitis) had a greater risk of hypertension compared with participants who had mild or no periodontal disease.

Hypertension prevalence increased with periodontitis severity, particularly among young participants (35-44 years). Therefore, participants with risk factors, particularly young adults, should engage in healthy lifestyle habits to improve their oral health. Accordingly, there is a need to improve the education and awareness of dental treatment and preventive management among individuals at risk for hypertension, particularly in younger population. Periodontitis and hypertension are chronic diseases; therefore, substantial exposure time may be necessary for their development. The exposure time to risk factors may be considerably shorter in younger individuals than that in older individuals. The influence of the longer exposure time to the common risk factors for periodontitis and hypertension in older individuals may mask the effects of

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periodontitis on the development of hypertension. When the confounding effects of the risk factors were removed, a link between periodontitis and hypertension was identified. Therefore, severe periodontitis may have a greater role in the development of hypertension among younger individuals than among older individuals. The association of periodontitis with hypertension was also present in never smokers and former smokers, who had less exposure to common risk factors. The greater susceptibility to hypertension among young individuals with severe periodontitis may be attributed to periodontal inflammation.

This study evaluated the association between periodontal status and hypertension risk among young and older adults. Hypertension prevalence increased with periodontitis severity, which was most prominent in individuals aged 35-44 years. Adult aged < 65 years with hypertension had significantly greater risks of stages III and IV periodontitis, compared with individuals who did not have hypertension. Therefore, healthcare providers should carefully monitor oral health status in their patients to prevent hypertension, particularly among adults; they should conduct regular oral examinations and engage in periodontal disease management.

The association between periodontitis and hypertension was also present in participants who had a greater proportion of teeth with BOP or deep periodontal pockets. The findings suggest that severe periodontal inflammation, as evidenced by the depth of the inflamed periodontal pocket and the number of bleeding sites, is associated with hypertension. In particular, the presence of BOP indicates acute inflammation, which may lead to systemic effects and subsequent hypertension. The association of

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inflammation (i.e., PD) with hypertension suggests that persistent, long-term inflammation may also underlie this relationship. Compared with AL, PD seems to be more closely related to hypertension. For example, significant differences of the percentages/numbers of PD ≧ 4mm and 6mm in 55-64 years were seen between hypertensive and normotensive individuals, but not in the percentages/numbers of AL ≧4mm and 6mm (Table 2 and 3). This is because AL is more related to periodontal attachment damage, while PD is more related to the existing periodontal inflammation. This also indicates that the correlation between periodontitis and hypertension may be related to the increase of systemic inflammation. Our study adds to the existing literature concerning oral health parameters associated with systemic outcomes [21, 22]. BOP and PD are the most appropriate clinical measures when the outcome of interest is an acute disease, whereas AL is more strongly correlated with chronic systemic conditions [21]. Our findings of an association between hypertension and the severity of periodontal inflammation (BOP and PD) are consistent with the results of previous studies [12, 18]. Although the causality of the observed association remains unclear, several hypotheses have been proposed, including endothelial dysfunction, oxidative stress, worsening of systemic inflammation in response to bacteraemia, and dissemination of inflammatory mediators from periodontal pockets, particularly BOP [23]. This association is further supported by the results of a randomised clinical trial that showed short-term benefits of periodontal therapy on hypertension [24]. Additionally, a recent study identified oral pathogens associated with high or uncontrolled BP, which supports our findings [25].

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Our finding of an association between the number of missing teeth and hypertension is consistent with the results reported by Taguchi et al [26]. Missing teeth are indicative of poor oral health; they presumably were lost because of caries and periodontal disease. Thus, the absence of several teeth suggests the presence of severe periodontal disease, caries, or other oral health problems; these may have contributed to the increased risk of hypertension. This association was strongest in younger adults. There were no residual confounding effects of age that may have affected our study results. Because of the high prevalence of hypertension in Chinese adults, further studies are needed to clarify the association between periodontitis and hypertension. Moreover, attention is needed concerning the prevention and treatment of periodontitis in the general population.

There is minimal knowledge concerning the natural history of the association between periodontal disease and hypertension [27-31]. A significant linear trend was observed between the severity of periodontal disease and hypertension in a cross-sectional study of 3,352 patients with periodontal disease and 902 controls [29]. A recent prospective cohort study of Japanese individuals demonstrated an increased incidence of hypertension among participants with periodontal pockets ≥ 4 mm at baseline [30]. Our findings are consistent with the results in a similar study of 6,617 men and 7,377 women who underwent dental examinations as part of the NHANES III in the USA [32]. In the present study, after multivariate adjustment, gingival bleeding (BOP) was associated with an increased risk of hypertension, whereas periodontitis severity (defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant

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Diseases and Conditions) and PD were positively associated with hypertension. Participants with severe periodontal disease (stages III and IV periodontitis) had a greater risk of hypertension compared with participants who had mild or no periodontal disease. Furthermore, there was a threshold relationship between severe periodontal disease and hypertension.

To our knowledge, the present study is one of few concerning the association between periodontal disease and hypertension in a large sample of Chinese adults, after adjustments for potential confounders. We evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.

The main limitation of the present study was that hypertension was self-report and not based on blood pressure measurements, which is inherent to any epidemiological cohort study. However, field measurements of blood pressure are regarded as validated tools, have been used in previous studies [21, 23], and are considered useful for the analysis of large samples. Furthermore, although recall and reporting bias could not be excluded, the results largely reflect real-world clinical practice. First, the self-reported diagnosis was based on a face-to-face interview to ensure the validity and accuracy of the information. Second, the reliability of the study results is supported by data from the China Hypertension Survey (2012-2015) [33], which showed an overall hypertension

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prevalence of 23.2% in the Chinese adult population; this prevalence is similar to the prevalence observed in our study (23.9%).

In summary, our epidemiological analysis revealed an association between periodontitis and hypertension. We collected high-quality, large-scale clinical data related to periodontal disease and hypertension. We also collected detailed information regarding potential confounders, including variables that reflect health behavior (e.g., flossing). However, there was no strong evidence of a causal relationship. Future studies should be conducted to improve the understanding of the underlying mechanisms and interactions between periodontitis and hypertension, which will further strengthen collaborations between the dental and medical communities. Preventive measures for periodontal disease in oral health promotion programs should be emphasised to improve systemic health outcomes.

Contributorship statement

YZ is the major contributor in writing the manuscript and participates in data analysis and collation. JJ participates in data analysis and collation. WJ participates in writing the manuscript. XF, BT, DH, HL, BW, CW, SZ, XL, WR, WW, XW, and YS conceive the study design and draft the protocol. HM conceives the study design, drafts the protocol, and revise the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interests.

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Data sharing statement

Dataset available from the Fourth National Oral Health Survey of China (2015-2016).

Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

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Table s1. Number of missing teeth by age groups and smoking status

	NT		HT		
	Mean	95% CI	Mean	95% CI	p*
35-44	0.70	0.65~0.75	1.01	0.74~1.28	0.024
55-64	3.26	3.10~3.43	3.42	3.15~3.69	0.305
65-74	6.04	5.79~6.30	5.70	5.39~6.01	0.104
Non-smoker	3.30	3.10~3.50	4.27	3.87~4.67	0.000
Current smoker	2.70	2.58~2.81	3.42	3.95~4.44	0.000
Former smoker	3.55	3.21~3.89	5.70	4.68~5.98	0.000
Total	2.94	2.84~3.04	4.35	4.15~4.55	0.000

HT = Hypertension; NT = Normotension;

* significant difference by Student's t test.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	10-13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association Between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey in China (2015-2016)

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Association Between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey in China (2015-2016)

Running title: Association between periodontitis and hypertension

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ABSTRACT

Objectives To evaluate the association between periodontitis severity and hypertension based on Chinese epidemiological data.

Design This cross-sectional survey enrolled adults from the Fourth National Oral Health Survey of China (2015-2016).

Setting The data were obtained from the Fourth National Oral Health Survey of China (2015-2016).

Participants The study included individuals aged 35-44 years (n = 4,409), 55-64 years (n = 4,568), and 65-74 years (n = 4,218).

Primary and secondary outcome measures Periodontal status, defined on the basis of the 2017 classification scheme, and periodontal parameters (e.g., bleeding on probing [BOP]) were compared between hypertensive and normotensive individuals. Smoothed scatterplots were constructed to demonstrate the associations of periodontal parameters and periodontal status with hypertension.

Results Severe periodontitis (stages III and IV) was present in 41.4% and 28.0% of hypertensive and normotensive individuals, respectively ($p < 0.001$). The prevalence of severe periodontitis was increase in hypertensive individuals than that in normotensive individuals among participants aged 35-44 years (18.0% and 10.1%, $p < 0.001$) and 55-64 years (40.2% and 36.7%, $p = 0.035$), but not in participants aged 65-74 years (46.4% and 45.1%, $p = 0.429$). Therefore, the difference in periodontal status between hypertensive and normotensive individuals decreased with age. There were increased prevalence of BOP, PD ≥ 4 mm, and PD ≥ 6 mm in hypertensive individuals than in normotensive individuals (52.1% vs 49.2%, 19.6% vs 14.7%, and 1.8% vs 1.1%, respectively). Periodontitis severity and the proportion of teeth with PD ≥ 4 or ≥ 6 mm were positively associated with hypertension.

Conclusion Periodontitis is associated with hypertension among Chinese adults. Hypertension prevalence increased with periodontitis severity, particularly among young participants. Accordingly, there is a need to improve the education and awareness of periodontal treatment and preventive management among individuals at risk for hypertension, particularly in younger population.

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Key Words: Hypertension, oral medicine, epidemiology, public health.

Strengths and limitations of this study

- The subject group was based on a large-scale national survey in China, and the sample size of the study was relatively large.
- Periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop.
- Hypertension was self-report and not based on blood pressure measurements.

INTRODUCTION

Hypertension, which affects 45% of the global population, is the most common cardiovascular disease (CVDs) worldwide [1,2]. It is defined as systolic or diastolic blood pressure (BP) of ≥140 or ≥90 mmHg, respectively. Hypertension is frequently poorly controlled and untreated [3]. It is a complex disease with multiple causes and a major risk factor for CVDs [4]. Oxidative stress, endothelial dysfunction, and inflammation are associated with the development of hypertension [5]. The results of experimental and clinical studies suggest that inflammation has a major role in the development of hypertension [6]. Chronic inflammation predisposes to the development of pro-hypertensive inflammation.

Periodontal disease, an immune-inflammatory reaction to plaque biofilms [7], has received substantial attention because of its association with CVDs. The Global Burden of Disease Study revealed that periodontitis was the sixth most prevalent disease

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worldwide. Periodontitis affects 743 million people worldwide (11.2% of the global population); the prevalence is higher in China than in other countries. The Fourth National Oral Health Survey of China showed that 90.9% individuals aged 35-44 years had periodontal disease [8, 9]. The low-grade inflammation associated with periodontitis has harmful effects on the endothelial function, which may result in hypertension [10]. A recent study revealed that individuals with periodontitis have increased risks of hypertension and antihypertensive treatment failure [11,12]. Previous studies have suggested that dental treatment can improve blood pressure, although the findings have been inconclusive and further studies are needed [13-16].

Periodontitis and hypertension are major health problems, and their association received considerable public health attention. Therefore, we evaluated the relationship between periodontitis and hypertension based on the data from the Fourth National Oral Health Survey of China. We sought to determine whether individuals with periodontitis are more likely to have hypertension compared with individuals who do not have periodontitis; we also sought to determine whether periodontitis severity is associated with hypertension.

MATERIALS AND METHODS

Study design and sample

This cross-sectional study obtained data from adult participants of the Fourth National Oral Health Survey of China (2015-2016) [8]. The planned sample size was 4,230 each for the age groups 35-44, 55-64 and 65-74 years. We excluded data from edentulous

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participants and from participants without complete information. Finally, 13,195 individuals were included (4,409, 4,568, and 4,218 individuals aged 35-44, 55-64, and 65-74 years, respectively).

Data collection

We collected data related to oral examination findings and questionnaire answers.

1. *Periodontal examination*

Periodontal examinations were performed using a community periodontal index probe. A full-mouth examination was performed, during which the probe was walked along the gingival crevices using a force of ≤ 20 g to assess bleeding on probing (BOP), the presence of calculus, probing depth (PD), and attachment loss (AL). For each parameter, each tooth was scored according to the condition of the most severely affected site. Training programs were conducted for examiner calibration before the survey. The reliability of the results was assessed using kappa values; kappa values for periodontal pocket depth were ≥ 0.6. Additionally, 5% of the participants were randomly selected for assessment of inter-examiner reproducibility. The kappa values for all age-groups were 0.76-0.80.

Patient and public involvement

The study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Study parameters

Supragingival and subgingival calculus were identified by visual examination and probing, respectively (0 = absent, 1 = present, 9 = tooth excluded, and X = tooth not present). PD was recorded as 0 (1–3 mm), 1 (4–5 mm), 2 (≥6 mm), 9 (tooth excluded), or X (tooth not present). BOP was recorded as 0 (absent), 1 (present), 9 (tooth excluded), or X (tooth not present). AL was measured as the distance from the cementoenamel junction to the bottom of the periodontal pocket; it was recorded as 0 (0–3 mm), 1 (4–5 mm), 2 (6–8 mm), 3 (9–11 mm), 4 (≥12 mm), 9 (tooth excluded), or X (tooth not present).

The classification scheme proposed at the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions was used to classify the periodontal status as periodontally healthy (< 10% BOP-positive sites and PD ≤ 3 mm) or gingivitis (≥ 10% BOP-positive sites and PD ≤ 3 mm). Periodontitis was staged using the algorithm developed by Tonetti *et al* [17]. For each tooth, stages I-III periodontitis were defined as AL of 1–2 mm, 3–4 mm, and ≥ 5 mm, respectively. We also considered the number of teeth lost when classifying periodontitis: stages I and II, no tooth loss; stage III, ≤ 4 teeth lost; and stage IV, ≥ 5 teeth lost. The cause of tooth loss was not considered. Finally, we evaluated the complexity of patient management. Stage II patients were reclassified as stage III if the maximum PD was ≥ 6 mm. Stage III patients were reclassified as stage IV if there were < 10 opposing pairs of teeth). Stages of periodontitis reflects the severity and complexity of managing the individual patient.

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2. *Interview data from the questionnaire*

Questionaires were administered during in-person interviews to collect data regarding demographics, socioeconomic status, habits, dental history, and health attitudes. The following information was collected for analysis: age (years), annual family income (in increments of 10,000 yuan), sex (male or female), duration of education (years), self-reported hypertension (yes or no), smoking status (current smoker, former smoker, or non-smoker), and region (urban or rural).

Statistical analyses

Statistical analyses were performed using SPSS (version 19; IBM Corp., Armonk, NY, USA) or R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The primary outcome was periodontal status (healthy, gingivitis, and stages I-IV periodontitis). The secondary outcomes were periodontal parameters (BOP-positive teeth, teeth with PD ≥ 4 and ≥ 6 mm, teeth with AL ≥ 4, ≥ 6, and ≥ 9 mm, presented as percentages of teeth affected and numbers of teeth affected) and missing teeth. First, descriptive analysis was performed. Quantitative data were reported as means and standard deviations; categorical data were reported as numbers and percentages. Periodontal parameters were compared between hypertensive and normotensive individuals; subgroup analyses were conducted according to age group and smoking status. Periodontal status and parameters were analyzed using the chi-square test. Additionally, smoothed scatterplots based on generalized additive models

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were constructed, with adjustment for confounders (sex, smoking status, region, duration of education, and annual family income), to evaluate the relationships of hypertension prevalence with periodontal status or parameters. The level of statistical significance was set at $p < 0.05$.

RESULTS

The participants were randomly selected from 31 provinces, autonomous regions, and municipalities in mainland China. In total, data from 13,195 individuals were included in the analysis; invalid data from five participants and data from 264 edentulous patients were excluded. The mean individual age was 56.43 ± 12.40 years. The sample consisted of 6,575 men (49.8%) and 6,620 women (50.2%). There were 3,470 non-smokers (26.3%), 8,405 current smokers (63.7%), and 1,318 former smokers (10.0%). Hypertension was present and absent in 3,154 (23.9%) and 10,041 (76.1%) participants, respectively.

Differences in periodontal status between hypertensive and normotensive participants decreased with age

Table 1 present the distributions of periodontal status according to age, gender, and smoking status in participants with and without hypertension.

Significantly increase proportions of hypertensive participants had stages I-IV periodontitis (70.3 % vs. 61.5%, p < 0.001) and severe periodontitis (stages III-IV, 41.4 % vs. 28.0%, p < 0.001), compared with normotensive participants. Stratified analysis

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by gender showed that the prevalence of periodontitis (stage I-IV) was significantly increase in hypertensive participants than in normotensive participants in females (66.5 % vs. 55.9 %, $p < 0.001$) but not in males (74.0 % vs. 67.1%, $p = 0.057$). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants both in males (46.1% vs. 32.7 %, $p < 0.001$) and females (36.6 % vs. 23.4 %, $p < 0.001$). Stratified analysis according to age showed that the prevalence of periodontitis (stage I-IV) was significantly increase in hypertensive participants than in normotensive participants among individuals aged 35-44 years (59.2% vs. 52.3%, $p = 0.030$), 55-64 years (72.7% vs. 69.1%, $p = 0.023$), and 65-74 years (70.3% vs. 66.2%, $p = 0.009$). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants among individuals aged 35-44 years (18.0% vs. 10.1%, $p < 0.001$) and 55-64 years (40.2% vs. 36.7%, $p = 0.035$), but not among individuals aged 65-74 years (46.4% vs. 45.1%, $p = 0.429$). Therefore, differences in periodontal status between hypertensive and normotensive participants decreased with age (Table 1). Stratified analysis by smoking status showed that the prevalence of periodontitis (stage I-IV) was significantly increase in hypertensive participants than in normotensive participants in current smokers (76.2 % vs. 68.1%, $p = 0.016$) and non-smokers (67.3 % vs. 57.4%, $p < 0.001$) but not in former smokers (73.8 % vs. 70.6%, $p = 0.972$). Severe periodontitis (stage III and stage IV) was more common in hypertensive participants than in normotensive participants in all three sub-groups: current smokers (48.4% vs. 34.7%,

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p < 0.001), non-smokers (36.9% vs. 23.7%, p < 0.001) and in former smokers (50.2 % vs. 38.0%, p < 0.001).

Table 1. Comparison of distribution of periodontal status according to the 2017 classification by age/gender/smoking groups between hypertensive and normotensive subjects.

Group	Periodontal status	NT			HT			p1*	p2#
		N	%	95% CI	N	%	95% CI		
Male	Health	598	11.9	11.1~12.9	159	10.2	8.7~11.7	0.057	< 0.001
	Gingivitis	1051	21.0	19.9~22.1	246	15.7	14.0~17.6		
	Stage I	844	16.8	15.8~17.9	171	10.9	9.5~12.6		
	Stage II	883	17.6	16.6~18.7	266	17.0	15.2~18.9		
	Stage III	906	18.1	17.0~19.2	357	22.8	20.8~25.0		
	Stage IV	730	14.6	13.6~15.6	364	23.3	21.2~25.4		
Female	Health	755	15.0	14.1~16.0	179	11.2	9.8~12.9	< 0.001	< 0.001
	Gingivitis	1461	29.1	27.8~30.3	355	22.3	20.3~24.4		
	Stage I	867	17.2	16.2~18.3	199	12.5	10.9~14.2		
	Stage II	770	15.3	14.3~16.3	277	17.4	15.6~19.3		
	Stage III	588	11.7	10.8~12.6	260	16.3	14.6~18.2		
	Stage IV	586	11.7	10.8~12.6	323	20.3	18.4~22.3		
35-44 years	Health	658	15.9	14.8~17.1	40	14.4	10.7~18.9	0.030	< 0.001
	Gingivitis	1312	31.8	30.3~33.2	73	26.4	21.4~31.8		
	Stage I	1133	27.4	26.1~28.8	70	25.3	20.4~30.6		
	Stage II	612	14.8	13.8~15.9	44	15.9	11.9~20.5		
	Stage III	360	8.7	7.9~9.6	40	14.4	10.7~18.9		
	Stage IV	57	1.4	1.1~1.8	10	3.6	1.9~6.3		
55-64 years	Health	347	10.6	9.6~11.7	116	9.0	7.5~10.6	0.023	0.035
	Gingivitis	661	20.2	18.9~21.6	239	18.4	16.4~20.6		
	Stage I	403	12.3	11.2~13.5	174	13.4	11.7~15.4		
	Stage II	658	20.1	18.8~21.5	247	19.1	17.0~21.3		
	Stage III	659	20.1	18.8~21.5	273	21.1	18.9~23.3		
	Stage IV	544	16.6	15.4~17.9	247	19.1	17.0~21.3		
65-74 years	Health	348	13.2	12.0~14.5	182	11.5	10.0~13.1	0.009	0.429
	Gingivitis	539	20.5	18.9~22.0	289	18.3	16.4~20.2		
	Stage I	175	6.6	5.7~7.6	126	8.0	6.7~9.4		
	Stage II	383	14.5	13.2~15.9	252	15.9	14.2~17.8		
	Stage III	475	18.0	16.6~19.5	304	19.2	17.3~21.2		

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	Stage IV	715	27.1	25.5~28.8	430	27.2	25.0~29.4		
Current smoker	Health	346	12.8	11.6~14.2	75	9.7	7.7~11.9		
	Gingivitis	512	19.0	17.6~20.5	110	14.2	11.8~16.7		
	Stage I	423	15.7	14.4~17.1	82	10.6	8.5~12.9	0.016	< 0.001
	Stage II	478	17.7	16.3~19.2	134	17.2	14.7~20.0		
	Stage III	491	18.2	16.8~19.7	198	25.5	22.5~28.6		
	Stage IV	443	16.5	15.1~17.9	178	22.9	20.1~26.0		
Non-smoker	Health	909	14.2	13.3~15.0	221	11.1	9.8~12.6		
	Gingivitis	1825	28.4	27.3~29.5	430	21.6	19.9~23.5		
	Stage I	1167	18.2	17.3~19.1	249	12.5	11.1~14.0	< 0.001	< 0.001
	Stage II	994	15.5	14.6~16.4	356	17.9	16.3~19.6		
	Stage III	803	12.5	11.7~13.3	337	17.0	15.4~18.6		
	Stage IV	721	11.2	10.5~12.0	395	19.9	18.2~21.7		
Former smoker	Health	98	10.6	8.7~12.7	42	10.7	8.0~14.1		
	Gingivitis	175	18.9	16.5~21.5	61	15.6	12.3~19.4		
	Stage I	121	13.1	11.0~15.3	39	10.0	7.3~13.2	0.972	< 0.001
	Stage II	181	19.5	17.1~22.2	53	13.6	10.4~17.2		
	Stage III	200	21.6	19.0~24.3	82	21.0	17.2~25.2		
	Stage IV	98	10.6	8.7~12.7	42	10.7	8.0~14.1		
Total	Health	1353	13.5	12.8~14.2	338	10.7	9.7~11.8		
	Gingivitis	2512	25.0	24.2~25.9	601	19.0	17.7~20.4		
	Stage I	1711	17.0	16.3~17.8	370	11.7	10.6~12.9	< 0.001	< 0.001
	Stage II	1653	16.5	15.8~17.2	543	17.2	15.9~18.6		
	Stage III	1494	14.9	14.2~15.6	617	19.6	18.2~21.0		
	Stage IV	1316	13.1	12.5~13.8	687	21.8	20.4~23.2		

HT = Hypertension; NT = Normotension.

*Significance values of differences of distribution proportion of periodontitis (stage I to IV) and non-periodontitis (health and gingivitis) between hypertensive and normotensive subjects by Chi square test;

#Significance values of differences of distribution proportion of severe periodontitis (stage III and IV) and non-severe-periodontitis (health, gingivitis, stage I and stage II) between hypertensive and normotensive subjects by Chi square test.

Periodontal parameters were significantly worse in hypertensive participants than in normotensive participants

Tables 2 and 3 present comparisons of periodontal parameters between hypertensive and normotensive participants. Compared with normotensive participants, hypertensive participants had significantly increase proportions of teeth with BOP (52.1% vs. 49.2%),

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PD ≥ 4 mm (19.6% vs. 14.7%), PD ≥ 6 mm (1.8% vs. 1.1%), AL ≥ 4 mm (23.6% vs. 17.2%), AL ≥ 6 mm (6.6% vs. 4.4%). Differences in the percentage of teeth with each periodontal parameters between hypertensive and normotensive participants were consistent in males and females, and among current smokers, former smokers, and non-smokers (except for BOP, whose significant differences were not found in males, current smokers and former smokers; and PD≥6 mm, whose significant differences were not found in former smokers). Differences in periodontal parameters between hypertensive and normotensive participants decreased with age. Difference in the mean prevalence of PD ≥ 4 mm were consistent in all age-groups. Compared with normotensive participants, hypertensive participants significantly increased numbers of teeth with PD ≥ 4 mm (4.5 vs. 3.5), PD ≥ 6 mm (0.4 vs. 0.2), AL ≥ 4 mm (5.0 vs. 3.8), and AL ≥ 6 mm (1.2 vs. 0.8). The mean number of BOP-positive teeth was not significant difference between hypertensive and normotensive participants (12.4 vs. 12.3). Differences in the mean number of teeth with each periodontal parameters between hypertensive and normotensive participants were consistent in males and females, and among current smokers, former smokers, and non-smokers (except for BOP, whose significant differences were found in females, and PD≥6 mm, whose significant differences were not found in former smokers). The difference in the mean number of teeth between hypertensive and normotensive participants decreased with age. Furthermore, differences in the number of teeth with PD ≥ 4 mm and PD ≥ 6 mm sites were consistent in all age-groups.

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Table 2. Comparison of the percentage of teeth with each periodontal parameter between hypertensive and normotensive subjects by gender, age groups and smoking status.

Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	50.9	49.9~51.9	52.2	50.4~54.0	0.232
	PD≥ 4mm	17.9	17.2~18.6	22.6	21.3~24.0	< 0.001
	PD≥ 6mm	1.5	1.3~1.6	2.3	1.9~2.7	< 0.001
	AL≥ 4mm	20.9	20.2~21.7	27.5	26.0~28.9	< 0.001
	AL≥ 6mm	5.7	5.3~6.1	8.3	7.5~9.1	< 0.001
Female	BOP+	47.4	46.5~48.4	52.1	50.4~53.8	< 0.001
	PD≥ 4mm	11.5	11.0~12.0	16.5	15.4~17.6	< 0.001
	PD≥ 6mm	0.7	0.6~0.8	1.3	1.0~1.6	< 0.001
	AL≥ 4mm	13.5	12.9~14.0	19.8	18.6~20.9	< 0.001
	AL≥ 6mm	3.2	2.9~3.4	4.8	4.2~5.4	< 0.001
35-44 years	BOP+	46.5	45.4~47.5	50.5	46.1~54.9	0.096
	PD≥ 4mm	10.5	9.9~11.1	15.8	12.8~18.8	0.001
	PD≥ 6mm	0.5	0.4~0.6	1.1	0.6~1.6	0.031
	AL≥ 4mm	6	5.6~6.4	10.1	7.8~12.4	0.001
	AL≥ 6mm	0.8	0.7~0.9	1.6	0.8~2.4	0.053
55-64 years	BOP+	52.5	51.3~53.7	54.0	52.1~56.0	0.188
	PD≥ 4mm	17.9	17.1~18.8	20.3	18.9~21.7	0.004
	PD≥ 6mm	1.4	1.2~1.6	1.9	1.6~2.2	0.024
	AL≥ 4mm	22.1	21.2~22.9	21.5	20.1~22.9	0.543
	AL≥ 6mm	5.3	4.9~5.8	5.5	4.8~6.2	0.722
65-74 years	BOP+	49.2	47.9~50.6	50.8	49.1~52.6	0.144
	PD≥ 4mm	17.4	16.5~18.3	19.6	18.4~20.8	0.004
	PD≥ 6mm	1.5	1.3~1.8	1.8	1.5~2.2	0.188
	AL≥ 4mm	28.7	27.6~29.8	27.6	26.3~29.0	0.239
	AL≥ 6mm	8.9	8.3~9.6	8.3	7.5~9.1	0.220
Current smoker	BOP+	49.7	48.3~51.1	51.3	48.8~53.9	0.286
	PD≥ 4mm	19.9	18.9~20.9	24.1	22.2~26.0	< 0.001
	PD≥ 6mm	1.6	1.4~1.9	2.4	1.9~3.0	0.007
	AL≥ 4mm	22.5	21.4~23.6	28.8	26.7~30.9	< 0.001
	AL≥ 6mm	6.6	6.0~7.2	8.8	7.6~10.0	0.001
Non-smoker	BOP+	48.5	47.7~49.4	52.3	50.7~53.8	< 0.001
	PD≥ 4mm	12.1	11.6~12.6	17.0	16.0~18.0	< 0.001
	PD≥ 6mm	0.7	0.6~0.8	1.4	1.1~1.6	< 0.001
	AL≥ 4mm	14.0	13.4~14.5	20.4	19.3~21.4	< 0.001
	AL≥ 6mm	3.3	3.0~3.5	5.1	4.6~5.7	< 0.001

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Former	BOP+	51.7	49.4~54.0	53.0	49.4~56.6	0.548
smoker	PD≥ 4mm	17.8	16.3~19.4	23.7	20.9~26.5	< 0.001
	PD≥ 6mm	1.9	1.4~2.4	2.6	1.8~3.4	0.129
	AL≥ 4mm	23.8	27.8~33.6	32.8	28.6~36.9	0.001
	AL≥ 6mm	6.2	5.3~7.1	9.4	7.6~11.1	0.002
Total	BOP+	49.2	48.5~49.9	52.1	50.9~53.4	< 0.001
	PD≥ 4mm	14.7	14.3~15.2	19.6	18.7~20.4	< 0.001
	PD≥ 6mm	1.1	1.0~1.2	1.8	1.6~2.0	< 0.001
	AL≥ 4mm	17.2	16.7~17.7	23.6	22.7~24.5	< 0.001
	AL≥ 6mm	4.4	4.2~4.7	6.6	6.0~7.1	< 0.001

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; PD = probing depth;

* significant difference by Student's t test.

Table 3. Comparison of the number of teeth with each periodontal parameter between hypertensive and normotensive subjects by gender, age groups and smoking status.

Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	12.7	12.5~13.0	12.3	11.8~12.8	0.111
	PD≥ 4mm	4.2	4.0~4.4	5.1	4.8~5.4	< 0.001
	PD≥ 6mm	0.3	0.3~0.3	0.5	0.4~0.6	< 0.001
	AL≥ 4mm	4.6	4.5~4.8	5.7	5.4~6.0	< 0.001
	AL≥ 6mm	1.1	1.0~1.1	1.5	1.3~1.6	< 0.001
Female	BOP+	11.9	11.7~12.1	12.6	12.1~13.0	0.013
	PD≥ 4mm	2.7	2.6~2.9	3.8	3.6~4.1	< 0.001
	PD≥ 6mm	0.1	0.1~0.2	0.3	0.2~0.3	< 0.001
	AL≥ 4mm	2.9	2.8~3.1	4.3	4.0~4.5	< 0.001
	AL≥ 6mm	0.6	0.5~0.6	0.9	0.8~1.0	< 0.001
35-44	BOP+	12.7	12.4~13.0	13.6	12.4~14.8	0.143
years	PD≥ 4mm	2.8	2.7~3.0	4.2	3.4~5.0	0.001
	PD≥ 6mm	0.1	0.1~0.2	0.3	0.1~0.4	0.036
	AL≥ 4mm	1.6	1.5~1.7	2.6	2.0~3.2	0.001
	AL≥ 6mm	0.2	0.2~0.2	0.4	0.2~0.6	0.049
55-64	BOP+	13.0	12.7~13.3	13.4	12.9~13.9	0.241
years	PD≥ 4mm	4.2	4.0~4.4	4.8	4.4~5.1	0.005
	PD≥ 6mm	0.3	0.2~0.3	0.4	0.3~0.5	0.003
	AL≥ 4mm	5.0	4.8~5.2	4.8	4.5~5.1	0.222
	AL≥ 6mm	1.1	1.0~1.2	1.1	1.0~1.2	0.914

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65-74 years	BOP+	10.9	10.6~11.3	11.5	11.0~11.9	0.051
	PD≥ 4mm	3.5	3.3~3.7	4.3	4.0~4.5	< 0.001
	PD≥ 6mm	0.3	0.2~0.3	0.4	0.3~0.4	0.042
	AL≥ 4mm	5.7	5.4~5.9	5.6	5.3~5.9	0.752
	AL≥ 6mm	1.5	1.4~1.6	1.4	1.3~1.5	0.508
Current smoker	BOP+	12.3	11.9~12.7	12.1	11.4~12.8	0.583
	PD≥ 4mm	4.6	4.4~4.8	5.5	5.0~6.0	0.001
	PD≥ 6mm	0.3	0.3~0.4	0.5	0.4~0.6	0.001
	AL≥ 4mm	4.9	4.6~5.1	6.1	5.7~6.6	< 0.001
	AL≥ 6mm	1.2	1.1~1.3	1.6	1.4~1.8	0.001
Non-smoker	BOP+	12.3	12.1~12.5	12.6	12.2~13.0	0.159
	PD≥ 4mm	2.9	2.8~3.0	3.9	3.7~4.2	< 0.001
	PD≥ 6mm	0.2	0.1~0.2	0.3	0.2~0.3	< 0.001
	AL≥ 4mm	3.1	3.0~3.2	4.4	4.2~4.6	< 0.001
	AL≥ 6mm	0.6	0.6~0.6	0.9	0.8~1.0	< 0.001
Former smoker	BOP+	12.7	12.1~13.3	12.2	11.3~13.1	0.359
	PD≥ 4mm	4.1	3.8~4.5	5.1	4.5~5.8	0.006
	PD≥ 6mm	0.4	0.3~0.4	0.5	0.4~0.7	0.069
	AL≥ 4mm	5.3	4.9~5.7	5.9	5.3~6.6	0.081
	AL≥ 6mm	1.2	1.0~1.3	1.7	1.4~2.0	0.005
Total	BOP+	12.3	12.2~12.5	12.4	12.1~14.8	0.574
	PD≥ 4mm	3.5	3.4~3.6	4.5	4.2~4.7	< 0.001
	PD≥ 6mm	0.2	0.2~0.2	0.4	0.3~0.4	< 0.001
	AL≥ 4mm	3.8	3.7~3.9	5.0	4.8~5.2	< 0.001
	AL≥ 6mm	0.8	0.8~0.9	1.2	1.1~1.3	< 0.001

AL= attachment loss; BOP = bleeding on probing; HT = Hypertension;

NT = Normotension; PD = probing depth;

* significant difference by Student's t test.

Hypertension prevalence increased with periodontitis severity

Multivariate regression analysis was performed to evaluate the relationship between hypertension and age stratified according to periodontal status, after adjustments for sex, smoking status, region, duration of education, and annual family income (Table 4). Compared with participants who did not have periodontitis, participants with stages III and IV periodontitis had a significant increased risk of hypertension (odds ratio [OR] =

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1.70, 95% confidence interval [CI] = 1.45-1.99, p < 0.001). However, the difference between participants with stages I and II periodontitis and participants without periodontitis was not statistically significant (OR = 1.03, 95% CI = 0.88-1.20, p = 0.717). Therefore, hypertension prevalence increased with periodontitis severity. Notably, the OR for participants with stages III and IV periodontitis decreased with age; it was not statistically significant in participants aged 65-74 years (Table 4).

Table 4. Relationships between blood pressure (hypertension vs. normotension) and periodontal status (compared with non-periodontitis) according to the 2017 classification analyzed by logistic regressions with adjustment for gender, smoking status, region, years of education, and annual family income

Age group	Periodontal stauts*	OR	95% CI	p
35-44 years	Periodontitis (stage III & IV)#	1.62	1.00~2.61	0.050
	Periodontitis (stage I & II)#	0.97	0.65~1.43	0.863
55-64 years	Periodontitis (stage III & IV)#	1.40	1.07~1.84	0.015
	Periodontitis (stage I & II)#	1.30	1.00~1.69	0.051
65-74 years	Periodontitis (stage III & IV)#	1.21	0.96~1.42	0.113
	Periodontitis (stage I & II)#	1.12	0.96~1.42	0.336
Total	Periodontitis (stage III & IV)#	1.70	1.45~1.99	< 0.001
	Periodontitis (stage I & II)#	1.03	0.88~1.20	0.717

* According to the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions [17].

Relationships of hypertension with periodontal parameters

Table 5 and Table 6 present the multivariate regression analyses of the relationships of hypertension with periodontal parameters, after adjustments for sex, smoking status,

region, duration of education, and annual family income. Hypertension prevalence increased with increases in the proportions of teeth with BOP (OR = 1.20, 95% CI = 1.05-1.38, p = 0.006), PD ≥ 4 mm (OR = 1.73, 95% CI = 1.43-2.10, p < 0.001), and PD ≥ 6 mm (OR = 2.44, 95% CI = 1.19-5.03, p = 0.015), but it decreased with increases in the proportions of teeth with AL ≥ 4 mm (OR = 0.87, 95% CI = 0.73-1.05, p = 0.155) and AL ≥ 6 mm (OR = 0.74, 95% CI = 0.53-1.04, p = 0.083). There were significant positive associations of hypertension with the number of teeth with BOP (OR = 1.01, 95% CI = 1.00-1.01, p = 0.001), PD ≥ 4 mm (OR = 1.03, 95% CI = 1.02-1.04, p < 0.001), and PD ≥ 6mm (OR = 1.07, 95% CI = 1.03-1.11, p < 0.001). There were statistically insignificant negative associations of the presence of hypertension with the proportions of teeth with AL ≥ 4 mm and AL ≥ 6 mm (Table 6).

Table 5. Relationships between blood pressure (hypertension vs. normotension) and percentage of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

Periodontal parameter	OR*	95% CI	p
BOP+	1.20	1.05~1.38	0.006
PD≥ 4mm	1.73	1.43~2.10	< 0.001
PD≥ 6mm	2.44	1.19~5.03	0.015
AL≥ 4mm	0.87	0.73~1.05	0.155
AL≥ 6mm	0.74	0.53~1.04	0.083

AL= attachment loss; BOP = bleeding on probing; PD = probing depth;

* The odds ratio as periodontal parameter increased by one percent (for example, as BOP+% increases by 1%, the odds of hypertension increase by 20%, in another word,

1.20 minus 1) [18,19].

Table 6. Relationships between blood pressure (hypertension vs. normotension) and number of teeth affected with different threshold of periodontal parameters analyzed by logistic regressions with adjustment for age, gender, smoking status, region, years of education, and annual family income.

Periodontal parameter	OR*	95% CI	p
BOP+	1.01	1.00~1.01	0.001
PD≥ 4mm	1.03	1.02~1.04	< 0.001
PD≥ 6mm	1.07	1.03~1.11	< 0.001
AL≥ 4mm	1.00	0.99~1.01	0.507
AL≥ 6mm	0.99	0.97~1.01	0.217

AL= attachment loss; BOP = bleeding on probing; PD = probing depth.

* The odds ratio as periodontal parameters increased by one percent (for example, as BOP+% increases by one tooth, the odds of hypertension increase by 1%, in another word, 1.01 minus 1) [18,19].

Significantly more teeth were missing in hypertensive participants than in normotensive participants

Table S1 presents a comparison of the number of missing teeth between participants with and without hypertension. Significantly more teeth were missing in hypertensive participants than in normotensive participants (4.4 vs. 2.9 teeth). The difference in the number of missing teeth between hypertensive and normotensive participants decreased with age. The differences in missing teeth between hypertensive and normotensive participants were generally consistent in males and females, and among current smokers, former smokers, and non-smokers.

DISCUSSION

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Based on data from the Fourth National Oral Health Survey of China, periodontitis is significantly and strongly associated with hypertension among Chinese adults, independent of the effects of age, sex, and smoking. The association between periodontitis and hypertension reported in this study is in agreement with that recently reported reviews [20,21]. This association between periodontitis and hypertension has considerable importance [22].

In recent systemic reviews analyzing the association between periodontitis and hypertension, the included studies had been conducted in different countries across Asia, Europe, America, and Africa, lacking the large-scale data from China [20,21]. In this study, we used data from a large-scale national survey in which participants were representative of the Chinese population. Besides, the lack of consistent measures of case definition and severity of periodontitis in the retrieved studies did not allow for a relevant analysis of extent and severity of periodontitis with hypertension. In the present study, periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop. The association of hypertension with periodontitis was assessed according to age and smoking status to minimize errors and the effects of confounding factors. Periodontitis was associated with an increase prevalence of hypertension among Chinese adults, independent of known confounders. In most of the studies, periodontal status was clinically evaluated through PD and/or clinical attachment level measurement [20,21]. Nevertheless, several definitions of periodontal diseases have been used across studies and only a few have distinguished severe forms of periodontitis. In the present study, periodontitis severity was defined

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using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. Participants with severe periodontal disease (stages III and IV periodontitis) had an increased risk of hypertension compared with participants who had mild or no periodontal disease.

Hypertension prevalence increased with periodontitis severity, particularly among young participants (35-44 years). Therefore, participants with risk factors, particularly young adults, should engage in healthy lifestyle habits to improve their oral health. Accordingly, there is a need to improve the education and awareness of dental treatment and preventive management among individuals at risk for hypertension, particularly in younger population. Periodontitis and hypertension are chronic diseases; therefore, substantial exposure time may be necessary for their development. The exposure time to risk factors may be considerably shorter in younger individuals than that in older individuals. The influence of the longer exposure time to the common risk factors for periodontitis and hypertension in older individuals may mask the effects of periodontitis on the development of hypertension. When the confounding effects of the risk factors were removed, a link between periodontitis and hypertension was identified. Therefore, severe periodontitis may have a greater role in the development of hypertension among younger individuals than among older individuals. The association of periodontitis with hypertension was also present in never smokers and former smokers, who had less exposure to common risk factors. The greater susceptibility to hypertension among young individuals with severe periodontitis may be attributed to periodontal inflammation.

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This study evaluated the association between periodontal status and hypertension risk among young and older adults. Hypertension prevalence increased with periodontitis severity, which was most prominent in individuals aged 35-44 years. Adult aged < 65 years with hypertension had significantly greater risks of stages III and IV periodontitis, compared with individuals who did not have hypertension. Therefore, healthcare providers should carefully monitor oral health status in their patients to prevent hypertension, particularly among adults; they should conduct regular oral examinations and engage in periodontal disease management.

This study exhibited the percentage of teeth with each periodontal status that means extension of periodontal pathology in the oral cavity. The association between periodontitis and hypertension was also present in participants who had a greater proportion of teeth with BOP or deep periodontal pockets. The findings suggest that severe and extensive periodontal inflammation, as evidenced by the depth of the inflamed periodontal pocket and the number of bleeding sites, is associated with hypertension. In particular, the presence of BOP indicates acute inflammation, which may lead to systemic effects and subsequent hypertension. The association of inflammation (i.e., PD) with hypertension suggests that persistent, long-term, and extensive inflammation may also underlie this relationship. Compared with AL, PD seems to be more closely related to hypertension. For example, significant differences of the percentages/numbers of PD≧4mm and 6mm in 55-64 years were seen between hypertensive and normotensive individuals, but not in the percentages/numbers of AL ≧4mm and 6mm (Table 2 and 3). This is because AL is more related to periodontal

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attachment damage, while PD is more related to the existing periodontal inflammation. This also indicates that the correlation between periodontitis and hypertension may be related to the increase of systemic inflammation. Our study adds to the existing literature concerning oral health parameters associated with systemic outcomes [23, 24]. BOP and PD are the most appropriate clinical measures when the outcome of interest is an acute disease, whereas AL is more strongly correlated with chronic systemic conditions [21]. Our findings of an association between hypertension and the severity of periodontal inflammation (BOP and PD) are consistent with the results of previous studies [12, 18]. Although the causality of the observed association remains unclear, several hypotheses have been proposed, including endothelial dysfunction, oxidative stress, worsening of systemic inflammation in response to bacteremia, and dissemination of inflammatory mediators from periodontal pockets, particularly BOP [25]. This association is further supported by the results of a randomized clinical trial that showed short-term benefits of periodontal therapy on hypertension [26]. Additionally, a recent study identified oral pathogens associated with high or uncontrolled BP, which supports our findings [27].

Our finding of an association between the number of missing teeth and hypertension is consistent with the results reported by Taguchi et al [28]. Missing teeth are indicative of poor oral health; they presumably were lost because of caries and periodontal disease. Thus, the absence of several teeth suggests the presence of severe periodontal disease, caries, or other oral health problems; these may have contributed to the increased risk of hypertension. This association was strongest in younger adults. There were no

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residual confounding effects of age that may have affected our study results. Because of the high prevalence of hypertension in Chinese adults, further studies are needed to clarify the association between periodontitis and hypertension. Moreover, attention is needed concerning the prevention and treatment of periodontitis in the general population.

There is minimal knowledge concerning the natural history of the association between periodontal disease and hypertension [29-33]. A significant linear trend was observed between the severity of periodontal disease and hypertension in a cross-sectional study of 3,352 patients with periodontal disease and 902 controls [31]. A recent prospective cohort study of Japanese individuals demonstrated an increased incidence of hypertension among participants with periodontal pockets ≥ 4 mm at baseline [32]. Our findings are consistent with the results in a similar study of 6,617 men and 7,377 women who underwent dental examinations as part of the NHANES III in the USA [34]. In the present study, after multivariate adjustment, gingival bleeding (BOP) was associated with an increased risk of hypertension, whereas periodontitis severity (defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions) and PD were positively associated with hypertension. Participants with severe periodontal disease (stages III and IV periodontitis) had an increased risk of hypertension compared with participants who had mild or no periodontal disease. Furthermore, there was a threshold relationship between severe periodontal disease and hypertension.

To our knowledge, the present study is one of few concerning the association between

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periodontal disease and hypertension in a large sample of Chinese adults, after adjustments for potential confounders. The assessment of extent of pathological condition for periodontal disease is thought to be important, however, the most severe pathological condition in the oral cavity is assessed in many studies. In this study, the extent of pathological condition for periodontal disease in the oral cavity was assessed the percentage of teeth with each periodontal status. In addition, we evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.

The main limitation of the present study was that hypertension was self-report and not based on blood pressure measurements, which is inherent to any epidemiological cohort study. However, field measurements of blood pressure are regarded as validated tools, have been used in previous studies [23, 25], and are considered useful for the analysis of large samples. Furthermore, although recall and reporting bias could not be excluded, the results largely reflect real-world clinical practice. First, the self-reported diagnosis was based on a face-to-face interview to ensure the validity and accuracy of the information. Second, the reliability of the study results is supported by data from the China Hypertension Survey (2012-2015) [35], which showed an overall hypertension prevalence of 23.2% in the Chinese adult population; this prevalence is similar to the prevalence observed in our study (23.9%).

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In summary, our epidemiological analysis revealed an association between periodontitis and hypertension. We collected high-quality, large-scale clinical data related to periodontal disease and hypertension. We also collected detailed information regarding potential confounders, including variables that reflect health behavior (e.g., flossing). However, there was no strong evidence of a causal relationship. Future studies should be conducted to improve the understanding of the underlying mechanisms and interactions between periodontitis and hypertension, which will further strengthen collaborations between the dental and medical communities. Preventive measures for periodontal disease in oral health promotion programs should be emphasised to improve systemic health outcomes.

Contributorship statement

YZ is the major contributor in writing the manuscript and participates in data analysis and collation. JJ participates in data analysis and collation. WJ participates in writing the manuscript. XF, BT, DH, HL, BW, CW, SZ, XL, WR, WW, XW, and YS conceive the study design and draft the protocol. HM conceives the study design, drafts the protocol, and revise the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interests.

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Data sharing statement

This study is based on the data of the Fourth National Oral Health Survey of China (2015-2016), which was provided by the Chinese Stomatological Association.

Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

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Table S1. Number of missing teeth by gender, age groups and smoking status

Group	NT		HT		p*
	Mean	95% CI	Mean	95% CI	
Male	3.0	2.9~3.2	4.5	4.2~4.8	<0.001
Female	2.8	2.7~3.0	4.2	4.0~4.5	<0.001
35-44 years	0.7	0.7~0.7	1.0	0.7~1.3	0.024
55-64 years	3.3	3.1~3.4	3.4	3.2~3.7	0.305
65-74 years	6.0	5.8~6.3	5.7	5.4~6.0	0.104
Current smoker	2.7	2.6~2.8	4.2	3.9~4.4	<0.001
Non-smoker	3.3	3.1~3.5	4.3	3.9~4.7	<0.001
Former smoker	3.5	3.2~3.9	5.3	4.7~6.0	<0.001
Total	2.9	2.8~3.0	4.4	4.2~4.6	<0.001

HT = Hypertension; NT = Normotension;

* significant difference by Student's t test.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	10-13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey of China (2015-2016)

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Association between Periodontitis and Hypertension: Cross-Sectional Survey from the Fourth National Oral Health Survey of China (2015-2016)

Running title: Association between periodontitis and hypertension

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ABSTRACT

Objectives To evaluate the association between periodontitis severity and hypertension based on Chinese epidemiological data.

Design This cross-sectional survey enrolled adults from the Fourth National Oral Health Survey of China (2015-2016).

Setting The data were obtained from the Fourth National Oral Health Survey of China (2015-2016).

Participants The study included individuals aged 35-44 years (n = 4,409), 55-64 years (n = 4,568), and 65-74 years (n = 4,218).

Primary and secondary outcome measures Periodontal status, defined on the basis of the 2017 classification scheme, and periodontal parameters (e.g., bleeding on probing [BOP]) were compared between hypertensive and normotensive individuals. Smoothed scatterplots were constructed to demonstrate the associations of periodontal parameters and periodontal status with hypertension.

Results Severe periodontitis (stages III and IV) was present in 41.4% and 28.0% of hypertensive and normotensive individuals, respectively ($p < 0.001$). The prevalence of severe periodontitis was higher in hypertensive individuals than that in normotensive individuals among participants aged 35-44 years (18.0% vs. 10.1%, $p < 0.001$) and 55-64 years (40.2% vs. 36.7%, $p = 0.035$), but not in participants aged 65-74 years (46.4% vs. 45.1%, $p = 0.429$). Therefore, the difference in periodontal status between hypertensive and normotensive individuals decreased with age. There were higher prevalences of BOP, probing depth [PD] ≥ 4 mm, and PD ≥ 6 mm in hypertensive individuals than in normotensive individuals (52.1% vs. 49.2%, 19.6% vs. 14.7%, and 1.8% vs. 1.1%, respectively). Periodontitis severity and the proportion of teeth with PD ≥ 4 or ≥ 6 mm were positively associated with hypertension.

Conclusion Periodontitis is associated with hypertension in Chinese adults. Hypertension prevalence increased with periodontitis severity, particularly among young participants. Accordingly, it is necessary to improve the education, awareness of periodontal treatment, and preventive management among individuals at risk of hypertension, particularly in the younger population.

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Key Words: Hypertension, oral medicine, epidemiology, public health.

Strengths and limitations of this study

- The participant group was based on a large-scale national survey in China, and the sample size of the study was relatively large.
- Periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop.
- Hypertension was self-reported and not based on blood pressure measurements.

INTRODUCTION

Hypertension, which affects 45% of the global population, is the most common cardiovascular diseases (CVDs) worldwide.[1 2] It is defined as systolic or diastolic blood pressure (BP) of ≥ 140 or ≥ 90 mmHg, respectively. Hypertension is frequently poorly controlled and untreated.[3] It is a complex disease with multiple causes and a major risk factor for CVDs.[4] Oxidative stress, endothelial dysfunction, and inflammation are associated with the development of hypertension.[5] The results of experimental and clinical studies suggest that inflammation has a major role in the development of hypertension.[6] Chronic inflammation predisposes to the development of pro-hypertensive inflammation.

Periodontal disease, an immune-inflammatory reaction to plaque biofilms,[7] has received substantial attention because of its association with CVDs. The Global Burden of Disease Study revealed that periodontitis was the sixth most prevalent disease

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worldwide. Periodontitis affects 743 million people worldwide (11.2% of the global population); the prevalence is higher in China than in other countries. The Fourth National Oral Health Survey of China showed that 90.9% of individuals aged 35-44 years had periodontal disease.[8] [9] The low-grade inflammation associated with periodontitis has harmful effects on endothelial function, which may result in hypertension.[10] A recent study revealed that individuals with periodontitis have increased risks of hypertension and antihypertensive treatment failure.[11] [12] Previous studies have suggested that dental treatment can improve blood pressure, although the findings have been inconclusive and further studies are needed.[13-16]

Periodontitis and hypertension are major health problems, and their association received considerable public health attention. Therefore, we evaluated the relationship between periodontitis and hypertension based on data from the Fourth National Oral Health Survey of China. We sought to determine whether individuals with periodontitis are more likely to have hypertension than are individuals who do not have periodontitis and whether periodontitis severity is associated with hypertension.

MATERIALS AND METHODS

Study design and sample

This cross-sectional study obtained data from adult participants of the Fourth National Oral Health Survey of China (2015-2016).[8] The planned sample size was 4,230 each for the age groups 35-44, 55-64 and 65-74 years. We excluded data from edentulous participants and from those without complete information. Finally, 13,195 individuals

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were included (4,409, 4,568, and 4,218 individuals aged 35-44, 55-64, and 65-74 years, respectively).

Data collection

We collected data related to oral examination findings and questionnaire answers.

1. *Periodontal examination*

Periodontal examinations were performed using a community periodontal index probe. A full-mouth examination was performed, during which the probe was walked along the gingival crevices using a force of ≤ 20 g to assess bleeding on probing (BOP), the presence of calculus, probing depth (PD), and attachment loss (AL). For each parameter, each tooth was scored according to the condition of the most severely affected site. Training programs were conducted for examiner calibration before the survey. The reliability of the results was assessed using kappa values; kappa values for periodontal pocket depth were ≥ 0.6. Additionally, 5% of the participants were randomly selected for assessment of inter-examiner reproducibility. The kappa values for all age-groups were 0.76-0.80.

Patient and public involvement

The study participants and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Study parameters

Supragingival and subgingival calculus were identified by visual examination and probing, respectively (0 = absent, 1 = present, 9 = tooth excluded, and X = tooth not present). PD was recorded as 0 (1–3 mm), 1 (4–5 mm), 2 (≥ 6 mm), 9 (tooth excluded),

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or X (tooth not present). BOP was recorded as 0 (absent), 1 (present), 9 (tooth excluded), or X (tooth not present). AL was measured as the distance from the cementoenamel junction to the bottom of the periodontal pocket; it was recorded as 0 (0–3 mm), 1 (4–5 mm), 2 (6–8 mm), 3 (9–11 mm), 4 (≥ 12 mm), 9 (tooth excluded), or X (tooth not present).

The classification scheme proposed at the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions was used to classify the periodontal status as periodontally healthy (< 10% BOP-positive sites and PD ≤ 3 mm) or gingivitis (≥ 10% BOP-positive sites and PD ≤ 3 mm). Periodontitis was staged using the algorithm developed by Tonetti *et al*.[17] For each tooth, periodontitis of stages I-III were defined as AL of 1–2 mm, 3–4 mm, and ≥ 5 mm, respectively. We also considered the number of teeth lost when classifying periodontitis: stages I and II, no tooth loss; stage III, ≤ 4 teeth lost; and stage IV, ≥ 5 teeth lost. The cause of tooth loss was not considered. Finally, we evaluated the complexity of patient management. Stage II patients were reclassified as stage III if the maximum PD was ≥ 6 mm. Stage III patients were reclassified as stage IV if there were < 10 opposing pairs of teeth). The stages of periodontitis reflect the severity and complexity of managing the individual patient.

2. *Interview data from the questionnaire*

Questionaries were administered during in-person interviews to collect data regarding demographics, socioeconomic status, habits, dental history, and health attitudes. The following information was collected for analysis: age (years), annual family income (in

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increments of 10,000 yuan), sex (male or female), duration of education (years), self-reported hypertension (yes or no), smoking status (current smoker, former smoker, or non-smoker), and region (urban or rural).

Statistical analyses

Statistical analyses were performed using SPSS (version 19; IBM Corp., Armonk, NY, USA) or R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). The primary outcome was periodontal status (health, gingivitis, and stages I-IV periodontitis). The secondary outcomes were periodontal parameters (BOP-positive teeth, teeth with PD ≥ 4 and ≥ 6 mm, and teeth with AL ≥ 4, ≥ 6, and ≥ 9 mm, presented as the percentages and numbers of teeth affected) and missing teeth. First, descriptive analysis was performed. Quantitative data are reported as means and standard deviations; categorical data are reported as numbers and percentages. Periodontal parameters were compared between hypertensive and normotensive individuals; subgroup analyses were conducted according to age group and smoking status. Periodontal status and parameters were analyzed using the Chi-square test. Additionally, smoothed scatterplots based on generalized additive models were constructed, with adjustment for confounders (gender, smoking status, region, duration of education, and annual family income), to evaluate the relationships of hypertension prevalence with periodontal status or parameters. The level of statistical significance was set at $p < 0.05$.

RESULTS

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The participants were randomly selected from 31 provinces, autonomous regions, and municipalities in mainland China. In total, data from 13,195 individuals were included in the analysis; invalid data from five participants and data from 264 edentulous patients were excluded. The mean participant age was 56.43 ± 12.40 years. The sample consisted of 6,575 men (49.8%) and 6,620 women (50.2%). There were 3,470 non-smokers (26.3%), 8,405 current smokers (63.7%), and 1,318 former smokers (10.0%). Hypertension was present and absent in 3,154 (23.9%) and 10,041 (76.1%) participants, respectively.

Differences in periodontal status between hypertensive and normotensive participants decreased with age

Table 1 presents the distributions of periodontal status according to age, gender, and smoking status in participants with and without hypertension.

Significantly greater proportions of hypertensive participants had stages I-IV periodontitis (70.3 % vs. 61.5%, $p < 0.001$) and severe periodontitis (stages III-IV, 41.4 % vs. 28.0%, $p < 0.001$), compared with normotensive participants. Stratified analysis according to gender showed that the prevalence of periodontitis (stages I-IV) was significantly higher in hypertensive participants than in normotensive participants in females (66.5 % vs. 55.9 %, $p < 0.001$), but not in males (74.0 % vs. 67.1%, $p = 0.057$). Severe periodontitis (stages III and IV) was more common in hypertensive participants than in normotensive participants in both males (46.1% vs. 32.7 %, $p < 0.001$) and females (36.6 % vs. 23.4 %, $p < 0.001$). Stratified analysis according to age showed

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that the prevalence of periodontitis (stages I-IV) was significantly higher in hypertensive participants than in normotensive participants among individuals aged 35-44 years (59.2% vs. 52.3%, p = 0.030), 55-64 years (72.7% vs. 69.1%, p = 0.023), and 65-74 years (70.3% vs. 66.2%, p = 0.009). Severe periodontitis (stages III and IV) was more common in hypertensive participants than in normotensive participants among individuals aged 35-44 years (18.0% vs. 10.1%, p < 0.001) and 55-64 years (40.2% vs. 36.7%, p = 0.035), but not among individuals aged 65-74 years (46.4% vs. 45.1%, p = 0.429). Therefore, differences in periodontal status between hypertensive and normotensive participants decreased with age (Table 1). Stratified analysis according to smoking status showed that the prevalence of periodontitis (stages I-IV) was significantly higher in hypertensive participants than in normotensive participants among current smokers (76.2 % vs. 68.1%, p = 0.016) and non-smokers (67.3 % vs. 57.4%, p < 0.001), but not in former smokers (73.8 % vs. 70.6%, p = 0.972). Severe periodontitis (stages III and IV) was more common in hypertensive participants than in normotensive participants in all three sub-groups: current smokers (48.4% vs. 34.7%, p < 0.001), non-smokers (36.9% vs. 23.7%, p < 0.001), and former smokers (50.2 % vs. 38.0%, p < 0.001).

Table 1. Comparison of distribution of periodontal status according to the 2017 classification by age/gender group between hypertensive and normotensive participants.

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	Periodontal status	N	HT Percentage (95% CI)	N	NT Percentage (95% CI)	p1*	p2#
Male	Health	598	11.1~12.9	159	8.7~11.7	0.057	< 0.001
	Gingivitis	1051	19.9~22.1	246	14.0~17.6		
	Stage I	844	15.8~17.9	171	9.5~12.6		
	Stage II	883	16.6~18.7	266	15.2~18.9		
	Stage III	906	17.0~19.2	357	20.8~25.0		
	Stage IV	730	13.6~15.6	364	21.2~25.4		
Female	Health	755	14.1~16.0	179	9.8~12.9	< 0.001	< 0.001
	Gingivitis	1461	27.8~30.3	355	20.3~24.4		
	Stage I	867	16.2~18.3	199	10.9~14.2		
	Stage II	770	14.3~16.3	277	15.6~19.3		
	Stage III	588	10.8~12.6	260	14.6~18.2		
	Stage IV	586	10.8~12.6	323	18.4~22.3		
35-44 years	Health	658	14.8~17.1	40	10.7~18.9	0.030	< 0.001
	Gingivitis	1312	30.3~33.2	73	21.4~31.8		
	Stage I	1133	26.1~28.8	70	20.4~30.6		
	Stage II	612	13.8~15.9	44	11.9~20.5		
	Stage III	360	7.9~9.6	40	10.7~18.9		
	Stage IV	57	1.1~1.8	10	1.9~6.3		
55-64 years	Health	347	9.6~11.7	116	7.5~10.6	0.023	0.035
	Gingivitis	661	18.9~21.6	239	16.4~20.6		
	Stage I	403	11.2~13.5	174	11.7~15.4		
	Stage II	658	18.8~21.5	247	17.0~21.3		
	Stage III	659	18.8~21.5	273	18.9~23.3		
	Stage IV	544	15.4~17.9	247	17.0~21.3		
65-74 years	Health	348	12.0~14.5	182	10.0~13.1	0.009	0.429
	Gingivitis	539	18.9~22.0	289	16.4~20.2		
	Stage I	175	5.7~7.6	126	6.7~9.4		
	Stage II	383	13.2~15.9	252	14.2~17.8		
	Stage III	475	16.6~19.5	304	17.3~21.2		
	Stage IV	715	25.5~28.8	430	25.0~29.4		
Total	Health	1353	12.8~14.2	338	9.7~11.8	< 0.001	< 0.001
	Gingivitis	2512	24.2~25.9	601	17.7~20.4		
	Stage I	1711	16.3~17.8	370	10.6~12.9		
	Stage II	1653	15.8~17.2	543	15.9~18.6		
	Stage III	1494	14.2~15.6	617	18.2~21.0		
	Stage IV	1316	12.5~13.8	687	20.4~23.2		

HT, hypertension; NT, normotension.

* Significance differences in the proportions of periodontitis (stages I-IV) and non-periodontitis (health and gingivitis) between hypertensive and normotensive

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participants according to the Chi-square test;

[#] Significance differences in the proportions of severe periodontitis (stages III and IV) and non-severe-periodontitis (health, gingivitis, stages I and II) between hypertensive and normotensive participants according to the Chi-square test.

Due to the limitation of the publishment format, the percentages of HT group and NT group and the distribution of periodontal status by smoking group are omitted in Table 1. The full table is uploaded as a supplementary material (Table S1).

Periodontal parameters were significantly worse in hypertensive participants than in normotensive participants

Tables 2, S2, 3, and S3 present comparisons of periodontal parameters between hypertensive and normotensive participants. Compared with normotensive participants, hypertensive participants had significantly increased proportions of teeth with BOP (52.1% vs. 49.2%), PD ≥ 4 mm (19.6% vs. 14.7%), PD ≥ 6 mm (1.8% vs. 1.1%), AL ≥ 4 mm (23.6% vs. 17.2%), and AL ≥ 6 mm (6.6% vs. 4.4%). The differences in the percentages of teeth with each periodontal parameter between hypertensive and normotensive participants were consistent in males and females, and among current smokers, former smokers, and non-smokers (except for BOP, which showed no significant difference in males, current smokers and former smokers; and PD ≥ 6 mm, which showed no significant difference in former smokers). Differences in periodontal parameters between hypertensive and normotensive participants decreased with age. The differences in the mean prevalence of PD ≥ 4 mm were consistent in all age

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groups. Compared with normotensive participants, hypertensive participants had significantly more teeth with PD ≥ 4 mm (4.5 vs. 3.5), PD ≥ 6 mm (0.4 vs. 0.2), AL ≥ 4 mm (5.0 vs. 3.8), and AL ≥ 6 mm (1.2 vs. 0.8). The mean number of BOP-positive teeth was not significantly different between hypertensive and normotensive participants (12.4 vs. 12.3). Differences in the mean number of teeth with each periodontal parameter between hypertensive and normotensive participants were consistent in males and females, and among current smokers, former smokers, and non-smokers (except for BOP, which had significant differences in females, and PD ≥ 6 mm, which had no significant difference in former smokers). The difference in the mean number of teeth between hypertensive and normotensive participants decreased with age. Furthermore, differences in the number of teeth with PD ≥ 4 mm and PD ≥ 6 mm sites were consistent in all age groups.

Table 2. Comparison of the percentage of teeth with each periodontal parameter between hypertensive and normotensive participants according to gender, age group.

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Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	50.9	49.9~51.9	52.2	50.4~54.0	0.232
	PD ≥ 4 mm	17.9	17.2~18.6	22.6	21.3~24.0	< 0.001
	PD ≥ 6 mm	1.5	1.3~1.6	2.3	1.9~2.7	< 0.001
	AL ≥ 4 mm	20.9	20.2~21.7	27.5	26.0~28.9	< 0.001
	AL ≥ 6 mm	5.7	5.3~6.1	8.3	7.5~9.1	< 0.001
Female	BOP+	47.4	46.5~48.4	52.1	50.4~53.8	< 0.001
	PD ≥ 4 mm	11.5	11.0~12.0	16.5	15.4~17.6	< 0.001
	PD ≥ 6 mm	0.7	0.6~0.8	1.3	1.0~1.6	< 0.001
	AL ≥ 4 mm	13.5	12.9~14.0	19.8	18.6~20.9	< 0.001
	AL ≥ 6 mm	3.2	2.9~3.4	4.8	4.2~5.4	< 0.001
35-44 years	BOP+	46.5	45.4~47.5	50.5	46.1~54.9	0.096
	PD ≥ 4 mm	10.5	9.9~11.1	15.8	12.8~18.8	0.001
	PD ≥ 6 mm	0.5	0.4~0.6	1.1	0.6~1.6	0.031
	AL ≥ 4 mm	6	5.6~6.4	10.1	7.8~12.4	0.001
	AL ≥ 6 mm	0.8	0.7~0.9	1.6	0.8~2.4	0.053
55-64 years	BOP+	52.5	51.3~53.7	54.0	52.1~56.0	0.188
	PD ≥ 4 mm	17.9	17.1~18.8	20.3	18.9~21.7	0.004
	PD ≥ 6 mm	1.4	1.2~1.6	1.9	1.6~2.2	0.024
	AL ≥ 4 mm	22.1	21.2~22.9	21.5	20.1~22.9	0.543
	AL ≥ 6 mm	5.3	4.9~5.8	5.5	4.8~6.2	0.722
65-74 years	BOP+	49.2	47.9~50.6	50.8	49.1~52.6	0.144
	PD ≥ 4 mm	17.4	16.5~18.3	19.6	18.4~20.8	0.004
	PD ≥ 6 mm	1.5	1.3~1.8	1.8	1.5~2.2	0.188
	AL ≥ 4 mm	28.7	27.6~29.8	27.6	26.3~29.0	0.239
	AL ≥ 6 mm	8.9	8.3~9.6	8.3	7.5~9.1	0.220
Total	BOP+	49.2	48.5~49.9	52.1	50.9~53.4	< 0.001
	PD ≥ 4 mm	14.7	14.3~15.2	19.6	18.7~20.4	< 0.001
	PD ≥ 6 mm	1.1	1.0~1.2	1.8	1.6~2.0	< 0.001
	AL ≥ 4 mm	17.2	16.7~17.7	23.6	22.7~24.5	< 0.001
	AL ≥ 6 mm	4.4	4.2~4.7	6.6	6.0~7.1	< 0.001

AL, attachment loss; BOP, bleeding on probing; HT, hypertension; NT, normotension; PD, probing depth

* Significant difference according to Student's t-test.

Due to the limitation of the publishment format, the comparison of the percentage of teeth with each periodontal parameter between hypertensive and normotensive

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participants according to smoking status are omitted in Table 2. The full table is uploaded as a supplementary material (Table S2).

Table 3. Comparison of the number of teeth with each periodontal parameter between hypertensive and normotensive participants according to gender, age group.

Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	12.7	12.5~13.0	12.3	11.8~12.8	0.111
	PD ≥ 4 mm	4.2	4.0~4.4	5.1	4.8~5.4	< 0.001
	PD ≥ 6 mm	0.3	0.3~0.3	0.5	0.4~0.6	< 0.001
	AL ≥ 4 mm	4.6	4.5~4.8	5.7	5.4~6.0	< 0.001
	AL ≥ 6 mm	1.1	1.0~1.1	1.5	1.3~1.6	< 0.001
Female	BOP+	11.9	11.7~12.1	12.6	12.1~13.0	0.013
	PD ≥ 4 mm	2.7	2.6~2.9	3.8	3.6~4.1	< 0.001
	PD ≥ 6 mm	0.1	0.1~0.2	0.3	0.2~0.3	< 0.001
	AL ≥ 4 mm	2.9	2.8~3.1	4.3	4.0~4.5	< 0.001
	AL ≥ 6 mm	0.6	0.5~0.6	0.9	0.8~1.0	< 0.001
35-44 years	BOP+	12.7	12.4~13.0	13.6	12.4~14.8	0.143
	PD ≥ 4 mm	2.8	2.7~3.0	4.2	3.4~5.0	0.001
	PD ≥ 6 mm	0.1	0.1~0.2	0.3	0.1~0.4	0.036
	AL ≥ 4 mm	1.6	1.5~1.7	2.6	2.0~3.2	0.001
	AL ≥ 6 mm	0.2	0.2~0.2	0.4	0.2~0.6	0.049
55-64 years	BOP+	13.0	12.7~13.3	13.4	12.9~13.9	0.241
	PD ≥ 4 mm	4.2	4.0~4.4	4.8	4.4~5.1	0.005
	PD ≥ 6 mm	0.3	0.2~0.3	0.4	0.3~0.5	0.003
	AL ≥ 4 mm	5.0	4.8~5.2	4.8	4.5~5.1	0.222
	AL ≥ 6 mm	1.1	1.0~1.2	1.1	1.0~1.2	0.914
65-74 years	BOP+	10.9	10.6~11.3	11.5	11.0~11.9	0.051
	PD ≥ 4 mm	3.5	3.3~3.7	4.3	4.0~4.5	< 0.001
	PD ≥ 6 mm	0.3	0.2~0.3	0.4	0.3~0.4	0.042
	AL ≥ 4 mm	5.7	5.4~5.9	5.6	5.3~5.9	0.752
	AL ≥ 6 mm	1.5	1.4~1.6	1.4	1.3~1.5	0.508
Total	BOP+	12.3	12.2~12.5	12.4	12.1~14.8	0.574
	PD ≥ 4 mm	3.5	3.4~3.6	4.5	4.2~4.7	< 0.001
	PD ≥ 6 mm	0.2	0.2~0.2	0.4	0.3~0.4	< 0.001
	AL ≥ 4 mm	3.8	3.7~3.9	5.0	4.8~5.2	< 0.001
	AL ≥ 6 mm	0.8	0.8~0.9	1.2	1.1~1.3	< 0.001

AL, attachment loss; BOP, bleeding on probing; HT, hypertension; NT, normotension;

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PD, probing depth

* Significant difference according to Student's t-test.

Due to the limitation of the publishment format, the comparison of the number of teeth with each periodontal parameter between hypertensive and normotensive participants according to smoking status are omitted in Table 3. The full table is uploaded as a supplementary material (Table S3).

Hypertension prevalence increased with periodontitis severity

Multivariate regression analysis was performed to evaluate the relationship between hypertension and age stratified according to periodontal status, after adjustments for sex, smoking status, region, duration of education, and annual family income (Table 4). Compared with participants who did not have periodontitis, participants with stages III and IV periodontitis had a significantly increased risk of hypertension (odds ratio [OR] = 1.70, 95% confidence interval [CI] = 1.45-1.99, $p < 0.001$). However, the difference between participants with stages I and II periodontitis and participants without periodontitis was not statistically significant (OR = 1.03, 95% CI = 0.88-1.20, $p = 0.717$). Therefore, hypertension prevalence increased with periodontitis severity. Notably, the OR for participants with stages III and IV periodontitis decreased with age; it was not statistically significant in participants aged 65-74 years (Table 4).

Table 4. Relationships between blood pressure (hypertension vs. normotension) and periodontal status (compared with non-periodontitis) according to the 2017

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classification, analyzed by logistic regression after adjusting for gender, smoking status, region, years of education, and annual family income

Age group	Periodontal status*	OR	95% CI	p
35-44 years	Periodontitis (stages III & IV)#	1.62	1.00~2.61	0.050
	Periodontitis (stages I & II)#	0.97	0.65~1.43	0.863
55-64 years	Periodontitis (stages III & IV)#	1.40	1.07~1.84	0.015
	Periodontitis (stages I & II)#	1.30	1.00~1.69	0.051
65-74 years	Periodontitis (stages III & IV)#	1.21	0.96~1.42	0.113
	Periodontitis (stages I & II)#	1.12	0.96~1.42	0.336
Total	Periodontitis (stages III & IV)#	1.70	1.45~1.99	< 0.001
	Periodontitis (stages I & II)#	1.03	0.88~1.20	0.717

* According to the 2017 World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions.[17]

Relationships of hypertension with periodontal parameters

Tables 5 and 6 present the multivariate regression analyses of the relationships of hypertension with periodontal parameters, after adjustments for gender, smoking status, region, duration of education, and annual family income. Hypertension prevalence increased with increases in the proportions of teeth with BOP (OR = 1.20, 95% CI = 1.05-1.38, p = 0.006), PD ≥ 4 mm (OR = 1.73, 95% CI = 1.43-2.10, p < 0.001), and PD ≥ 6 mm (OR = 2.44, 95% CI = 1.19-5.03, p = 0.015), but it decreased with increases in the proportions of teeth with AL ≥ 4 mm (OR = 0.87, 95% CI = 0.73-1.05, p = 0.155) and AL ≥ 6 mm (OR = 0.74, 95% CI = 0.53-1.04, p = 0.083). There were significant positive associations of hypertension with the number of teeth with BOP (OR = 1.01, 95% CI = 1.00-1.01, p = 0.001), PD ≥ 4 mm (OR = 1.03, 95% CI = 1.02-1.04, p < 0.001), and PD ≥ 6 mm (OR = 1.07, 95% CI = 1.03-1.11, p < 0.001).

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There were statistically insignificant negative associations of the presence of hypertension with the proportions of teeth with AL ≥ 4 mm and AL ≥ 6 mm (Table 6).

Table 5. Relationships between blood pressure (hypertension vs. normotension) and percentage of teeth affected by different thresholds of periodontal parameters, analyzed by logistic regression after adjusting for age, gender, smoking status, region, years of education, and annual family income.

Periodontal parameter	OR*	95% CI	p
BOP+	1.20	1.05~1.38	0.006
PD ≥ 4 mm	1.73	1.43~2.10	< 0.001
PD ≥ 6 mm	2.44	1.19~5.03	0.015
AL ≥ 4 mm	0.87	0.73~1.05	0.155
AL ≥ 6 mm	0.74	0.53~1.04	0.083

AL, attachment loss; BOP, bleeding on probing; PD, probing depth

* The odds ratio as the periodontal parameter increased by 1% (for example, as the BOP+% increases by 1%, the odds of hypertension increase by 20%; in other words, 1.20 minus 1). [18 19]

Table 6. Relationships between blood pressure (hypertension vs. normotension) and the number of teeth affected by different thresholds of periodontal parameters, analyzed by logistic regression after adjusting for age, gender, smoking status, region, years of education, and annual family income.

Periodontal parameter	OR*	95% CI	p
BOP+	1.01	1.00~1.01	0.001
PD ≥ 4 mm	1.03	1.02~1.04	< 0.001
PD ≥ 6 mm	1.07	1.03~1.11	< 0.001
AL ≥ 4 mm	1.00	0.99~1.01	0.507
AL ≥ 6 mm	0.99	0.97~1.01	0.217

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AL, attachment loss; BOP, bleeding on probing; PD, probing depth

* The odds ratio as the periodontal parameter increased by 1% (for example, as BOP+% increases by one tooth, the odds of hypertension increase by 1%; in other words, 1.01 minus 1).[18 19]

Significantly more teeth were missing in hypertensive participants than in normotensive participants

Table S4 presents a comparison of the number of missing teeth between participants with and without hypertension. Significantly more teeth were missing in hypertensive participants than in normotensive participants (4.4 vs. 2.9 teeth). The difference in the number of missing teeth between hypertensive and normotensive participants decreased with age. The differences in missing teeth between hypertensive and normotensive participants were generally consistent in males and females, and among current smokers, former smokers, and non-smokers.

DISCUSSION

Based on data from the Fourth National Oral Health Survey of China, periodontitis is significantly and strongly associated with hypertension among Chinese adults, independent of the effects of age, gender, and smoking. The association between periodontitis and hypertension reported here is in agreement with recent reviews.[20 21] This association between periodontitis and hypertension has considerable importance since the high prevalence of both in the population and the serious impact on oral health

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and general health.[22]

In recent systemic reviews analyzing the association between periodontitis and hypertension, the included studies had been conducted in different countries across Asia, Europe, America, and Africa, but large-scale data from China were lacking.[20 21] In this study, we used data from a large-scale national survey in which participants were representative of the Chinese population. In addition, the lack of consistent definitions of case and the severity of periodontitis in the retrieved studies did not allow for a relevant analysis of the extent and severity of periodontitis with hypertension. In the present study, periodontitis was diagnosed in accordance with the classification proposed at the 2017 World Workshop. The association of hypertension with periodontitis was assessed according to age and smoking status to minimize errors and the effects of confounding factors. Periodontitis was associated with a higher prevalence of hypertension among Chinese adults, independent of known confounders. In most studies, periodontal status was evaluated clinically via PD or clinical attachment level measurements.[20 21] Nevertheless, several definitions of periodontal disease have been used across studies, and only a few have distinguished severe forms of periodontitis. In the present study, periodontitis severity was defined using the new 2017 classification mentioned above. Participants with severe periodontal disease (stages III and IV periodontitis) had an increased risk of hypertension compared with participants who had mild or no periodontal disease.

Hypertension prevalence increased with periodontitis severity, particularly among young participants (35-44 years). Therefore, participants with risk factors, particularly

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young adults, should engage in healthy lifestyle habits to improve their oral health. Accordingly, there is a need to improve the education and awareness of dental treatment and preventive management among individuals at risk for hypertension, particularly in the younger population. Periodontitis and hypertension are chronic diseases; therefore, substantial exposure time may be necessary for their development. The exposure time to risk factors may be considerably shorter in younger individuals than in older individuals. The influence of the longer exposure time to the common risk factors for periodontitis and hypertension in older individuals may mask the effects of periodontitis on the development of hypertension. When the confounding effects of the risk factors were removed, a link between periodontitis and hypertension was identified. Therefore, severe periodontitis may have a greater role in the development of hypertension among younger individuals than among older individuals. The association of periodontitis with hypertension was also present in never smokers and former smokers, who had less exposure to common risk factors. The greater susceptibility to hypertension among young individuals with severe periodontitis may be attributed to periodontal inflammation. Periodontitis is a chronic infection that leads to inflammation. Previous evidence suggested the connection between periodontal disease and systemic inflammation, which in turn was associated with an increased risk of hypertension.[13-16] The inflammatory response with periodontal disease has been proposed as one of the factors that induces vascular inflammation leading to endothelial dysfunction and exerts an adverse effect on the regulation of hypertension.[23] After periodontal therapy, endothelial dysfunction is reversible in hypertension patients.[23 24] Periodontal treatment

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can improve the endothelial function effectively.[25] In addition, the periodontal pathogens may directly invade the arterial wall and lead to vascular inflammation.[26] There is growing evidence indicating that periodontitis induces excessive production of reactive oxygen species (ROS) in periodontal tissue.[27-29] The production of ROS increases in response to periodontal inflammation; then ROS enter the systemic circulation.[30] ROS is one of the regulator for vascular inflammation and vasoconstriction.[13 23] It has been reported that high BP was related to the unbalance between ROS production and antioxidant.[23 31 32]

This study evaluated the association between periodontal status and hypertension risk among young and older adults. Hypertension prevalence increased with periodontitis severity, which was most prominent in individuals aged 35-44 years. Adults aged < 65 years with hypertension had significantly greater risks of stages III and IV periodontitis, compared with individuals who did not have hypertension. Therefore, healthcare providers should carefully monitor oral health status in their patients to prevent hypertension, particularly among adults; they should conduct regular oral examinations and engage in periodontal disease management.

This study showed the percentage of teeth of each periodontal status that reflected the extent of periodontal pathology in the oral cavity. The association between periodontitis and hypertension was also present in participants who had a greater proportion of teeth with BOP or deep periodontal pockets. The findings suggest that severe extensive periodontal inflammation, as evidenced by the depth of the inflamed periodontal pocket and the number of bleeding sites, is associated with hypertension.

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In particular, the presence of BOP indicates acute inflammation, which may lead to systemic effects and subsequent hypertension. The association of inflammation (i.e., PD) with hypertension suggests that persistent, long-term, extensive inflammation may also underlie this relationship. Compared with AL, PD seems to be more closely related to hypertension. For example, significant differences in the percentages/numbers of teeth with PD ≥ 4 mm and ≥ 6 mm, but not AL ≥ 4 mm and ≥ 6 mm, in those 55-64 years old were seen between hypertensive and normotensive individuals (Tables 2 and 3). This is because AL is more related to periodontal attachment damage, while PD is more closely related to the existing periodontal inflammation. This also indicates that the correlation between periodontitis and hypertension may be related to the increase in systemic inflammation. Our study adds to the existing literature concerning oral health parameters associated with systemic outcomes.[33 34] BOP and PD are the most appropriate clinical measures when the outcome of interest is an acute disease, whereas AL is more strongly correlated with chronic systemic conditions.[21] Our findings of an association between hypertension and the severity of periodontal inflammation (BOP and PD) are consistent with the results of previous studies.[12 18] Although the causality of the observed association remains unclear, several hypotheses have been proposed, including endothelial dysfunction, oxidative stress, worsening of systemic inflammation in response to bacteraemia, and dissemination of inflammatory mediators from periodontal pockets, particularly BOP.[35] This association is further supported by the results of a randomized clinical trial that showed short-term benefits of periodontal therapy on hypertension.[36] Additionally, a recent study identified oral pathogens

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associated with high or uncontrolled BP, which supports our findings.[37]

Our finding of an association between the number of missing teeth and hypertension is consistent with the results reported by Taguchi et al.[38] Missing teeth are indicative of poor oral health; they presumably were lost because of caries and periodontal disease. Thus, the absence of several teeth suggests the presence of severe periodontal disease, caries, or other oral health problems; these may have contributed to the increased risk of hypertension. This association was strongest in younger adults. There were no residual confounding effects of age that may have affected our study results. Because of the high prevalence of hypertension in Chinese adults, further studies are needed to clarify the association between periodontitis and hypertension. Moreover, attention is needed concerning the prevention and treatment of periodontitis in the general population.

There is minimal knowledge concerning the natural history of the association between periodontal disease and hypertension.[39-43] A significant linear trend was observed between the severity of periodontal disease and hypertension in a cross-sectional study of 3,352 patients with periodontal disease and 902 controls.[41] A recent prospective cohort study of Japanese individuals demonstrated an increased incidence of hypertension among participants with periodontal pockets ≥ 4 mm at baseline.[42] Our findings are consistent with the results in a similar study of 6,617 men and 7,377 women who underwent dental examinations as part of the NHANES III in the USA.[44] In the present study, after multivariate adjustment, gingival bleeding (BOP) was associated with an increased risk of hypertension, whereas periodontitis severity

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(defined using the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions) and PD were positively associated with hypertension. Participants with severe periodontal disease (stages III and IV periodontitis) had a higher risk of hypertension than participants who had mild or no periodontal disease. Furthermore, there was a threshold relationship between severe periodontal disease and hypertension.

To assess the association between the two diseases accurately, several potential confounders were adjusted for, and the associations were evaluated in multiple ways, including not only periodontal severity but also several clinical parameters. The assessment of the extent of the pathological condition in periodontal disease is considered important; however, the most severe pathological condition in the oral cavity has been assessed in many studies. In this study, the extent of the pathological condition of periodontal disease in the oral cavity was assessed using the percentage of teeth of each periodontal status. In addition, we evaluated several clinical measures of periodontal disease that allowed analysis of the relationships between various aspects of periodontal disease and hypertension. We found consistent associations between PD and hypertension. PD may be indicative of poor oral health and periodontal inflammation. When the periodontal tissues are inflamed, the PD increases, allowing more bacteria to accumulate and exacerbating the inflammation.[45] The total surface area of the pocket epithelium in contact with subgingival bacteria and their products in patients with generalised moderate periodontitis is estimated to be approximately the size of an adult hand palm, with even larger exposure areas in cases with more advanced

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periodontal destruction.[46] Therefore, the PD can be used as an indicator of the severity of periodontitis. It was positively associated with hypertension, suggesting a link between inflammation and hypertension.

The main limitation of our study was that hypertension was self-reported and not based on blood pressure measurements, which is inherent to any epidemiological cohort study. However, field measurements of blood pressure are regarded as validated tools, have been used in previous studies,[33 35] and are considered useful for the analysis of large samples. Furthermore, although recall and reporting bias could not be excluded, the results largely reflect real-world clinical practice. First, the self-reported diagnosis was based on a face-to-face interview to ensure the validity and accuracy of the information. Second, the reliability of the study results is supported by data from the China Hypertension Survey (2012-2015),[47] which showed an overall hypertension prevalence of 23.2% in the Chinese adult population; this prevalence is similar to the prevalence observed in our study (23.9%).

In summary, our epidemiological analysis revealed an association between periodontitis and hypertension. We collected high-quality, large-scale clinical data related to periodontal disease and hypertension. We also collected detailed information regarding potential confounders, including variables that reflect health behaviour (e.g., flossing). As this study was a cross-sectional study, we cannot draw a causal relationship between periodontitis and hypertension. Future studies should be conducted to improve the understanding of the underlying mechanisms and interactions between periodontitis and hypertension, which will further strengthen collaborations

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between the dental and medical communities. Preventive measures for periodontal disease in oral health promotion programs should be emphasised to improve systemic health outcomes.

Contributorship statement

YZ contributed largely to writing the manuscript and to the data analysis and collation. JJ participated in the data analysis and collation. WJ helped write the manuscript. XF, BT, DH, HL, BW, CW, SZ, XL, WR, WW, XW, and YS conceived the study design and drafted the protocol. HM conceived the study design, drafted the protocol, and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no conflict of interests.

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Data sharing statement

This study is based on the data of the Fourth National Oral Health Survey of China (2015-2016), which was provided by the Chinese Stomatological Association.

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Ethics approval

The study protocol was approved by the Ethics Committee of the Chinese Stomatological Association (approval no.: 2014-003). Written informed consent was obtained from all participants. This study was performed in accordance with the 2013 revision of the Declaration of Helsinki.

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Table S1. Comparison of distribution of periodontal status according to the 2017 classification by age/gender/smoking group between hypertensive and normotensive participants.

Group	Periodontal status	NT			HT			p1*	p2#
		N	%	95% CI	N	%	95% CI		
Male	Health	598	11.9	11.1~12.9	159	10.2	8.7~11.7		
	Gingivitis	1051	21.0	19.9~22.1	246	15.7	14.0~17.6		<
	Stage I	844	16.8	15.8~17.9	171	10.9	9.5~12.6	0.057	0.
	Stage II	883	17.6	16.6~18.7	266	17.0	15.2~18.9		00
	Stage III	906	18.1	17.0~19.2	357	22.8	20.8~25.0		1
	Stage IV	730	14.6	13.6~15.6	364	23.3	21.2~25.4		
Female	Health	755	15.0	14.1~16.0	179	11.2	9.8~12.9		
	Gingivitis	1461	29.1	27.8~30.3	355	22.3	20.3~24.4		
	Stage I	867	17.2	16.2~18.3	199	12.5	10.9~14.2	<	<
	Stage II	770	15.3	14.3~16.3	277	17.4	15.6~19.3	0.001	0.001
	Stage III	588	11.7	10.8~12.6	260	16.3	14.6~18.2		
	Stage IV	586	11.7	10.8~12.6	323	20.3	18.4~22.3		
35-44 years	Health	658	15.9	14.8~17.1	40	14.4	10.7~18.9		
	Gingivitis	1312	31.8	30.3~33.2	73	26.4	21.4~31.8		
	Stage I	1133	27.4	26.1~28.8	70	25.3	20.4~30.6	0.030	<
	Stage II	612	14.8	13.8~15.9	44	15.9	11.9~20.5		0.001
	Stage III	360	8.7	7.9~9.6	40	14.4	10.7~18.9		
	Stage IV	57	1.4	1.1~1.8	10	3.6	1.9~6.3		
55-64 years	Health	347	10.6	9.6~11.7	116	9.0	7.5~10.6		
	Gingivitis	661	20.2	18.9~21.6	239	18.4	16.4~20.6		
	Stage I	403	12.3	11.2~13.5	174	13.4	11.7~15.4	0.023	0.035
	Stage II	658	20.1	18.8~21.5	247	19.1	17.0~21.3		
	Stage III	659	20.1	18.8~21.5	273	21.1	18.9~23.3		
	Stage IV	544	16.6	15.4~17.9	247	19.1	17.0~21.3		
65-74 years	Health	348	13.2	12.0~14.5	182	11.5	10.0~13.1		
	Gingivitis	539	20.5	18.9~22.0	289	18.3	16.4~20.2		
	Stage I	175	6.6	5.7~7.6	126	8.0	6.7~9.4	0.009	0.429
	Stage II	383	14.5	13.2~15.9	252	15.9	14.2~17.8		
	Stage III	475	18.0	16.6~19.5	304	19.2	17.3~21.2		
	Stage IV	715	27.1	25.5~28.8	430	27.2	25.0~29.4		
Current smoker	Health	346	12.8	11.6~14.2	75	9.7	7.7~11.9		
	Gingivitis	512	19.0	17.6~20.5	110	14.2	11.8~16.7		
	Stage I	423	15.7	14.4~17.1	82	10.6	8.5~12.9	0.016	<
	Stage II	478	17.7	16.3~19.2	134	17.2	14.7~20.0		0.001
	Stage III	491	18.2	16.8~19.7	198	25.5	22.5~28.6		

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	Stage IV	443	16.5	15.1~17.9	178	22.9	20.1~26.0		
Non-smoker	Health	909	14.2	13.3~15.0	221	11.1	9.8~12.6		
	Gingivitis	1825	28.4	27.3~29.5	430	21.6	19.9~23.5		
	Stage I	1167	18.2	17.3~19.1	249	12.5	11.1~14.0	<	<
	Stage II	994	15.5	14.6~16.4	356	17.9	16.3~19.6	0.001	0.001
	Stage III	803	12.5	11.7~13.3	337	17.0	15.4~18.6		
	Stage IV	721	11.2	10.5~12.0	395	19.9	18.2~21.7		
Former smoker	Health	98	10.6	8.7~12.7	42	10.7	8.0~14.1		
	Gingivitis	175	18.9	16.5~21.5	61	15.6	12.3~19.4		
	Stage I	121	13.1	11.0~15.3	39	10.0	7.3~13.2	0.972	<
	Stage II	181	19.5	17.1~22.2	53	13.6	10.4~17.2		0.001
	Stage III	200	21.6	19.0~24.3	82	21.0	17.2~25.2		
	Stage IV	98	10.6	8.7~12.7	42	10.7	8.0~14.1		
Total	Health	1353	13.5	12.8~14.2	338	10.7	9.7~11.8		
	Gingivitis	2512	25.0	24.2~25.9	601	19.0	17.7~20.4		
	Stage I	1711	17.0	16.3~17.8	370	11.7	10.6~12.9	<	<
	Stage II	1653	16.5	15.8~17.2	543	17.2	15.9~18.6	0.001	0.001
	Stage III	1494	14.9	14.2~15.6	617	19.6	18.2~21.0		
	Stage IV	1316	13.1	12.5~13.8	687	21.8	20.4~23.2		

HT, hypertension; NT, normotension.

* Significance differences in the proportions of periodontitis (stages I-IV) and non-periodontitis (health and gingivitis) between hypertensive and normotensive participants according to the Chi-square test;

Significance differences in the proportions of severe periodontitis (stages III and IV) and non-severe-periodontitis (health, gingivitis, stages I and II) between hypertensive and normotensive participants according to the Chi-square test.

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Table S2. Comparison of the percentage of teeth with each periodontal parameter between hypertensive and normotensive participants according to gender, age group, and smoking status.

Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	50.9	49.9~51.9	52.2	50.4~54.0	0.232
	PD ≥ 4 mm	17.9	17.2~18.6	22.6	21.3~24.0	< 0.001
	PD ≥ 6 mm	1.5	1.3~1.6	2.3	1.9~2.7	< 0.001
	AL ≥ 4 mm	20.9	20.2~21.7	27.5	26.0~28.9	< 0.001
	AL ≥ 6 mm	5.7	5.3~6.1	8.3	7.5~9.1	< 0.001
Female	BOP+	47.4	46.5~48.4	52.1	50.4~53.8	< 0.001
	PD ≥ 4 mm	11.5	11.0~12.0	16.5	15.4~17.6	< 0.001
	PD ≥ 6 mm	0.7	0.6~0.8	1.3	1.0~1.6	< 0.001
	AL ≥ 4 mm	13.5	12.9~14.0	19.8	18.6~20.9	< 0.001
	AL ≥ 6 mm	3.2	2.9~3.4	4.8	4.2~5.4	< 0.001
35-44 years	BOP+	46.5	45.4~47.5	50.5	46.1~54.9	0.096
	PD ≥ 4 mm	10.5	9.9~11.1	15.8	12.8~18.8	0.001
	PD ≥ 6 mm	0.5	0.4~0.6	1.1	0.6~1.6	0.031
	AL ≥ 4 mm	6	5.6~6.4	10.1	7.8~12.4	0.001
	AL ≥ 6 mm	0.8	0.7~0.9	1.6	0.8~2.4	0.053
55-64 years	BOP+	52.5	51.3~53.7	54.0	52.1~56.0	0.188
	PD ≥ 4 mm	17.9	17.1~18.8	20.3	18.9~21.7	0.004
	PD ≥ 6 mm	1.4	1.2~1.6	1.9	1.6~2.2	0.024
	AL ≥ 4 mm	22.1	21.2~22.9	21.5	20.1~22.9	0.543
	AL ≥ 6 mm	5.3	4.9~5.8	5.5	4.8~6.2	0.722
65-74 years	BOP+	49.2	47.9~50.6	50.8	49.1~52.6	0.144
	PD ≥ 4 mm	17.4	16.5~18.3	19.6	18.4~20.8	0.004
	PD ≥ 6 mm	1.5	1.3~1.8	1.8	1.5~2.2	0.188
	AL ≥ 4 mm	28.7	27.6~29.8	27.6	26.3~29.0	0.239
	AL ≥ 6 mm	8.9	8.3~9.6	8.3	7.5~9.1	0.220
Current smoker	BOP+	49.7	48.3~51.1	51.3	48.8~53.9	0.286
	PD ≥ 4 mm	19.9	18.9~20.9	24.1	22.2~26.0	< 0.001
	PD ≥ 6 mm	1.6	1.4~1.9	2.4	1.9~3.0	0.007
	AL ≥ 4 mm	22.5	21.4~23.6	28.8	26.7~30.9	< 0.001
	AL ≥ 6 mm	6.6	6.0~7.2	8.8	7.6~10.0	0.001
Non-smoker	BOP+	48.5	47.7~49.4	52.3	50.7~53.8	< 0.001
	PD ≥ 4 mm	12.1	11.6~12.6	17.0	16.0~18.0	< 0.001
	PD ≥ 6 mm	0.7	0.6~0.8	1.4	1.1~1.6	< 0.001
	AL ≥ 4 mm	14.0	13.4~14.5	20.4	19.3~21.4	< 0.001
	AL ≥ 6 mm	3.3	3.0~3.5	5.1	4.6~5.7	< 0.001

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Former	BOP+	51.7	49.4~54.0	53.0	49.4~56.6	0.548
smoker	PD ≥ 4 mm	17.8	16.3~19.4	23.7	20.9~26.5	< 0.001
	PD ≥ 6 mm	1.9	1.4~2.4	2.6	1.8~3.4	0.129
	AL ≥ 4 mm	23.8	27.8~33.6	32.8	28.6~36.9	0.001
	AL ≥ 6 mm	6.2	5.3~7.1	9.4	7.6~11.1	0.002
Total	BOP+	49.2	48.5~49.9	52.1	50.9~53.4	< 0.001
	PD ≥ 4 mm	14.7	14.3~15.2	19.6	18.7~20.4	< 0.001
	PD ≥ 6 mm	1.1	1.0~1.2	1.8	1.6~2.0	< 0.001
	AL ≥ 4 mm	17.2	16.7~17.7	23.6	22.7~24.5	< 0.001
	AL ≥ 6 mm	4.4	4.2~4.7	6.6	6.0~7.1	< 0.001

AL, attachment loss; BOP, bleeding on probing; HT, hypertension; NT, normotension;

PD, probing depth

* Significant difference according to Student's t-test.

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Table S3. Comparison of the number of teeth with each periodontal parameter between hypertensive and normotensive participants according to gender, age group, and smoking status.

Group	Periodontal parameter	NT		HT		p*
		Mean	95% CI	Mean	95% CI	
Male	BOP+	12.7	12.5~13.0	12.3	11.8~12.8	0.111
	PD ≥ 4 mm	4.2	4.0~4.4	5.1	4.8~5.4	< 0.001
	PD ≥ 6 mm	0.3	0.3~0.3	0.5	0.4~0.6	< 0.001
	AL ≥ 4 mm	4.6	4.5~4.8	5.7	5.4~6.0	< 0.001
	AL ≥ 6 mm	1.1	1.0~1.1	1.5	1.3~1.6	< 0.001
Female	BOP+	11.9	11.7~12.1	12.6	12.1~13.0	0.013
	PD ≥ 4 mm	2.7	2.6~2.9	3.8	3.6~4.1	< 0.001
	PD ≥ 6 mm	0.1	0.1~0.2	0.3	0.2~0.3	< 0.001
	AL ≥ 4 mm	2.9	2.8~3.1	4.3	4.0~4.5	< 0.001
	AL ≥ 6 mm	0.6	0.5~0.6	0.9	0.8~1.0	< 0.001
35-44 years	BOP+	12.7	12.4~13.0	13.6	12.4~14.8	0.143
	PD ≥ 4 mm	2.8	2.7~3.0	4.2	3.4~5.0	0.001
	PD ≥ 6 mm	0.1	0.1~0.2	0.3	0.1~0.4	0.036
	AL ≥ 4 mm	1.6	1.5~1.7	2.6	2.0~3.2	0.001
	AL ≥ 6 mm	0.2	0.2~0.2	0.4	0.2~0.6	0.049
55-64 years	BOP+	13.0	12.7~13.3	13.4	12.9~13.9	0.241
	PD ≥ 4 mm	4.2	4.0~4.4	4.8	4.4~5.1	0.005
	PD ≥ 6 mm	0.3	0.2~0.3	0.4	0.3~0.5	0.003
	AL ≥ 4 mm	5.0	4.8~5.2	4.8	4.5~5.1	0.222
	AL ≥ 6 mm	1.1	1.0~1.2	1.1	1.0~1.2	0.914
65-74 years	BOP+	10.9	10.6~11.3	11.5	11.0~11.9	0.051
	PD ≥ 4 mm	3.5	3.3~3.7	4.3	4.0~4.5	< 0.001
	PD ≥ 6 mm	0.3	0.2~0.3	0.4	0.3~0.4	0.042
	AL ≥ 4 mm	5.7	5.4~5.9	5.6	5.3~5.9	0.752
	AL ≥ 6 mm	1.5	1.4~1.6	1.4	1.3~1.5	0.508
Current smoker	BOP+	12.3	11.9~12.7	12.1	11.4~12.8	0.583
	PD ≥ 4 mm	4.6	4.4~4.8	5.5	5.0~6.0	0.001
	PD ≥ 6 mm	0.3	0.3~0.4	0.5	0.4~0.6	0.001
	AL ≥ 4 mm	4.9	4.6~5.1	6.1	5.7~6.6	< 0.001
	AL ≥ 6 mm	1.2	1.1~1.3	1.6	1.4~1.8	0.001
Non-smoker	BOP+	12.3	12.1~12.5	12.6	12.2~13.0	0.159
	PD ≥ 4 mm	2.9	2.8~3.0	3.9	3.7~4.2	< 0.001
	PD ≥ 6 mm	0.2	0.1~0.2	0.3	0.2~0.3	< 0.001
	AL ≥ 4 mm	3.1	3.0~3.2	4.4	4.2~4.6	< 0.001
	AL ≥ 6 mm	0.6	0.6~0.6	0.9	0.8~1.0	< 0.001

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Former	BOP+	12.7	12.1~13.3	12.2	11.3~13.1	0.359
smoker	PD ≥ 4 mm	4.1	3.8~4.5	5.1	4.5~5.8	0.006
	PD ≥ 6 mm	0.4	0.3~0.4	0.5	0.4~0.7	0.069
	AL ≥ 4 mm	5.3	4.9~5.7	5.9	5.3~6.6	0.081
	AL ≥ 6 mm	1.2	1.0~1.3	1.7	1.4~2.0	0.005
Total	BOP+	12.3	12.2~12.5	12.4	12.1~14.8	0.574
	PD ≥ 4 mm	3.5	3.4~3.6	4.5	4.2~4.7	< 0.001
	PD ≥ 6 mm	0.2	0.2~0.2	0.4	0.3~0.4	< 0.001
	AL ≥ 4 mm	3.8	3.7~3.9	5.0	4.8~5.2	< 0.001
	AL ≥ 6 mm	0.8	0.8~0.9	1.2	1.1~1.3	< 0.001

AL, attachment loss; BOP, bleeding on probing; HT, hypertension; NT, normotension; PD, probing depth

* Significant difference according to Student's t-test.

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Table S4. Number of missing teeth by gender, age group and smoking status

Group	NT		HT		p*
	Mean	95% CI	Mean	95% CI	
Male	3.0	2.9~3.2	4.5	4.2~4.8	< 0.001
Female	2.8	2.7~3.0	4.2	4.0~4.5	< 0.001
35-44 years	0.7	0.7~0.7	1.0	0.7~1.3	0.024
55-64 years	3.3	3.1~3.4	3.4	3.2~3.7	0.305
65-74 years	6.0	5.8~6.3	5.7	5.4~6.0	0.104
Current smoker	2.7	2.6~2.8	4.2	3.9~4.4	< 0.001
Non-smoker	3.3	3.1~3.5	4.3	3.9~4.7	< 0.001
Former smoker	3.5	3.2~3.9	5.3	4.7~6.0	< 0.001
Total	2.9	2.8~3.0	4.4	4.2~4.6	< 0.001

HT, hypertension; NT, normotension

* Significant difference by Student's t-test.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	8-9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	10-13

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Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-13
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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