Periodontal Diseases and the Risk of Metabolic Syndrome: An Updated Systematic Review and Meta-Analysis

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Background: Periodontitis and metabolic syndrome (MetS) are two major global health problems that are widely prevalent in the world, although the former is a common infection in developing countries and the latter is a non-infectious but prevalent disease in developed countries. This study aims to provide an updated review on the existence and magnitude of the relationship between periodontal disease and the risk of MetS.

Methods: We searched the PubMed, Web of Science, ScienceDirect, Chinese National Knowledge Infrastructure, and Wanfang databases for original studies assessing the association between periodontitis and MetS published before August 2019. We calculated the pooled crude and adjusted odds ratios (ORs) together with the 95% confidence intervals (95% CIs) to estimate the strength of this association. Subgroup analysis was performed by considering the diagnostic method or the country where the studies were performed.

Results: We identified 43 potentially eligible articles for this systematic review, including 32 cross-sectional studies, eight case–control studies, and three cohort studies. Among them, 39 articles presented enough information to be included in the meta-analysis. The pooled crude and adjusted ORs were 1.99 (95% CI: 1.75–2.25) and 1.46 (95% CI: 1.31–1.61), respectively. Subgroup analysis showed a consistent relation stratified by either the diagnostic method or the country where the studies were performed. The pooled OR was 1.68 (95% CI: 1.41–2.00) for Japan, 1.75 (95% CI: 1.31–2.34) for the USA, 1.81 (95% CI: 1.35–2.42) for Korea, and 2.29 (95% CI: 1.53–3.41) for China.

Conclusion: Our results provide compelling evidence for the association between periodontitis and MetS. Patients with periodontal disease are a critical screening population for MetS. We also recommend that people exhibiting components of MetS should receive a periodontal check-up and pay attention to their oral health.

Keywords: periodontal disease, periodontitis, periodontal pocket, clinical attachment loss, metabolic syndrome, meta-analysis
INTRODUCTION

Oral health is an undervalued parameter of global health and has been considered inferior on the agendas of policymakers (1). There has been increasing scientific interest regarding the interactions between oral health and systemic diseases. In 2007, the World Health Organization (WHO) called on the integration of health policies regarding oral and general health (1). The European Union and the USA have also emphasized the importance of oral health in overall health (2). Numerous studies have shown a relationship between deficient oral hygiene and different systemic disorders, such as cardiovascular disease (CVD) and metabolic syndrome (MetS). A variety of theories have been proposed, of which a bulk of them hypothesize the mediation of the inflammatory response (3). Periodontitis is one of the most common chronic oral diseases and is characterized by the pathological loss of the periodontal ligament and adjacent supporting alveolar bone. It can also be described as a bacteria-induced complex chronic inflammatory disease (4). It is estimated that approximately 20 to 60% of the world's population may have some degree of periodontal disease (5). Periodontitis is not merely a consequence of plaque accumulation; it is also affected by host factors (6). If discovered in the initial stage, it can be managed successfully without causing much morbidity.

MetS is a prevalent and multifactorial disorder that consists of a cluster of several clinical physical conditions and biological abnormalities that increase the risk of mortality; MetS is affected

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**FIGURE 1** | PRISMA flowchart of the search for studies and their selection and inclusion.
| Year | Author          | Country   | Study design | Sample size | Mean age (years) | Male (%) | Female (%) | Current smokers (%) | Criteria for periodontitis diagnosis | Subjects with periodontitis (%) | Criteria for MetS diagnosis | Subjects with MetS (%) | Measures of association OR/RR (95% CI) |
|------|-----------------|-----------|--------------|-------------|------------------|----------|------------|---------------------|--------------------------------------|-------------------------------|-----------------------------|--------------------------|----------------------------------|
| 2007 | LI PENG         | CHINA     | CASE–CONTROL | 501         | 61.4             | 40.6      | 59.4       | 23.2                | CAL/PPD COMPLETE                     | 72.4                         | IDF (2005)                  | 47.9                     | Association was not reported   |
| 2007 | SHIMAZAKI Y.    | JAPAN     | CROSS–SECTIONAL | 584         | 55.7             | NIL       | 100        | 6.7                 | CAL/PPD PARTIAL (1) PPD: 17.1 (2) CAL: 6.3 | NCEP ATP III                | 16.8                        |                          | OR: (1) 6.8 (95% CI: 2.6–16.4); (2) 4.2 (95% CI: 1.2–14.8) |
| 2008 | D’AUTO FRANCESCO | UNITED STATES | CROSS–SECTIONAL | 13677       | 48               | 50.6      | 49.4       | 30.2                | CAL/PPD PARTIAL                       | 14                           | IDF (2005)                  | 20.3                     |                          |
| 2008 | KHADER YOUSEF    | JORDAN    | CASE–CONTROL  | 156         | 47.2             | 35.9      | 64.1       | 41                  | CAL/PPD COMPLETE                      | 27.6                         | NCEP ATP III                | 50                       |                          |
| 2009 | LI PENG         | CHINA     | CASE–CONTROL  | 192         | 60.8             | 40.9      | 59.1       | 20.2                | CAL COMPLETE                          | 72.4                         | IDF (2005)                  | 72.9                     |                          |
| 2009 | MORITA TOYOKO   | JAPAN     | CROSS–SECTIONAL | 2478        | 43.3             | 81.8      | 18.2       | 32                  | CPI code 3–4 PARTIAL                  | 25.9                         | JSIM/IDF (2005, MODIFIED JAPANESE) | 8.2                     |                          |
| 2009 | KUSHIYAMA MITOSHI | JAPAN     | CROSS–SECTIONAL | 1070        | 55               | 26.3      | 73.7       | 9.3                 | CPI code 3–4 COMPLETE                 | 29.5                         | NCEP ATP III                | 9.1                      |                          |
| 2010 | ANDRIANKAJA OM  | UNITED STATES | CROSS–SECTIONAL | 7431        | 40.1             | 47.3      | 52.7       | 26.8                | PPD PARTIAL                           | 5.8                          | NCEP ATP III                | 19.7                     |                          |
| 2010 | NESBITT MARK J. | UNITED STATES | CROSS–SECTIONAL | 200         | 56.8             | 57.8      | 42.5       | 57.5                | Radiographic distance CEJ-crestal bone ≥ 3 mm COMPLETE | 21.5                         | NCEP ATP III                | 17.5                     |                          |
| 2010 | BENGUGUI CATHERINE | FRANCE   | CROSS–SECTIONAL | 255         | 58               | 54.9      | 45.1       | 19.2                | Page & Eke 2007 COMPLETE               | 78.8                         | NCEP ATP III                | 28.6                     |                          |
| 2010 | HAN D-H         | SOUTH KOREA | CROSS–SECTIONAL | 1046        | 42.3             | 43.7      | 56.3       | 26.5                | CPI CODE 3–4 PARTIAL                 | 34                           | IDF (2009)                  | 22.4                     |                          |
| 2010 | TIMONEN P.      | FINLAND   | CROSS–SECTIONAL | 2050        | 47               | 39.3      | 60.7       | NIL                 | PPD COMPLETE                          | 3.4                          | EGIR (2002)                | 16.4                     |                          |
| 2010 | ZHANG JIAN-QUAN | CHINA     | CROSS–SECTIONAL | 120         | 53               | 41.7      | 58.3       | 24.2                | CAL/PPD PARTIAL                       | 85.8                         | CHINESE INTERNAL MEDICINE PROTOCOL AHA (2009) | 100                     | Adjusted complete case analysis, participants with severe periodontal disease were 1.5 times more likely to have metabolic syndrome |
| 2011 | BENSLEY LILIAN  | UNITED STATES | CROSS–SECTIONAL | 481         | 48               | 41.5      | 58.5       | 21.7                | SELF-REPORTED NOT APPLICABLE          | 45.1                         |                          |                          | OR: 1.55 (1.32–1.83)          |
| 2011 | KWON YOUNG-EUN  | KOREA     | CROSS–SECTIONAL | 6520        | 46.4             | 39.5      | 60.5       | 39.1                | CPI CODE 3–4 PARTIAL                 | 45.6                         | NCEP ATP III                | 28.4                     |                          |

(Continued)
| Year | Author          | Country | Study design  | Sample size | Mean age (years) | Male (%) | Female (%) | Current smokers (%) | Criteria for periodontitis diagnosis | Periodontal examination protocol | Subjects with periodontitis (%) | Criteria for MetS diagnosis | Subjects with MetS (%) | Measures of association OR/RR (95% CI) |
|------|----------------|---------|---------------|-------------|-----------------|----------|------------|---------------------|-------------------------------------|---------------------------------|-------------------------------|--------------------------|---------------------------|----------------------------------|
| 2011 | CHEN LI-PING   | TAIWAN  | CROSS-SECTIONAL | 253         | 58.8            | 46.2     | 53.8       | 29.6                | No periodontitis; PDI score of 0–3; mild periodontitis: 3 < PDI score ≤ 4; moderate-to-severe periodontitis: 4 < PDI score ≤ 6 | PARTIAL                        | 58.9                          | NCEP ATP III                | 57.3                          | OR: 2.73 (1.29–5.79)             |
| 2012 | HAN D-H        | KOREA   | CASE-CONTROL  | 322         | 49.5            | 56.6     | 43.4       | 31.9                | CPI CODE 3-4                      | PARTIAL                        | 41.9                          | IDF (2009)                 | 50                           | OR: 1.76 (95% CI: 1.06–2.93)         |
| 2012 | FUKUI NAO      | JAPAN   | CROSS-SECTIONAL | 6421        | 44.5            | 77       | 23         | 25.2                | PPD                                | COMPLETE                       | 25.5                          | NCEP ATP III                | 14.9                          | OR: 1.35 (95% CI: 1.03–1.77)          |
| 2012 | YU Z.R.        | CHINA   | CROSS-SECTIONAL | 903         | 62.6            | 50.5     | 49.5       | 20.2                | CAL/PPD                            | COMPLETE                       | 88.4                          | JOINT INTERIM STATEMENT/IDF (2009) | 69.7                          | OR: 1.524 (95% CI: 1.066–2.328)       |
| 2013 | TU YU-KANG     | TAIWAN  | CROSS-SECTIONAL | 33740       | 49.8            | 45.3     | 54.7       | NOT SPECIFIED        | At least ONE tooth with periodontitis | PARTIAL                        | 30.8                          | NCEP ATP III                | NOT SPECIFIED                | Females—OR: 1.52 (95% CI: 1.41–1.63) |
| 2013 | SORA NICOLETA  | USA     | CROSS-SECTIONAL | 283         | 55.3            | 24       | 76         | 14.8                | CAL/PPD                            | COMPLETE                       | 10.9                          | NCEP ATP III                | 85.9                          | RR: 2.77 (95% CI: 1.11–6.93); Women—OR: 3.60 (1.30–12.61); Men—OR: 1.21 (0.59–2.49) |
| 2013 | FURATA MICHIKO | JAPAN   | CROSS-SECTIONAL | 2370        | 59.5            | 43.9     | 56.1       | 26.3                | NHANES III                        | COMPLETE                       | 33.2                          | JOINT INTERIM STATEMENT/IDF (2009) | 35.1                          | OR: 2.10 (95% CI: 1.03–4.28)          |
| 2014 | LAMONTE        | UNITED STATES | CROSS-SECTIONAL | 657         | 65.5            | NIL      | 100        | 2.1                 | Osteo-periodontitis                | COMPLETE                       | 72.6                          | NCEP ATP III                | 25.6                          | OR: 1.11 (95% CI: 0.71–1.75)           |
| 2014 | THANAKUN       | THAILAND| CROSS-SECTIONAL | 125         | 47              | 42.4     | 57.6       | 8.8                 | 1) AAP 2) PD ≥ 4 mm                | COMPLETE                       | 46.4                          | IDF (2009)                 | 64.8                          | OR: 3.60 (95% CI: 1.34–9.65)          |
| 2015 | ALHABASHNEH RO A | JORDAN | CROSS-SECTIONAL | 280         | 53.8            | 50.7     | 49.3       | 21.8                | CAL/PPD                            | COMPLETE                       | 39.6                          | IDF (2005)                 | 83.2                          | OR: 3.28 (95% CI: 1.30–8.30)          |
| 2015 | MINAGAWA K.    | JAPAN   | CROSS-SECTIONAL | 234         | 80              | 47.4     | 52.6       | 5.6                 | AAP/CDC (MODIFIED)                | COMPLETE                       | 77.4                          | IDF (2005, MODIFIED JAPANESE)       | 24.4                          | OR: 2.10 (95% CI: 1.03–4.28)          |
| 2015 | IWASAKI MANASORI | JAPAN | COHORT        | 125         | 70              | 44       | 56         | 39.2                | CAL                                | COMPLETE                       | NOT SPECIFIED                | NCEP ATP III                | 21.6                          | RR: 2.58 (95% CI: 1.17–5.67)          |
| 2016 | CHEN X.        | CHINA   | CROSS-SECTIONAL | 303         | 34.9            | 100      | NIL        | 31                  | CPI                                | COMPLETE                       | 23.1                          | JOINT INTERIM STATEMENTS/IDF (2009, MODIFIED CHINESE) | 38.3                          | OR: 3.378 (95% CI: 1.889–5.924)        |
| 2016 | JARAMILLO ADRIANA | COLUMBIA | CASE-CONTROL | 651         | 46.5            | 36.1     | 63.9       | 20.1                | CAL/PPD                            | COMPLETE                       | 66.2                          | AACE (2003)                 | 5.2                           | OR: 2.72 (95% CI: 1.09–6.79)          |
| 2016 | KUMAR NARESH   | INDIA   | CASE-CONTROL  | 259         | 38.5            | 52.9     | 47.1       | 13.1                | CAL                                | COMPLETE                       | 50.2                          | NCEP ATP III                | 22                            | OR: 2.64 (95% CI: 1.36–5.18)          |
| 2016 | GOMES-FILHO ISAAC SUZART | BRAZIL | CROSS-SECTIONAL | 419         | 59              | 38.2     | 61.8       | 29.8                | CAL/PPD                            | COMPLETE                       | 34.6                          | NCEP ATP III/IDF (2005)           | NCEP: 60.9; IDF: 67.1 | OR: 2.11 (95% CI: 1.01–4.40)          |

(Continued)
| Year  | Author                      | Country       | Study design   | Sample size | Mean age (years) | Male (%)  | Female (%) | Current smokers (%) | Criteria for periodontitis diagnosis | Periodontal examination protocol | Subjects with periodontitis (%) | Criteria for MetS diagnosis | Subjects with MetS (%) | Measures of association OR/RR (95% CI) |
|-------|-----------------------------|---------------|----------------|-------------|------------------|-----------|-------------|---------------------|-------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| 2016  | KAYE E.K.                   | UNITED STATES | COHORT         | 751         | 61               | 100        | NIL         | 3                   | CAL/PPD                            | COMPLETE                      | 25.4                          | IDF (2009)                    | 1.37 (1.14–1.65)            | 37.6 (95% CI)                 |
| 2016  | MUSS-KOPF MARTA L.          | BRAZIL        | CROSS-SECTIONAL | 363         | 47.5             | 36.1       | 63.9        | 44.1                | CAL/PPD                            | COMPLETE                      | 26.9                          | IDF (2009)                    | 54.8                         |
| 2016  | WU WEI                      | CHINA         | CROSS-SECTIONAL | 1000        | 28-58            | 89.5       | 10.5        | 60                  | CAL/PPD                            | COMPLETE                      | 75.6                          | CHINESE INTERNAL MEDICINE PROTOCOL | 39.7                         |
| 2017  | ZUK ALEKSANDRA KIKU MIKI    | CANADA        | CROSS-SECTIONAL | 1383        | 49               | 50.5       | 49.5        | 18.1                | CAL                                | PARTIAL                        | 16.2                          | AHA/NHLBI                     | 15.3                         |
| 2017  | ZUK ALEKSANDRA KIKU MIKI    | JAPAN         | CROSS-SECTIONAL | 1856        | 66.4             | 41.6       | 58.4        | 19.3                | CPI                                | PARTIAL                        | 50.3                          | JOINT INTERIM STATEMENT/IDF (2009) | 36.4                         |
| 2017  | ZHANG LI                    | CHINA         | CROSS-SECTIONAL | 1415        | 39.9             | 50         | 50          | 6.7                 | CPI                                | COMPLETE                      | 39.7                          | IDF (2009)                    | 18.3                         |
| 2018  | KIM O.S                     | KOREA         | CROSS-SECTIONAL | 5078        | 64.7             | 41.6       | 58.4        | 10.7                | CDC/AAP                            | PARTIAL                        | 48.7                          | IDF (2009)                    | 48.6                         |
| 2018  | PHAM ANH-VU THUY            | VIETNAM       | CASE-CONTROL   | 412         | 57.8             | 27.7       | 72.3        | 9                   | CDC/AAP (2012)                     | COMPLETE                      | 28.6                          | JOINT INTERIM STATEMENT/IDF (2009) | 50.0                         |
| 2018  | KOO HO SEOK                 | KOREA         | CASE-CONTROL   | 10340       | 57.2             | 51.8       | 48.2        | 21                  | CPI CODE 3-4                       | PARTIAL                        | 51.4                          | NCEP ATP III                 | 33.0                         |
| 2018  | NASCIMENTO GIUSTAVO G.      | BRAZIL        | COHORT         | 539         | 51               | 50.6       | 49.4        | NOT SPECIFIED       | AAP/CDC                            | COMPLETE                      | 14.3                          | NCEP ATP III                 | 13.3                         |
| 2019  | ABDALLA-ASLAN RAGDA         | ISRAEL        | CROSS-SECTIONAL | 470         | 55.8             | 45.8       | 54.2        | 38.1                | AAP                                | COMPLETE                      | 75.3                          | NCEP ATP III                 | 37.4                         |
| 2019  | KIM JI-SOO                  | KOREA         | CROSS-SECTIONAL | 8314        | 55               | 46.4       | 53.6        | 19.6                | CPI                                | PARTIAL                        | 37.3                          | NCEP ATP III                 | 34.1                         |
by insulin resistance and promotes cardiovascular diseases (7). These conditions/diseases include glucose intolerance/insulin resistance/hyperglycemia, hypertension, visceral obesity, and dyslipidemia (8). MetS has an estimated prevalence of 17–32% in the general population (9), which suggests that nearly one-quarter of adults throughout the world are affected (10).

The association between periodontitis and MetS has gained research interest in the scientific literature. There is variation in the reported degree of association, which may be due to the different definitions of MetS, the methodology used to assess periodontitis, and criteria for subject enrollment (11). In addition, there are several different approaches to determine the association between these two diseases/conditions. The American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP) have emphasized that more studies are needed to assess the association between periodontitis and various systemic conditions, including MetS (12). This study aims to provide an updated review on the existence and magnitude of the relationship between periodontal disease and the risk of MetS. A better understanding of periodontal diseases in the development of MetS and vice versa is required for medical and dental professionals to provide the general population with appropriate care.

METHODS

Literature Search and Study Selection

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were used (Supplementary Table 1) (13). We searched the PubMed, ScienceDirect, Web of Science (WOS), Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases for studies that reported an association between periodontitis and MetS in adults up to August 2019. Studies were limited to human studies and those published in either English or Chinese. Related keywords used for PubMed were as follows: Periodontal disease OR periodontitis OR periodontal pocket OR clinical attachment loss AND metabolic syndrome OR metabolic disease OR syndrome X OR Reaven’s syndrome OR MetS. PubMed MeSH terms were as follows: Metabolic Syndrome/Syndrome X (MeSH term Metabolic Syndrome X for both) and Periodontal Diseases, Periodontitis, Pocket Depth (No MeSH term), Periodontal Pocket, Periodontal Pouching (MeSH term Periodontal Pocket), Attachment Loss (MeSH term Periodontal Attachment Loss), and Clinical Attachment Loss (MeSH term Tooth Mobility). Keywords for WOS and ScienceDirect searches were metabolic syndrome/periodontal disease, metabolic syndrome/periodontitis, metabolic syndrome/pocket depth, and metabolic syndrome/periodontal pocket. The terms we used were explored to ensure the retrieval of all the items needed concerning the specific search terms. Titles and abstracts of selected studies were examined for their possible relevance to the association between periodontitis and MetS. Studies were considered eligible using the following criteria: original epidemiological studies; observational studies including a cross-sectional, case–control, or cohort design; adult samples; having at least one diagnostic standard for periodontitis that was clearly defined; and having clear criteria for the diagnosis of MetS. Studies matching the eligibility criteria were considered for this systematic review. Abstracts and reviews were excluded; however, references in reviews were used for a supplementary literature search. In total, 43 studies (38 published in English and five published in Chinese) met the inclusion criteria for the systematic review with a total sample size of 114,181 participants. Among them, 39 studies had enough information to be included in the meta-analysis. A random-effect model was conducted to estimate the pooled odds ratios (ORs) together with 95% confidence intervals (95% CIs) to establish the strength of association.

Data Extraction

Two reviewers independently identified eligible studies on the above topic, assessed the publication validity, and subsequently extracted data. The discrepancies were discussed and resolved, and the studies were concluded after consultation with the supervisor of this research. We collected data on the year of publication, the first author, study country, study design, sample size, mean age, sex, current tobacco smoking status, criteria for periodontitis diagnosis, periodontal examination protocol, the number of subjects diagnosed with periodontitis, criteria for MetS diagnosis, the number of subjects diagnosed with MetS, and the strength of the association [OR, relative risk (RR) and 95% CI].

Quality Assessment

We used the Newcastle–Ottawa scale to evaluate the quality of the studies. A “star system” was used to judge the study in the following three contexts: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or the outcome of interest. The results varied across the selected studies, which is shown in Supplementary Table 1. The scale has a score of 0–9 stars for each article. A higher number of stars indicates a higher quality of the study (14).
The associations between periodontitis and MetS were assessed by the pooled ORs with the corresponding 95% CIs. Data from 39 studies were collected individually, and a crude OR was calculated, followed by the random-effect model. Then, the second analysis, consisting of the pooled adjusted OR, was derived from the given adjusted ORs from each study. I^2 was also used to test the heterogeneity among the included studies. Consequently, subgroup analysis was first performed on the method used to diagnose periodontitis, that is, either partial-mouth periodontal examination or full-mouth periodontal examination. The second subgroup analysis was on the criteria for the diagnosis of MetS, which are the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, the 2005 International Diabetes Federation (IDF, 2005) criteria, or the 2009 IDF criteria. Finally, the subgroup analysis was performed by country, namely, China, Japan, the USA, and Korea, the countries where most of the published studies have

FIGURE 3 | Pooled crude odds ratios of the association between periodontitis and metabolic syndrome.
been conducted. The subgroup analysis was performed using both the crude and the adjusted ORs separately. Stata version 15.0 (StataCorp, College Station, Texas, USA) was used to analyze the data.

RESULTS

Description of Studies

During the literature search, 1,125 articles were selected, and to find other associated studies, articles listed in their references were also screened. Duplicates and other non-related articles were not considered for the systematic review. Then, among these, 86 of the articles were retrieved, and their titles, abstracts, and full texts were scrutinized for possible relevance. Finally, 43 articles were selected for the systematic review, and 39 were enrolled in this meta-analysis where the crude ORs were calculated individually (Figure 1). Additionally, 35 studies with adjusted ORs were used from the specified studies (6, 10, 12, 15–54).

The characteristics of each study are listed in Table 1. Forty-three studies published from 2007 to 2019 were analyzed. There were studies from eastern Asia as well as western Asia, European countries, and North and South American countries. Thirty-eight were published in English, while 5 of them were published in Chinese. The sample size ranged from 120 (27) to 33,740. (33) Of the studies meeting the inclusion criteria for analysis, three were cohort studies (40, 45, 53), 32 were cross-sectional studies, and 8 were case–control studies. The criteria used for the diagnosis of periodontitis were different in these studies. Some used the CPI index, while others used the CAL or PPD.

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| D’AIUTO (2008) | 1.45 (0.91, 2.33) | 2.87 |
| MORITA (2009) | 2.40 (1.70, 2.70) | 4.36 |
| KUSHIYAMA (2009) | 2.13 (1.22, 3.70) | 1.20 |
| ANDRIANKAJA (Men) (2010) | 1.00 (0.70, 1.60) | 4.82 |
| ANDRIANKAJA (Women) (2010) | 2.10 (1.20, 3.70) | 1.18 |
| NESBITT (2010) | 2.61 (1.10, 6.10) | 0.33 |
| BENGUIGUI (2010) | 3.97 (1.22, 12.90) | 0.06 |
| HAN (2010) | 1.70 (1.22, 2.37) | 3.74 |
| KWON (2011) | 1.55 (1.32, 1.83) | 7.00 |
| CHEN (2011) | 2.73 (1.29, 5.79) | 0.40 |
| HAN (2012) | 1.76 (1.06, 2.93) | 1.92 |
| FUKUI (2012) | 1.35 (1.03, 1.77) | 5.67 |
| YU (2012) | 1.52 (1.07, 2.33) | 3.34 |
| TU (Men) (2013) | 1.04 (0.96, 1.12) | 8.67 |
| TU (Women) (2013) | 1.52 (1.41, 1.63) | 8.47 |
| FURATA (Men) (2013) | 1.21 (0.59, 2.49) | 1.87 |
| FURATA (Women) (2013) | 3.80 (1.30, 12.61) | 0.07 |
| LAMONTE (2014) | 1.11 (0.71, 1.75) | 4.18 |
| THANAKUN (2014) | 3.60 (1.34, 9.65) | 0.12 |
| ALHABASHNEH (2015) | 3.28 (1.30, 8.30) | 0.17 |
| MINAGAWA (2015) | 2.10 (1.03, 4.28) | 0.74 |
| CHEN (2016) | 3.38 (1.89, 5.92) | 0.50 |
| JARAMILLO (2016) | 2.72 (1.09, 6.79) | 0.26 |
| KUMAR (2016) | 2.64 (1.36, 5.18) | 0.55 |
| GOMES-FILHO (2016) | 2.11 (1.01, 4.40) | 0.69 |
| KAYE (2016) | 1.19 (1.00, 1.41) | 7.57 |
| ZUK (2017) | 1.28 (0.68, 2.40) | 2.18 |
| KIKUI (2017) | 1.89 (1.31, 2.73) | 2.87 |
| ZHANG (2017) | 1.26 (1.08, 1.48) | 7.63 |
| PHAM (2018) | 4.06 (2.11, 7.84) | 0.25 |
| KOO (2018) | 1.12 (1.01, 1.24) | 8.44 |
| KIM (2019) | 1.42 (1.26, 1.61) | 7.89 |
| Overall (I-squared = 73.5%, p = 0.000) | 1.45 (1.31, 1.60) | 100.00 |

NOTE: Weights are from random effects analysis.

FIGURE 4 | Pooled adjusted odds ratios of the association between periodontitis and metabolic syndrome.
Twenty-seven studies had complete full-mouth examination, 15 had partial-mouth examination, and one study (28) was self-reported periodontitis. The proportion of periodontitis ranged from 3.4 to 88.4% among the mentioned studies. For the diagnosis of MetS, 21 studies used NCEP ATP III criteria, 5 used the 2005 IDF criteria, 13 used the 2009 IDF criteria, and the remaining studies used different methods. The percentage range of patients with MetS ranged from 5.2 to 100% among the studies. The funnel plot for the investigation of publication bias was drawn by plotting the standard error of the logOR against the logOR. As shown in the plot, the risk of publication bias was not significant (Figure 2).

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Partial Periodontal Examination | | |
| SHIMAZAKI (2007) | 2.62 (1.59, 4.32) | 2.46 |
| D’AIUTO (2008) | 2.41 (2.17, 2.67) | 3.84 |
| MORITA (2009) | 2.34 (1.62, 3.40) | 2.95 |
| ANDRIANKAJA (2010) | 1.53 (1.23, 1.91) | 3.52 |
| HAN (2010) | 2.88 (2.14, 3.89) | 3.24 |
| KWON (2011) | 2.54 (2.27, 2.84) | 3.83 |
| CHEN (2011) | 2.18 (1.30, 3.63) | 2.41 |
| HAN (2012) | 1.77 (1.14, 2.76) | 2.68 |
| ZUK (2017) | 2.28 (1.62, 3.22) | 3.06 |
| KIKUI (2017) | 1.38 (1.04, 1.87) | 3.63 |
| KIM (2017) | 1.12 (0.97, 1.29) | 3.76 |
| KOO (2018) | 1.30 (1.20, 1.41) | 3.88 |
| KIM (2019) | 1.96 (1.79, 2.15) | 3.87 |
| Subtotal (I-squared = 94.0%, p = 0.000) | 1.91 (1.58, 2.31) | 43.13 |
| Complete Periodontal Examination | | |
| LI (2007) | 1.69 (1.09, 2.62) | 2.68 |
| KHADER (2008) | 3.13 (1.48, 6.62) | 1.66 |
| LI (2009) | 1.59 (0.80, 3.16) | 1.83 |
| KUSHIYAMA (2009) | 3.13 (1.42, 6.86) | 2.74 |
| NESBITT (2010) | 2.04 (1.34, 3.12) | 1.57 |
| BENGUGUI (2010) | 2.34 (1.08, 5.07) | 1.60 |
| TIMONEN (2010) | 1.40 (0.78, 2.52) | 2.16 |
| FUKUI (2012) | 1.51 (1.30, 1.75) | 3.75 |
| YU (2012) | 1.55 (1.02, 2.37) | 2.16 |
| SORA (2013) | 2.57 (0.59, 11.24) | 0.63 |
| FURATA (2013) | 1.32 (1.10, 1.57) | 3.67 |
| LAMONTE (2014) | 0.96 (0.65, 1.42) | 2.87 |
| THANAKUN (2014) | 2.98 (1.36, 6.52) | 1.58 |
| ALHABASHNEH (2015) | 4.61 (1.98, 10.71) | 1.44 |
| MINAGAWA (2015) | 2.51 (1.06, 5.92) | 1.41 |
| CHEN (2016) | 9.31 (4.96, 17.46) | 2.01 |
| JARAMILLO (2016) | 2.03 (0.87, 4.75) | 1.43 |
| KUMAR (2016) | 2.64 (1.42, 4.93) | 2.02 |
| GOMES-FILHO (2016) | 0.86 (0.56, 1.31) | 2.74 |
| KAYE (2016) | 1.69 (1.22, 2.35) | 3.11 |
| MUSSKOF (2016) | 1.93 (1.19, 3.12) | 2.51 |
| WU (2016) | 2.47 (1.78, 3.41) | 3.14 |
| ZHANG (2017) | 1.83 (1.40, 2.40) | 3.34 |
| PHAM (2018) | 2.53 (1.62, 3.95) | 2.66 |
| ABDALLA-ASLAN (2019) | 14.22 (6.44, 31.41) | 1.56 |
| Subtotal (I-squared = 78.3%, p = 0.000) | 2.11 (1.74, 2.55) | 58.87 |
| Overall (I-squared = 88.0%, p = 0.000) | 2.00 (1.76, 2.27) | 100.00 |

NOTE: Weights are from random effects analysis.

FIGURE 5 | Subgroup analysis of pooled crude odds ratios of the association between periodontitis and metabolic syndrome by the method of examination used to diagnose periodontitis.
Meta-Analysis

From the data extracted, 39 of the studies showed an association of MetS and periodontitis, with a crude pooled OR of 1.99 (95% CI: 1.75–2.25). The heterogeneity test showed that $I^2 = 87.7\%$ and $P < 0.001$ (Figure 3). We further summarized the adjusted ORs, which were mentioned in 32 studies, and showed a pooled adjusted OR of 1.45 (CI: 1.31–1.60). The heterogeneity test showed that $I^2 = 73.5\%$ and $P < 0.001$ (Figure 4).

Subgroup Analysis

Subgroup analysis on the tooth examination used to diagnose periodontitis showed a crude OR of 1.91 (95% CI: 1.58–2.31, $I^2 = 94.0\%, P < 0.001$) for partial periodontal examination and a crude OR of 2.11 (95% CI: 1.74–2.55, $I^2 = 78.3\%, P < 0.001$) for complete periodontal examination (Figure 5). The pooled adjusted OR was 1.38 (95% CI: 1.18, 1.57, $I^2 = 24.3\%$, $P = 0.180$) for the complete periodontal examination and 1.47 (95% CI: 1.27–1.66, $I^2 = 86.4\%, P < 0.001$) for the partial periodontal examination (Figure 6).

Subgroup analysis by the diagnostic criteria of MetS showed that the crude OR was 1.83 (95% CI: 1.45–2.30, $I^2 = 86.6\%, P < 0.001$) for the 2009 IDF criteria, 2.08 (95% CI: 1.69–2.55, $I^2 = 90.7\%, P < 0.001$) for the NCEP ATP III criteria, and 2.17 (95% CI: 1.62–2.93, $I^2 = 25.9\%, P = 0.249$) for the 2005 IDF criteria.
FIGURE 7 | Subgroup analysis of pooled crude odds ratios of the association between periodontitis and metabolic syndrome by diagnostic criteria for metabolic syndrome.

(Figure 7). The pooled adjusted OR was 1.34 (95% CI: 1.16, 1.52, $I^2 = 83.5\%$, $P < 0.001$) for the NCEP ATP III criteria, 1.48 (95% CI: 1.24–1.72, $I^2 = 38.0\%$, $P = 0.088$) for the 2009 IDF criteria, and 2.39 (95% CI: 1.92–2.86, $I^2 = 0.0\%$, $P = 0.830$) for the 2005 IDF criteria (Figure 8).

Subgroup analysis by country showed crude ORs of 1.68 (95% CI: 1.41–2.00, $I^2 = 63.5\%$, $P = 0.011$) for Japan, 1.75 (95% CI: 1.31–2.34, $I^2 = 81.9\%$, $P < 0.001$) for the USA, 1.81 (95% CI: 1.35–2.42, $I^2 = 96.6\%$, $P < 0.001$) for Korea, and 2.29 (95% CI: 1.53–3.41, $I^2 = 81.5\%$, $P < 0.001$) for China (Figure 9). The adjusted OR was 1.19 (95% CI: 1.02–1.36, $I^2 = 0.0\%$, $P = 0.471$) for the USA, 1.41 (95% CI: 1.17–1.66, $I^2 = 76.7\%$, $P = 0.002$) for Korea, 1.51 (95% CI: 0.93–2.08, $I^2 = 57.3\%$, $P = 0.096$) for China, and 1.81 (95%...
There is undoubtedly a positive association between periodontitis and MetS based upon the studies that were reviewed in this meta-analysis. There are a multitude of variables that can have ramifications in the association between periodontitis and MetS, including study population/subjects as well as ethnicity/geography, which have not been studied. Studies involved in this systematic review were conducted in 15 different countries worldwide, and the majority of the studies demonstrated a higher risk of MetS for patients with periodontal diseases.

The human body has multiple organ systems, and these systems are intimately and mutually dependent on each other. As a result, ailments in some organs or their components may play a contributing factor in the occurrence and evolution of a particular disease in other body locations (55, 56). The influence of oral health on one's general health has been scrutinized for the last decennium by a multitude of surveys (57). A systematic

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**FIGURE 8** | Subgroup analysis of pooled adjusted odds ratios of the association between periodontitis and metabolic syndrome by diagnostic criteria for metabolic syndrome.

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| NCEP ATP III | 2.13 (1.12, 3.70) | 1.29 |
| KUSHIYAMA (2009) | 1.61 (0.70, 3.70) | 1.27 |
| ANDRIANKAJA (Men) (2010) | 2.61 (1.10, 6.10) | 0.36 |
| ANDRIANKAJA (Women) (2010) | 1.55 (1.32, 1.83) | 7.36 |
| NESBITT (2010) | 2.73 (1.29, 5.79) | 0.43 |
| KWON (2011) | 1.35 (1.03, 1.77) | 5.99 |
| CHEN (2011) | 1.04 (0.96, 1.12) | 9.05 |
| FUKUI (2012) | 1.52 (1.41, 1.63) | 8.85 |
| TU (Men) (2013) | 1.11 (0.71, 1.75) | 4.45 |
| TU (Women) (2013) | 2.64 (1.36, 5.18) | 0.59 |
| LAMONTE (2014) | 1.12 (1.01, 1.24) | 8.81 |
| KUMAR (2016) | 1.42 (1.26, 1.61) | 8.26 |
| KOO (2018) | 1.34 (1.16, 1.52) | 81.62 |
| Subtotal (I-squared = 83.5%, p = 0.000) | | |
| IDF 2009 | 1.70 (1.22, 2.37) | 3.98 |
| HAN (2010) | 1.76 (1.06, 2.93) | 2.06 |
| HAN (2012) | 1.62 (1.07, 2.33) | 3.57 |
| YU (2012) | 1.21 (0.59, 2.99) | 0.00 |
| FURATA (Men) (2013) | 1.60 (1.34, 9.65) | 0.13 |
| THANAXUN (2014) | 3.38 (1.89, 5.92) | 0.53 |
| CHEN (2015) | 2.72 (1.09, 6.79) | 0.28 |
| JARAMILLO (2016) | 2.11 (1.01, 4.40) | 0.74 |
| GOMES-FILHO (2016) | 1.19 (1.00, 1.41) | 7.94 |
| KAYE (2016) | 1.89 (1.31, 2.73) | 3.07 |
| KIKUI (2017) | 1.26 (1.08, 1.48) | 7.99 |
| ZHANG (2017) | 4.06 (2.11, 7.84) | 0.27 |
| PHAM (2018) | 1.48 (1.24, 1.72) | 32.56 |
| Subtotal (I-squared = 38.0%, p = 0.088) | | |
| IDF 2005 | 2.40 (1.70, 2.70) | 4.63 |
| MORITA (2009) | 3.28 (1.30, 8.30) | 0.18 |
| ALHABASHNEH (2015) | 2.10 (1.03, 4.28) | 0.80 |
| MINAGAWA (2015) | 3.27 (1.92, 2.86) | 5.61 |
| Subtotal (I-squared = 0.0%, p = 0.830) | | |
| Overall (I-squared = 76.6%, p = 0.000) | 1.46 (1.31, 1.61) | 100.00 |

NOTE: Weights are from random effects analysis

CI: 1.33–2.29, I$^2$ = 61.2%, $P = 0.024$ for Japan, respectively (Figure 10).
A review including 72 studies and data from 291,170 individuals in 37 countries estimated that the global prevalence of severe periodontitis in 2010 was 10.8% (95% CI: 10.1–11.6%), thus making severe periodontitis rank 6th in the Global Burden of Disease (58).

The observation of a relationship between periodontitis and systemic diseases may significantly expand the scope and appreciation of oral health and dental practice. The general population, as well as non-dental medical professionals, should be informed that periodontal diseases play an important role in overall health. Due to a possible etiopathogenic relationship between periodontitis and various systemic diseases, patients with severe periodontal disease should be referred to screen for CVD, diabetes, MetS, and other systemic diseases. Patients prone to or diagnosed with certain systemic diseases may also be referred to dentists to check for and treat periodontal...
disease. Oral inflammatory lesions have different mechanisms concerning the possible association with systemic diseases (59–62). The oral cavity hosts several cell populations expressing mesenchymal stem cell like-features (63). The human periapical cyst mesenchymal stem cells (hPCy-MSCs) collected from the surgically removed periapical cysts exhibit interesting and valuable potentialities that could be of high impact in the future regenerative medicine applications (63). It is necessary to strengthen the cooperation between different clinical departments and treat the disease with a holistic view.

The main limitation of this particular review is that the analysis and comparison of ORs using the data available may be debatable, as the percentage of patients considered to have been diagnosed with periodontitis and MetS was determined with different diagnostic criteria. The fact that there is no global consensus on one specific set of diagnostic criteria for these two diseases is an enigma. Different researchers use different criteria depending upon the country where the study is being conducted, availability, and the accessibility of resources as well as specialized human resources to conduct the examination part of the survey, and this may affect the results of each study. Furthermore, most of the studies reviewed on this related issue are cross-sectional studies, and they do demonstrate an association of periodontal disease with MetS, but the prevalence ferreted at a single point thereby gives only a transient excerpt or cause–effect cannot be determined. An additional consideration is that many of the definitions of MetS allow the inclusion of subjects who have already been on medication for the treatment of
some components of MetS, for instance, hypertension, diabetes, or dyslipidemia. The consequence of these medications on systemic inflammation is concealed, and some might have anti-inflammatory actions; thus, patients might have different periodontal statuses. One study reported by Shimazaki et al. showed that MetS increased the risk of periodontitis, with ORs for greater pocket depth and clinical attachment loss exhibited in 4 or 5 components of 6.6 (95% CI: 2.6–16.4) and 4.2 (95% CI: 1.2–14.8), respectively (16). Due to the lack of longitudinal studies, it is difficult to determine the relative contribution of periodontitis to MetS and the contribution of MetS to periodontitis. However, this does not affect our suggestion that clinicians and the general public should pay attention to the relationship between oral health and systemic disease.

CONCLUSION

Our results provide compelling evidence for the association between periodontitis and MetS. Patients with periodontal disease are a critical screening population for MetS. We also recommend that people exhibiting components of MetS should receive a periodontal check-up and pay attention to their oral health. Among the golden rules for maintaining good oral hygiene is that one should visit a dentist at least twice a year, brush at least twice daily, floss regularly, and have a healthy diet, thereby avoiding too many sweet and sticky foodstuffs. Particular attention should be given to children, and oral hygiene, as well as healthy lifestyle habits, should be implemented in the educational curriculum so that from an early age, one is made aware of these basics to have a healthier and brighter future generation. Policymakers should invest in the promotion and prevention of these issues so that the financial impact due to the treatment and rehabilitation of these diseases is less.

AUTHOR CONTRIBUTIONS

RG, DT, and JW conceived the study, analyzed the data, and drafted the manuscript. QL participated in the study design and helped refine the manuscript. All authors contributed to the study and have read and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2020.00336/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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