

# The Relationship Between Physical Activity Levels and Periodontal Health Status Among College Students: A Cross-Sectional Study

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**Objective:** This study aimed to investigate the relationship between physical activity levels and periodontal health status among college students in Shanghai, with the goal of informing oral health policy recommendations.

**Methods:** A cross-sectional study was conducted from March 2023 to March 2024 involving 120 university students aged 18–29. Data was collected using the World Health Organization (WHO) oral health survey methods. Periodontal status was assessed using the Community Periodontal Index (CPI), and physical activity was measured with a simplified version of the International Physical Activity Questionnaire (IPAQ). Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM, USA), employing chi-square tests and multivariable logistic regression.

**Results:** Among the participants (77 males, 43 females), 70% met physical activity guidelines. Adjusting for gender, age, tooth brushing frequency, and dental floss use, insufficient physical activity was associated with higher odds of periodontitis (adjusted model: OR = 5.293, 95% CI = 1.334 to 20.993,  $p = 0.018$ ). High-intensity physical activity significantly reduced the incidence of periodontitis ( $p = 0.006$ ), while sedentary behavior showed no significant correlation ( $p = 0.176$ ).

**Conclusion:** Promoting physical activity among college students may enhance periodontal health, underscoring the need to integrate oral and public health initiatives.

**Keywords:** college students, oral health, periodontitis, physical activity, public health

## Introduction

Periodontitis, one of the two major diseases influencing oral health, affects approximately 70% of the population to varying degrees. It damages periodontal tissues such as gums, periodontal ligaments, and alveolar bone, originating from dental plaque. This chronic infectious condition primarily affects the periodontal tissues and encompasses gingivitis and periodontitis.<sup>1</sup> Typical symptoms of gingivitis include bleeding during tooth brushing, halitosis, and gingival swelling. If inflammation persists and affects deeper periodontal tissues, it may progress to periodontitis, characterized by symptoms such as gingival bleeding, gingival recession, tooth mobility, damage to periodontal ligaments, and alveolar bone resorption, eventually leading to tooth mobility or even loss.<sup>2</sup> According to the Fourth National Oral Health Epidemiological Survey of China, the prevalence rates of gingival bleeding and calculus detection in the 15-year-old age group were 64.7% and 73.6%, respectively, while the periodontal health and oral hygiene conditions in the middle-aged and elderly population demonstrated even poorer outcomes.<sup>3</sup>

Periodontitis is not merely a localized infection of the periodontal tissues; it can also trigger systemic inflammatory responses. Inflammatory markers such as C-reactive protein, tumor necrosis factor- $\alpha$ , and interleukin-6 are typically elevated in individuals with periodontitis compared to healthy individuals. These factors may affect insulin sensitivity, thereby impacting blood glucose control levels and increasing the risk of metabolic disorders such as obesity and diabetes.<sup>4</sup> Furthermore, periodontal pathogens

and their toxins may enter bloodstream from deep part within periodontal pockets during chewing or tooth brushing, triggering systemic inflammation or extraoral infections, and may even lead to cardiovascular diseases.<sup>4,5</sup> Additionally, elevated inflammatory factors in patients may directly trigger other inflammatory conditions, such as rheumatoid arthritis.<sup>6</sup> In summary, oral health is closely related to systemic health, and periodontitis may pose a threat to the overall health of the host.

Physical activity refers to bodily movements generated by skeletal muscles that require more energy compared to the basal metabolic state, including activities of daily living, work, rest, exercise, and transportation.<sup>7</sup> According to the recommendations of the WHO, adults aged 18 to 64 should engage in at least 150 minutes of moderate-intensity physical activity per week or 75 minutes of vigorous-intensity physical activity. It is further recommended to achieve over 300 minutes of moderate-intensity physical activity or over 150 minutes of vigorous-intensity physical activity per week, with limitations on prolonged sedentary behavior.<sup>8</sup> Maintaining a moderate level of physical activity helps reduce the risk of developing periodontitis-related conditions such as diabetes, obesity, and anxiety. Additionally, it improves blood circulation, reduces insulin resistance, promotes skeletal muscle health, decreases inflammatory factors and oxidative stress in the body, thereby lowering the risk of periodontitis.<sup>9</sup> Current investigations on the correlation between physical activity levels and periodontal health status predominantly focus on obese or diabetic individuals. Previous clinical analysis and experimental studies have shown a negative correlation between physical activity levels and the incidence of periodontitis.<sup>10–14</sup> Adequate physical activity can reduce levels of inflammatory factors, diminish bone loss, and mitigate loss of epithelial attachment.<sup>10</sup>

Whereas research concerning the relationship between physical activity levels and periodontal health status among college students remains insufficiently explored.<sup>15</sup> Furthermore, the National Oral Health Epidemiological Survey of China did not encompass the age group of college students, leading to inadequate understanding of the oral health status of this population. Statistics indicate that the detection rate of periodontitis among Chinese college students ranges from 20.14% to 57.26%, with gingival bleeding and calculus detection rates as high as 90%.<sup>16</sup> It is projected that by 2024, China will have 11.79 million college graduates, and this sizable cohort will constitute a significant force in societal development. However, the periodontal health issues among college students may have notable repercussions on chewing function, aesthetics, and overall physical and mental well-being.

This study aims to explore the relationship between physical activity levels and periodontal health status among college students, providing a basis for developing oral healthcare policies tailored to this demographic. The findings are expected to help identify strategies for integrating physical activity promotion into oral health interventions, ultimately contributing to improved oral health outcomes and general well-being in this critical population.

## Materials and Methods

### Study Population

This study was approved by the Ethics Review Committee of the Tongji Affiliated Stomatology Hospital (Approval No.: [2023]-SR-25) and adhered to the ethical principles of the Declaration of Helsinki. All participants voluntarily provided written informed consent before enrollment. To respect individual preferences and ensure privacy, undergraduate, master's, and doctoral students were recruited from diverse academic disciplines enrolled in universities between March 2023 and March 2024. Participants were required to be in good general health and free from systemic diseases. Trained researchers performed periodontal examinations and collected demographic and physical activity data through questionnaires. Inclusion and exclusion criteria were defined based on the study objectives.

### Inclusion Criteria

1. College students aged 18–29 years.
2. In good general health, without systemic diseases.
3. Willing to participate and able to provide written informed consent.

### Exclusion Criteria

1. Presence of systemic diseases, including cardiovascular conditions, immune system disorders, or diabetes.
2. Use of immunosuppressive drugs, antibiotics, antioxidants, or anti-inflammatory medications within the past six months.
3. Pregnancy or menstruation (for female participants).

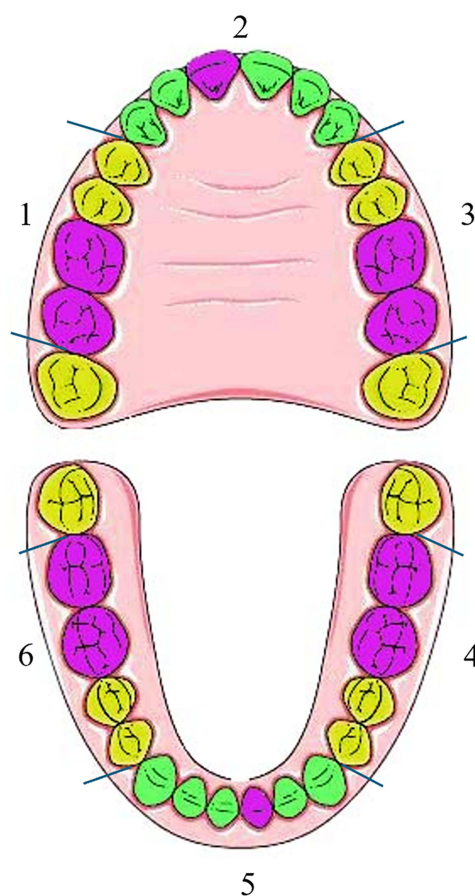
## Methods

### Periodontal Examination

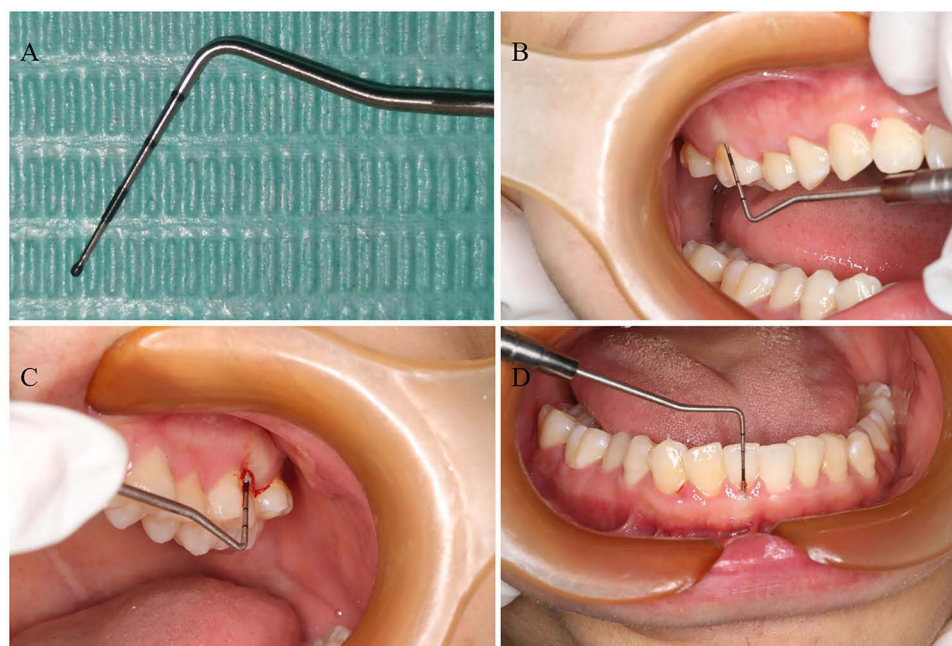
Following the basic methods for oral health surveys established by the WHO, the study employed the WHO-recommended CPI probe and mouth mirror. Under artificial lighting, oral examinations were performed on participants using a combination of visual inspection and probing. This approach was used to measure the CPI and attachment loss (AL).<sup>17</sup>

The CPI probe features a small ball tip with a diameter of 0.5 mm. A black band is present 3.5–5.5 mm from the tip, with additional circular markings at 8.5 mm and 11.5 mm. CPI measurements include 10 index teeth (17, 16, 11, 26, 27, 47, 46, 31, 36, 36, 37) across six regions (17–14, 13–23, 24–27, 37–34, 33–43, 44–47) (Figure 1).<sup>17</sup> During the examination, the CPI probe was gently inserted into the gingival sulcus or periodontal pocket, oriented parallel to the long axis of the tooth, and aligned with the root surface. As the probe moved from distal to mesial along the gingival sulcus, short vertical vibrations were applied to detect subgingival calculus. Simultaneously, gingival bleeding was observed, and the depth of the periodontal pocket was recorded based on the probe scale. Each tooth was examined at six sites: buccal, mesiobuccal, distobuccal, lingual, mesiolingual, and distolingual. Examinations began in the upper right posterior region and progressed clockwise. Attachment loss was assessed as the distance from the cementoenamel junction (CEJ) to the base of the periodontal pocket, measured concurrently with the CPI index (Figure 2).

The CPI index and attachment loss of each index tooth were recorded, and the highest CPI index and attachment loss score of the index teeth were used as the individual's CPI index and attachment loss score, respectively. Each area must have at least two teeth to determine the index. If no index teeth were present, all teeth in that segment were examined. The CPI score was divided into 5 levels: CPI 0: Healthy gums; CPI 1: Gingival bleeding; CPI 2: Presence of plaque (calculus) or subgingival plaque; CPI 3: Periodontal pocket depth of 3–6 millimeters; CPI 4: Presence of plaque



**Figure 1** The six areas and the teeth coded (highlighted in purple) by the Community.



**Figure 2** (A). CPI probe. (B-D). Periodontal examination process.

(calculus) or subgingival plaque, and periodontal pocket depth  $\geq 6$  millimeters. Similarly, attachment loss score was divided into 5 levels: 0 points, 0–3mm (CEJ not visible and periodontal pocket depth less than 6mm); 1 point, 4–5mm (CEJ located within the black portion of the probe); 2 points, 6–8mm (CEJ located between the black quadrant and the 8.5mm mark); 3 points, 9–11mm (CEJ located between the 8.5mm and 11.5mm marks); 4 points, above 12mm (CEJ exceeds the 11.5mm mark). Based on the periodontal condition, the samples were divided into non-periodontitis group (CPI 0 to CPI 2, including normal and gingivitis) and periodontitis group (CPI 3 or CPI 4).<sup>18,19</sup> If the CPI score is 3–4 points or the attachment loss score was  $\geq 1$  point, it indicated the presence of periodontitis and necessitates periodontal treatment.<sup>1</sup>

The sample size was calculated based on the estimated prevalence of periodontitis among Chinese college students, reported to be 57.3% in previous studies.<sup>16</sup> With a 95% confidence level and a margin of error of 5%, the minimum required sample size was determined to be 94 participants. To account for potential non-responses or incomplete data, the sample size increased by 20%, yielding a final sample size of 120. Before the main survey, two dentists completed a calibration training program for CPI measurements. To assess examiner reliability, inter-examiner and intra-examiner reliability tests were conducted using repeated measurements on 10 subjects. Each examiner performed five test-retest measurements for intra-examiner reliability, and five inter-examiner comparisons were conducted between the two dentists. Kappa values for intra-examiner reliability (categorizing CPI scores as 0–2 for non-periodontitis and 3–4 for periodontitis) were 0.85 and 0.93 for the two dentists, respectively. The inter-examiner reliability kappa value between the two dentists was 0.64.

### General Information and Physical Activity Level

General information about the study participants was collected through questionnaires, which included data on age, height, weight, gender, education level, parental education level, and whether they were only children. Lifestyle habits, such as smoking status, alcohol consumption, sleep duration, tooth cleaning methods and frequency, and gingival bleeding during tooth brushing, were also recorded. Body mass index (BMI) was calculated as the ratio of weight (in kilograms) to the square of height (in meters), with the measurement methods and obesity definitions described elsewhere.<sup>17</sup> Physical activity levels were assessed using the IPAQ short form.<sup>20,21</sup> Participants reported the frequency and duration of high-intensity physical activity, moderate-intensity physical activity, walking, and sedentary behavior over the past week. The total time spent on each type of physical activity was converted into metabolic equivalents

(METs) using the following formula: walking (W) = 3.3 METs \* duration, moderate-intensity physical activity (MPA) = 4.0 METs \* duration, and high-intensity physical activity (HPA) = 8.0 METs \* duration. Total physical activity was calculated as the sum of W, MPA, and HPA. According to the intensity standards recommended by the WHO, individuals with a total physical activity metabolic equivalent exceeding 600 METs were classified as meeting the recommended physical activity level. Overall physical activity levels were categorized as low, moderate, or high, based on automatic IPAQ reporting.<sup>22</sup>

### Statistical Analysis

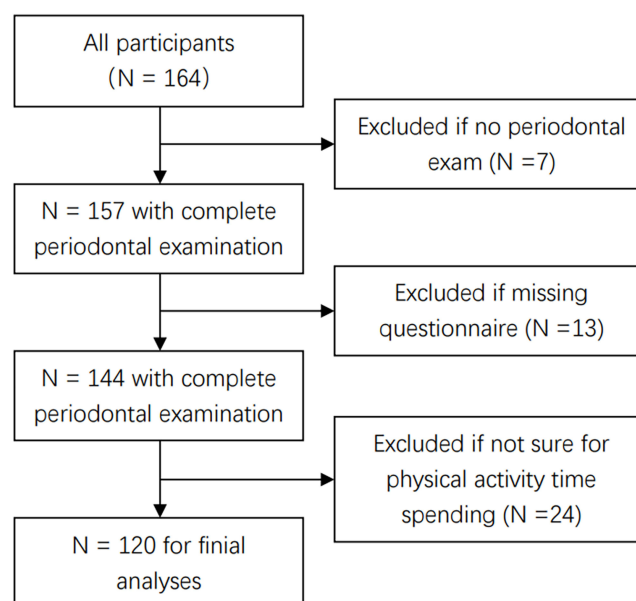
The periodontal examination records obtained in this study were initially recorded on paper by project members and later digitized into electronic format. Questionnaire survey results were directly exported from the online survey platform, and CPI scores were calculated based on these data. Data entry was performed using Excel software, and statistical analyses were conducted with SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Descriptive statistics, including frequencies and percentages, were used to summarize categorical data. Associations between categorical variables were analyzed using chi-square tests. Multivariable logistic regression models were employed to evaluate the association between physical activity levels and periodontal health status, adjusting for potential confounders. Additionally, structural equation modeling was applied to examine potential indirect effects of physical activity on periodontal health. For all analyses, statistical significance was defined as  $p < 0.05$ .

## Result

### Basic Characteristics of the Sample and Association with Periodontitis

The study involved a total of 120 participants (Figure 3). The age ranged from 18 to 29 years old, with a mean age of 22 years old and a standard deviation of 2.07 years old. The association between basic characteristics and the incidence of periodontitis is presented in Table 1. Due to the small number of university students with attachment loss ( $n = 2$ ), this indicator was not included in the statistical analysis. Significant differences in the incidence of periodontitis were observed among demographic groups. The study revealed a significantly higher proportion of periodontitis cases among non-only children compared to only children ( $p = 0.046$ ). There was a significant association between the incidence of periodontitis and toothbrushing frequency, with participants brushing their teeth more than twice a day having a significantly lower risk of periodontitis compared to other groups ( $p < 0.001$ ). Furthermore, the frequency of toothpick use was significantly correlated with the incidence of periodontitis; the more frequently toothpicks were used,



**Figure 3** Flowchart of the study.

**Table 1** Comparison of Demographic Data Among Covariates and the Status and Severity of Periodontal Disease

Characteristic	All (n = 120) (weighted column %)	No Periodontitis (CPI 0–2) N (%)	Periodontitis (CPI 3–4) N (%)	P
<b>Gender</b>				0.967
Male	77 (64.2)	23 (63.9)	54 (64.3)	
Female	43 (35.8)	13 (36.1)	30 (35.7)	
Age (years)	101 (100)			
<b>Only child</b>				0.046
No	54 (45.0)	11 (30.6)	43 (51.2)	
Yes	66 (55.0)	25 (69.4)	36 (48.8)	
<b>Education</b>				1.000
Undergraduate	108 (90.0)	24 (91.7)	65 (89.3)	
Master	11 (9.2)	3 (8.3)	8 (9.5)	
PhD	1 (0.8)	0 (0.0)	1 (1.2)	
<b>Parents' education</b>				0.470
Bachelor's degree or above	39 (32.5)	11 (30.6)	28 (33.3)	
Undergraduate degree and below	81 (67.5)	25 (69.4)	56 (66.7)	
<b>Smoking</b>				0.530
No	103 (85.8)	32 (88.9)	71 (84.5)	
Yes	17 (14.2)	4 (11.1)	13 (15.5)	
<b>Drinking</b>				0.713
No	73 (60.8)	21 (58.3)	52 (61.9)	
Yes	47 (39.2)	15 (41.7)	32 (38.1)	
<b>Sleep duration (hours)</b>				0.633
<6	18 (15.0)	5 (13.9)	13 (15.5)	
6–8	93 (77.5)	27 (75.0)	66 (78.6)	
>8	9 (7.5)	4 (11.1)	5 (6.0)	
<b>BMI index</b>				0.122
<18.5	17 (14.2)	5 (13.9)	12 (14.3)	
18.5–24	72 (60.0)	26 (72.2)	46 (54.8)	
24–28	21 (17.5)	2 (5.6)	19 (22.6)	
>28	10 (8.3)	3 (8.3)	7 (8.3)	
<b>Brushing frequency</b>				<0.001
≥2 times a day	83 (69.2)	34 (94.4)	49 (58.3)	
1 time a day	30 (25.0)	0 (0.0)	30 (35.7)	
2–6 times a week	6 (5.0)	2 (5.6)	4 (4.8)	
Seldom/Never	1 (0.8)	0 (0.0)	1 (1.2)	
<b>Toothpick</b>				0.04
≥2 times a day	4 (3.3)	0 (0.0)	4 (4.8)	
1 time a day	4 (3.3)	3 (8.3)	1 (1.2)	
2–6 times a week	7 (5.8)	3 (8.3)	4 (4.8)	
1 time a week	10 (8.3)	0 (0.0)	10 (11.9)	
1–3 times a month	4 (3.3)	1 (2.8)	3 (3.6)	
Seldom/Never	91 (75.8)	29 (80.6)	62 (73.8)	
<b>Dental floss</b>				0.125
≥2 times a day	13 (10.8)	8 (22.2)	5 (6.0)	
1 time a day	18 (15.0)	4 (11.1)	14 (16.7)	
2–6 times a week	24 (20.0)	9 (25.0)	15 (17.9)	
1 time a week	21 (17.5)	6 (16.7)	15 (17.9)	
1–3 times a month	10 (8.3)	2 (5.6)	8 (9.5)	
Seldom/Never	34 (28.3)	7 (19.4)	27 (32.1)	

the lower the likelihood of periodontitis ( $p = 0.04$ ). No significant associations were found between smoking, alcohol consumption, sleep duration, and periodontitis among college students.

## Periodontitis Induced by Physical Activity and Sedentary Behavior

According to the results in Table 2, individuals who achieved the recommended level of physical activity (greater than 600 METs) had a lower prevalence of periodontitis compared to those who did not meet the standard level of physical activity ( $p = 0.001$ ). Among the three different levels of physical activity, a lower prevalence of periodontitis was significantly associated with a higher intensity of physical activity ( $p = 0.006$ ). Furthermore, individuals with lower overall sedentary behavior had a lower likelihood of periodontitis compared to those with higher overall sedentary behavior, although this relationship was not statistically significant ( $p = 0.176$ ).

## Multivariable Logistic Regression Analysis of the Impact of Physical Activity and Sedentary Behavior on the Odds of Periodontitis Occurrence

According to the results in Table 3, the multivariable logistic regression model revealed an association between whether physical activity met the recommended level and the prevalence of periodontitis. Figures 4 and 5 present the impacts on

**Table 2** Periodontal Disease Status and Severity Stratified by Levels of Physical Activity and Sedentary Behavior

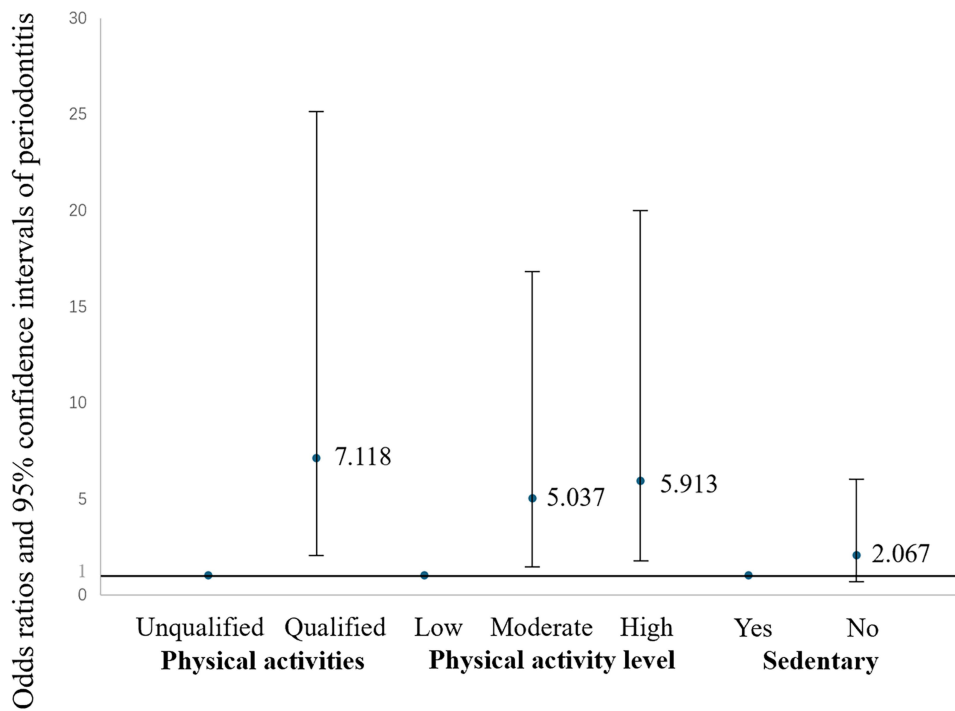
Characteristic	All (n = 120) (weighted column %)	No Periodontitis (CPI 0–2) N (%)	Periodontitis (CPI 3–4) N (%)	P
Physical activities				0.001
Qualified	84 (70.0)	33 (91.7)	51 (60.7)	
Unqualified	36 (30.0)	3 (8.3)	33 (39.3)	
Physical activity level				0.006
High	39 (32.5)	16 (44.4)	23 (27.4)	
Moderate	43 (35.8)	16 (44.4)	27 (32.1)	
Low	38 (31.7)	4 (11.1)	34 (40.5)	
Sedentary				0.176
No	94 (78.3)	31 (86.1)	63 (75.0)	
Yes	26 (21.7)	5 (13.9)	21 (25.0)	

**Table 3** Multivariable Logistic Regression Determining the Odds of Periodontal Disease Occurrence by Physical Activity or Sedentary Behavior

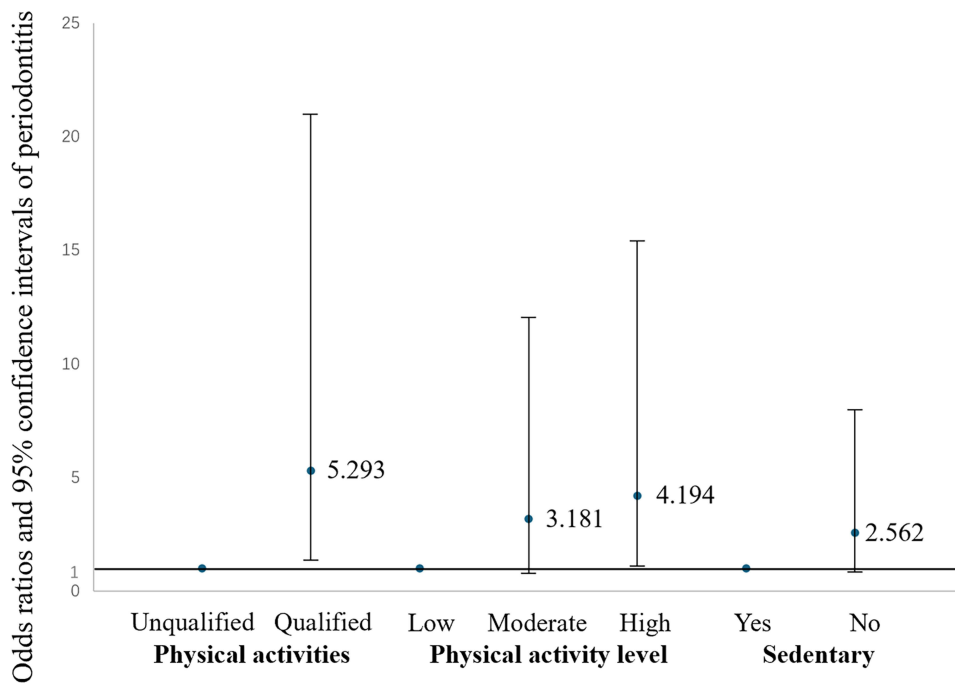
Characteristic	Unadjusted Model		Adjusted Model	
	OR (95% CI)	p	OR (95% CI)	p
Physical activities				
Qualified	7.118 (2.018–25.103)	0.002	5.293 (1.334–20.993)	0.018
Unqualified	I (Ref)		I (Ref)	
Physical activity level				
High	5.913 (1.751–19.963)	0.004	4.194 (1.142–15.403)	0.031
Moderate	5.037 (1.507–16.833)	0.009	3.181 (0.838–12.076)	0.838
Low	I (Ref)		I (Ref)	
Sedentary				
No	2.067 (0.712–6.000)	0.182	2.562 (0.824–7.969)	0.104
Yes	I (Ref)		I (Ref)	

**Note:** I (Ref) = reference; omitted for collinearity.

**Abbreviations:** OR, Odds Ratio; CI, Confidence Interval.



**Figure 4** The effects of physical activity and sedentary behavior on periodontitis before adjusting the model.



**Figure 5** The effects of physical activity and sedentary behavior on periodontitis after adjusting the model.

periodontitis of exercise and sedentary behavior, before and after adjusting the model, respectively. Individuals who did not meet the standard level of physical activity had a higher likelihood of periodontitis (unadjusted model: OR = 7.118, 95% CI = 2.018 to 25.103,  $p = 0.002$ ; adjusted model: OR = 5.293, 95% CI = 1.334 to 20.993,  $p = 0.018$ ). The study found that in the adjusted model, the odds of not having periodontitis among individuals engaged in high-intensity



physical activity were 4.194 times higher than those engaged in low-intensity physical activity (OR = 4.194, 95% CI = 1.142 to 15.403,  $p = 0.031$ ). However, there was no significant association between the prevalence of periodontitis among individuals engaged in moderate-intensity physical activity compared to those engaged in low-intensity physical activity ( $p = 0.089$ ). The unadjusted model also demonstrated a significant association between the intensity level of physical activity and the prevalence of periodontitis. However, there was no significant association between sedentary behavior and the prevalence of periodontitis, regardless of whether covariates were adjusted.

## Discussion

The study revealed that more than half of the university students exhibited varying degrees of periodontitis, highlighting a widespread concern for the periodontal health of this population. The findings demonstrated a significant negative association between physical activity levels and the prevalence of periodontitis among university students in Shanghai. Across all adjusted models, the results consistently indicated that low physical activity levels were associated with a higher incidence of periodontitis. This observation aligns with previous research suggesting that moderate physical activity may help reduce the risk of periodontitis.<sup>9-14</sup> Notably, a significant association was found between high-intensity physical activity and a lower incidence of periodontitis, underscoring the potential role of higher physical activity levels in promoting oral health and preventing periodontal conditions.

Periodontitis is a chronic inflammatory condition primarily affecting the periodontal tissues, with dental plaque identified as its principal cause. Beyond the oral cavity, periodontitis has been linked to various systemic conditions, including cardiovascular disease, diabetes, and obesity.<sup>4-6</sup> These systemic conditions are associated with elevated levels of inflammatory markers such as C-reactive protein, tumor necrosis factor- $\alpha$ , and interleukin-6. Physical activity has been shown to lower these inflammatory markers, potentially reducing the risk of periodontitis.<sup>9</sup> In addition to its systemic effects, physical activity directly supports oral health by enhancing blood circulation and increasing saliva flow. These mechanisms may help reduce dental plaque accumulation and improve immune responses to slow the progression of periodontitis.<sup>10</sup> Although this study found no significant association between sedentary behavior and the prevalence of periodontitis among university students, extensive research suggests that low physical activity levels combined with sedentary behaviors (eg, reading, writing, and driving) heighten the risk of various diseases and adversely affect overall health.<sup>23</sup> Unhealthy sedentary behaviors are associated with risk factors such as poor dietary habits<sup>24</sup> and increased snacking,<sup>25</sup> both of which contribute to dental erosion<sup>26</sup> and elevate the risk of periodontitis.<sup>27</sup> Thus, promoting regular physical activity and minimizing sedentary behavior among university students are essential strategies for preventing periodontitis.

However, not all research findings are consistent with the results of this study. For instance, some studies have reported no significant association between physical activity and periodontitis, suggesting that factors such as genetic predisposition, dietary habits, and oral hygiene practices may have a more substantial impact than physical activity.<sup>28,29</sup> These conflicting findings underscore the multifactorial nature of periodontal health and highlight the need for more comprehensive and nuanced research in this area.

It is also important to acknowledge several limitations of this study. Although the sample size was relatively large and multivariate analysis was employed to adjust for potential confounders, the cross-sectional design precludes any inference of causal relationships. Moreover, as the sample was drawn exclusively from universities within the same region, the findings may have limited generalizability to other populations. Additionally, the assessment of physical activity relied on self-reported data, which is susceptible to memory and reporting biases, potentially affecting the accuracy of the results.

Considering these limitations, future research should adopt a prospective cohort study design and include university students from diverse regions and backgrounds to establish the causal relationship between physical activity and periodontal health. Additionally, the use of objective tools for monitoring physical activity is recommended to enhance the accuracy of activity level data. Further exploration of the biological mechanisms underlying the relationship between physical activity intensity and periodontitis is also a critical area for future investigation. Such studies will provide valuable insights into how physical activity can be more effectively utilized in the prevention and treatment of periodontitis.

The findings of this study emphasize the importance of promoting moderate and high-intensity physical activity among college students, as it may improve their periodontal health and reduce the risks of periodontitis and related systemic conditions. Moreover, given the association between periodontitis and various systemic illnesses, improving periodontal health through physical activity promotion could serve as an effective public health strategy, warranting attention from policymakers and healthcare professionals.

## Conclusion

This study highlights an association between high-intensity physical activity and a lower prevalence of periodontitis among college students. While the findings suggest that promoting physical activity, particularly of higher intensity, could be a valuable strategy for improving oral health, the cross-sectional design of this research precludes causal inference. Future longitudinal and interventional studies are needed to confirm these findings and clarify the underlying mechanisms.

## Data Sharing Statement

Datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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