Review Article

Association Between Periodontitis and Metabolic Syndrome in Females: A Systematic Review and Meta-analysis

Ghousia Sayeed[1], Sheeja S. Varghese[2]

[1]Department of Preventive Dentistry, College of Dentistry, Riyadh Elm University, Riyadh, Saudi Arabia, [2]Department of Periodontics, Saveetha Dental College, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, India

ABSTRACT

Background: Metabolic syndrome (MetS) and periodontal diseases (PDs) have shown a bidirectional and vice versa relationship. Hence, this study aimed to identify the extent and magnitude between MetS and PDs in females. **Materials and Methods:** A published literature was explored by considering case–control, cross-sectional, and cohort studies that involved patients with measurements of MetS and PD. Ovid MEDLINE, EMBASE, LILACS, and Cochrane Library databases were used for the search. This study examined the relationship between the MetS and PD among females. **Results:** Of the initial 4150 titles screened, a total of 37 reported papers were eligible for quantitative review. A gender-wise analysis of the findings revealed a crude odds ratio (OR) of 1.385 [95% confidence interval (CI): 1.043–1.839, I^2 = 94.61%, P < 0.001] for the females relative to the average OR of 1.54 (95% CI: 1.39–1.71, I^2 = 90.95%, P < 0.001). Further subgroup analysis for directionality in females revealed the crude ORs of 1.28 (95% CI: 0.91–1.79, I^2 = 96.44%, P < 0.001) for the relationship between PD and MetS, whereas an OR of 2.12 (95% CI: 0.78–5.73, I^2 = 88.31%, P < 0.001) was found between MetS and PDs. **Conclusion:** This study lacks convincing proof of a link between MetS and PDs in females when compared with an overall association between MetS and PDs. Directionality indicated higher odds of linking between MetS and PD than PD and MetS among females. Further longitudinal and treatment trials are needed to confirm the association among females.

KEYWORDS: *Females, metabolic syndrome, periodontal diseases, systematic review*

INTRODUCTION

Metabolic syndrome (MetS) is a group of health conditions involving belly fat, increased blood sugar, hypertension, raised triglycerides, and reduced high-density lipoprotein (HDL) cholesterol. The root causes of MetS include increased weight and obesity, insulin tolerance, hereditary conditions, inappropriate eating, lack of physical activity, and aging. The worldwide prevalence of MetS in the adult population increases with an approximate prevalence of 20–25%.[1] Adults suffering with Mets have a five times more severe chance of having type 2 diabetes and are thrice at risk of heart attack or stroke than those without MetS.[1-3] In this backdrop, MetS is deemed a public

health problem worldwide.[4,5] Periodontal disease (PD) is a group of conditions affecting the tooth's supporting tissues including the gingiva, periodontal ligament, cementum, and alveolar bone. It most frequently develops as a response to chronic infection and inflammation, usually resulting from the presence of pathogenic bacteria.[6]

Cumulative evidence over the years suggests that PDs are associated with glucose intolerance, dyslipidemia,

Address for correspondence: Dr. Ghousia Sayeed,
Department of Preventive Dentistry, College of Dentistry,
Annamuthajiya Campus,
Riyadh Elm University (REU), P. O. Box 84891,
Riyadh 11681, Saudi Arabia.
E-mail: docghousia@gmail.com

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elevated blood pressure (BP), and a low-grade systemic inflammation,[7-11] along with other systemic diseases and conditions such as cardiovascular disease, diabetes, and obesity.[12,13] The supposed link may be attributed to the various common risk factors,[14] the release of inflammatory cytokines,[15] abdominal obesity,[16] oxidative stress,[17] proatherogenic lipoproteins,[18] and cross-reactivity and molecular mimicry,[19] which could a play role in these associations.

In females, the association between PDs and MetS and vice versa has not been fully reported. Hence, this systematic review aims to identify the extent and a possible bidirectional association between PDs and the presence of MetS in females. Furthermore, the extent and directionality of the associations were compared with the overall findings.

MATERIALS AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in this study. The broad research question included is: "is there any bi-directional association between PDs and MetS among females?" The review strategy adhered to the PECO format.

STUDY SELECTION

The observational studies of case–control, cross-sectional, cohort studies, and population surveys involving female subjects with measures of MetS and PDs and/or controls were included in the review.

SEARCH STRATEGY

The literature search was carried out using the electronic databases MedLine, EMBASE, LILACS, and Cochrane library. The unpublished databases were complemented by a search through reference lists. Only English Language articles were included in the search. Peer-reviewed studies, reports, book chapters, conference abstracts, and theses were screened among published literatures. Narrative reviews on the topic were searched in order to identify suitable papers. Ahead-of-print publications were sought by contacting editors of the journals with the impact on our search (dental, metabolic, cardiovascular). The search was updated on December 31, 2019.

The search strategy included the following search words: MeSH terms in all trees/subheadings: "periodontal diseases" and "insulin resistance." Keywords for PD are: "tooth loss," "alveolar bone loss," "periodont*," and "gingiva*." Similarly, keywords for MetS included "metabolic syndrome," "syndrome X," "obesity," "hypertension," "diabetes mellitus," "insulin resistance," "hypertriglyceridemia," "hyperlipidemia," "hypercholesterolemia," "dyslipidemia," "hyperglycemia," and "hyperinsulinism."

A study selection involved first stage of initial screening of potentially suitable titles and abstracts based on inclusion criteria. The second stage consisted of screening of the full papers that were identified as possibly relevant in the initial screening. In the third stage, a full database was built after careful analysis listing of selected studies.

DEFINITIONS OF PDS AND METS

Due to the lack of similar diagnostic criteria of PD and MetS in various published articles, the following criteria have been applied.

1. Diagnosis of periodontitis

a. Periodontitis included a minimum of two areas of different teeth having clinical attachment level (CAL): at least two sites on different teeth with CAL ≥ 6 mm and at least one site with probing pocket depth (PPD) ≥ 4 mm[20] or minimum two areas of non-adjacent teeth proximal attachment loss ≥ 3 mm,[21] or community periodontal index (CPI) score of 4 in at least one quadrant.[22] However, in situations with no reported CAL or PPD, a radiographic alveolar bone loss was ≥ 30% of root length or ≥ 5 mm in at least two teeth.

2. Diagnosis of gingivitis

Gingivitis included a minimum of 30% of sites with bleeding on probing or mean bleeding index = 1[23] or at least 15 bleeding sites.[24] In some cases, gingivitis referred to unspecified gingival inflammation.

3. Diagnosis of MetS

a. MetS refers to the condition when any three of the five risk factors were recorded: increased waist circumference (≥88 cm in women), increased fasting triglycerides (≥150 mg/dL or on drug treatment for elevated triglycerides), decreased HDL cholesterol (<50 mg/dL in women or on drug treatment for reduced HDL cholesterol), increased BP (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg, or on antihypertensive drug treatment in patients with history of hypertension), and increased fasting glucose (≥100 mg/dL or on drug treatment for elevated glucose).[25]

DATA EXTRACTION

Descriptive information including the study outcomes and odds ratios (ORs) were extracted from each study, as shown in Table 1.

Table 1: Main characteristics of studies included in the review

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
1	Shimazaki et al.[26]	MetS to PD	Cross-sectional	584 females	100	55.7	Average CAL ≥ 3 mm	6.3	NCEP-ATP III	16.8	3.3 (1.2–8.8)
2	D'Aiuto et al.[11]	PD to MetS	Cross-sectional	13,994	38	40.7	Page and Eke[20]	14.0 (moderate to severe)	IDF 2005	37	Severe periodontitis and MetS assoc. 1.74 (1.10–2.76) ($P <$ 0.05) if age >44 years
3	Khader et al.[27]	MetS to PD	Cross-sectional	156	64.1	47.2	No categorical definition applied	Not reported	NCEP-ATP III	50	PD ($P <$0.0005), CAL ($P <$0.0005)
4	Kushiyama et al.[28]	MetS to PD	Cross-sectional	1070	73.3	63.3	CPI code 4	29.5	NCEP-ATP III	5	Association between MetS and PD: OR 2.13 (1.22–3.70)
5	Li et al.[29]	PD to MetS	Case–control	208	43.3	60.9	Greater than 33% sites, ≥ 3 mm CAL	72.4	IDF 2005	72.9	Association between MS and PD: OR for % CAL ≥3 and MS tertiles: 0–33 OR 6.91 (1.07–44.77), 33–67 OR 9.89 (1.50–65.24), 67–100 OR 15.60 (2.20–110.43)
6	Morita et al.[30]	PD to MetS	Cross-sectional	2478 (450 females, 2028 males)	18.2	43.3	CPI code 3–4	25.9	Modified (Japanese) IDF 2005	8.2	2.4 (1.7–2.7), P <0.01
7	Andriankaja et al.[16]	MetS to PD	Cross-sectional	7431	52.7	40.4	Mean PD ≥2.5 mm	5.8	NCEP-ATP III	19.7	4.7 (2.0–11.2) ($P<$ 0.001), only in females
8	Benguigui et al.[31]	MetS to PD	Cross-sectional	255	45.1	57.9	Page and Eke[20]	78.8	ATP III	28.6	Association between MS and PD: moderate: OR 1.54 (0.59–4.01), severe: OR 1.97 (0.74–5.23)
9	Han et al.[32]	MetS to PD	Cross-sectional	1046 (589 females, 457 males)	56.3	42.3	CPI code 3–4	34	IDF 2009	22.4	No. of positive components of MetS and periodontitis (CPI 3–4) OR 1.7 (1.22–2.37), $P = 0.002$

Table 1: Continued

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
10	Morita et al.[12]	PD to MetS	Longitudinal	1023	29	37.3	CPI code 3–4	20	Modified (Japanese) IDF 2005	0% at baseline	If two or more positive components, 2.2 (1.1–1.4), $P < 0.05$
11	Nesbitt et al.[33]	PD to MetS	Cross-sectional data of longitudinal	200	39	56.8	Distance between CEJ and crest of alveolar bone measured on panoramic radiograph. None or slight bone loss: 1–2 mm, moderate: 3–4 mm, or severe ≥ 5 mm	21.5	Modified ATP III	17.5	Moderate-to-severe bone loss assoc. 2.61 (1.1–6.1) ($P < 0.05$)
12	Timonen et al.[34]	MetS to PD	Cross-sectional	2050	60.8	46	No categorical definition applied	Not reported	EGIR	16.4	Association between MS and PD: RR of 1.19 (1.01–1.42) for PPD ≥4; RR of 1.5 (0.96–2.36) for PPD ≥6
13	Bensley et al.[35]	PD to MetS	Cross-sectional	672	51	48	Self-reported	42	AHA 2009	64	No P-value
14	Chen et al.[36]	PD to MetS	Cross-sectional	253 subjects undergoing hemodialysis	53.8	58.8	PI (Silness and Loe), GI (Loe and Silness), Ramfjord Periodontal Disease Index, gingival inflammation designated: no inflammation (PDI 0), mild gingivitis (PDI 1), moderate gingivitis (PDI 2), and advanced gingivitis (PDI 3). Attachment loss 0–2 mm (PDI 4), 3–6 mm (PDI 5), and >6 mm (PDI 6)	80	NCEP-ATP III	57.3	If moderate-to-severe periodontitis OR 2.73 (1.29–5.79) ($P = 0.008$)

Table 1: Continued

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
15	Kwon et al.[13]	MetS to PD	Cross-sectional	7178	62.5	45.6	CPI code 3-4	45.7	NCEP-ATP III	28.3	Association between PD and MS: OR 1.55 (1.32–1.83)
16	Fukui et al.[37]	PD to MetS	Cross-sectional	6421 Japanese (1477 females, 4944 males)	23.1	43.4	PD and CAL measured at MB sites: none/ mild if ≤3 mm, moderate if 4–5 mm, severe if ≥6 mm	42.6	NCEP-ATP III	14.9	Severe periodontitis associated with MetS 1.35 (1.03–1.77) (P < 0.05)
17	Han et al.[15]	PD to MetS	Case–control	332	43.3	42.2	CPI code 3-4	41.8	Joint/unified classification, except that the fasting plasma glucose level cutoff >110 mg/dL rather than 100 mg/dL	50	1.76 (1.06–2.973) (P = 0.029) in overall subjects
18	Furuta et al.[38]	MetS to PD	Cross-sectional	2370 (1330 females, 1040 males, from Hisayama Health Examination 2007)	56.1	59.5	MB and MdB sites; CAL, PD, % sites with BOP. Subjects with at least 10 teeth	64	Joint/unified classification (waist circumferences ≥90 cm in male, ≥80 cm in female)	35	Mean PD ≥3 or 3.5 mm , then MetS associated in females (P < 0.05), but not in males
19	Sora et al.[39]	MetS to PD	Cross-sectional	283	76	55.3	Extent of severe periodontitis, defined as total tooth-sites per person measuring 6+ mm for CAL and 5+ mm for PPD, evaluated separately	70.6	NCEP-ATP III	85.8	Association between MS and PD: Sites with PPD ≥5 mm: RR 2.18 (0.98–4.87) Sites with CAL ≥ 6 mm: RR 2.77 (1.11–6.93)

Table 1: Continued

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
20	Tu et al.[40]	PD to MetS	Cross-sectional	33,740 Taiwanese	54.7	50	Periodontal disease defined as combination of the following: tooth mobility, gingival inflammation, periodontal pocketing (no specific values were given)	30	NCEP-ATP III	23	MetS assoc. with periodontitis in females: 1.52 (1.41–1.63) (P < 0.001), males: 1.04 (0.96–1.12) (P = 0.317) non-significant
21	LaMonte et al.[41]	MetS to PD	Cross-sectional	657 females	100	65.5	Page and Eke[20]	77	NCEP-ATP III	25.6	1.08 (0.67–1.74) (P <0.05 each)
22	Lee et al.[42]	MetS to PD	Longitudinal	399	57.1	72.3	CPI code 3–4	26.2	Combination of different classifications: BMI ≥25, BP ≥140/90 mmHg, FGL ≥126 mg/dL, HC ≥240 mg/dL	22.3	If two or more MetS components, more likely to have periodontal disease (P < 0.05), 10.53 (4.98–22.28)
23	Thanakun et al.[43]	MetS to PD	Case–control	125	57.6	47	AAP	72	IDF 2009	64.8	3.60 (1.34–9.65)
24	Alhabashneh et al.[44]	MetS to PD	Cross-sectional	280	49.3	53.8	Periodontitis was defined as presence of four or more teeth with highest reading of PPD ≥3 mm and CAL ≥3 mm	39.6	IDF 2005	83.2	Association between MS and PD: OR 3.28 (1.30–8.30)
25	Iwasaki et al.[45]	PD to MetS	Data part of longitudinal study	125	56	75	Full-mouth CAL was recorded, six sites around each tooth	Not reported	Modified NCEP-ATP III	27.6	Relative risk = 2.58, 95% confidence interval = 1.17–5.67
26	Han et al.[46]	PD to MetS	Cross-sectional	941	37.3	15	CPI code = 1 was clearly classified into gingivitis group	23.1 (gingivitis)	NCEP-ATP III	3.5 (at risk of MetS)	Correlation of MetS with gingivitis 3.29 (95% CI: 1.24–8.71)

Table 1: Continued

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
27	Minagawa et al.[47]	MetS to PD	Cross-sectional	234 (123 females, 111 males)	52.5	80	(i) Severe periodontitis: having six or more interproximal sites with CAL ≥ 6 mm and three or more interproximal sites with probing pocket depth (PPD) ≥ 5 mm (not on the same tooth), (ii) moderate periodontitis: having six or more interproximal sites with CAL ≥ 4 mm or six or more interproximal sites with PPD ≥ 5 mm (not on the same tooth), and (iii) no or mild periodontitis: neither "moderate" nor "severe" periodontitis	77.3	Modified (Japanese) IDF 2005	24.4	Crude odds ratio = 2.24, 95% confidence interval = 1.14–4.41
28	Gomes-Filho et al.[48]	PD to MetS	Cross-sectional	419	61.8	59	Page and Eke[20]	55	IDF 2005	61	Association between PD and MS: diagnosis of periodontitis: 0.98 (0.62–1.53). Severe periodontitis: 2.11 (1.01–4.40)

Table 1: Continued

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
29	Kumar et al.[49]	PD to MetS	Cross-sectional	259	47.1	38.7	AAP	50.1	NCEP-ATP III	22	OR: 2.64, 95% CI: 1.36–5.18, and P < 0.003
30	Jaramillo et al.[50]	MetS to PD	Case–control	651	63.9	55.5	Page and Eke[20]	66.2	AACE 2003	9.8	Association between PD and MS: OR 2.72 (1.09–6.79)
31	Kikui et al.[51]	MetS to PD	Cross-sectional	1780	58.2	66.5	CPI code 3–4	50.1	Modified (Japanese) IDF 2009	26.6	Association between PD and MS components: three components: OR 1.42 (1.03–1.96), four components: OR 1.89 (1.31–2.73)
32	Musskopf et al.[52]	PD to MetS	Cross-sectional	363	63.9	58.5	Page and Eke[20]	26.9	IDF 2009	54.8	Association between MS and severe PD: PR 1.62 (1.13–2.34)
33	Shin[53]	PD to MetS	Cross-sectional	13,066	55.9	≥ 20 years	CPI code 3–4	29.1	IDF 2009	27.3	AOR = 1.19, 95% CI: 1.04–1.36 for 20–27 teeth, AOR = 1.37, 95% CI: 1.12–1.67 for 0–19 teeth
34	Doğan et al.[54]	MetS to PD	Cross-sectional	176 females	100	50	Full-mouth periodontal examinations conducted at six sites around each tooth were examined. Pocket depth and CAL were recorded.	Not reported	NCEP-ATP III	27.8	Not reported

	Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
							Table 1: Continued				
35	Kim et al.[55]	PD to MetS	Cross-sectional	5078	58.3	72	AAP	16.1	IDF 2009	48.7	Men: 1.43 (1.17–1.73), women: 1.08 (0.98–1.20), 95% confidence interval
36	Koo and Hong[56]	MetS to PD	Case–control	13,196	47.9	57.3	CPI code 3-4	29	NCEP-ATP III	32.9	OR = 1.12, 95% CI: 1.01–1.24
37	Pham[57]	PD to MetS	Case–control	412	72.3	57.8 ± 5.7 years	Page and Eke[20]	28.5	NCEP-ATP III	50	OR = 4.06 (95% CI: 2.11–7.84) (P < 0.001).
38	Shearer et al.[58]	PD to MetS	Data part of longitudinal study	952	49.2	38	Periodontal examinations were conducted with full-mouth examinations and third molars and implants were excluded. Three sites (mesiobuccal, buccal, and distolingual) per tooth were examined. Gingival recession and pocket depth and CAL were recorded.	34.7	NCEP-ATP III	16.9	OR (95% CI) 1.03 (0.99, 1.07)
39	Tanaka et al.[59]	PD to MetS	Retrospective	3722	22.2	44.5 ± 8.2 years	Periodontal status was assessed in terms of the PD and CAL at the mesio-buccal and mid-buccal sites for all teeth except for the third molars.	32.7	IDF 2009	11.1	OR = 1.44, 95% CI: 1.16–1.77
40	Abdalla-Aslan et al.[60]	MetS to PD	Cross-sectional	470	54.2	55.8	AAP	75.3	NCEP-ATP III	37.4	OR= 14.28, 95% CI: 6.66–31.25
41	Kim et al.[61]	PD to MetS	Cross-sectional	8314	53.5	57	CPI code 3 -4	37	NCEP-ATP III	32.2	OR = 1.42, 95% CI: 1.26–1.61

Table 1: Continued

Author (year)	Directionality	Study design	Sample size	Female sample (%)	Mean age (years)	Criteria for PD	% With PD	Criteria for MetS	% With MetS	OR
42 Nascimento et al.[62]	MetS to PD	Data part of longitudinal study	539	50	31	AAP/CDC	37.3	NCEP-ATP III	13.3	Results from the final SEM revealed that MetS is positively associated with "advanced" [coef. 0.11; P-value 0.01; comparative fit index (CFI): 0.99; Tucker Lewis index (TLI): 0.99; root mean square error of approximation (RMSEA): 0.01 (95% CI: 0.00–0.02)]
43 Ruiz[63]	Bi-directional	Cross-sectional	1761	51.1	≥ 30 years	AAP/CDC	49.27	IDF 2009	42.8	OR = 0.88, 95% CI: 0.60–1.28

STATISTICAL ANALYSIS

A random-effects model was used to determine the pooled prevalence and 95% CI. The general effect size was obtained using the reported OR for the PD to MetS and MetS to PD. The heterogeneity of the study results was assessed using I^2 test. Significant heterogeneity was considered for $P < 0.10$ and $I^2 > 50\%$. A subgroup analysis considered the directionality (MetS to PD and PD to MetS), gender, and study design. Statistical analysis was performed by the use of the Open Meta Analyst (version 3.13).

RESULTS

Of the 4150 titles, 65 were considered suitable after initial screening. After the full-text reading, 22 papers were excluded due to: (1) not reporting outcomes of interest ($n = 10$); (2) duplicate reports ($n = 3$); (3) reviews ($n = 4$); and (4) focussed on medical subgroups ($n = 5$) [Figure 1]. Hence, a total of 43 studies were included in the qualitative analysis and 37 papers considered in the quantitative analysis. These studies were published in various countries of the world. The study participants ranged from 125 patients in a study by Thanakun et al.[43] and Iwasaki et al.[45] to 33,740 in the Taiwanese population by Tu et al.[40] (median number of subjects 941). Six studies included data as part of longitudinal studies: Morita et al.[12]; Nesbitt et al.[33]; Lee et al.[42]; Iwasaki et al.[45]; Nascimento et al.[62]; and Shearer et al.[64] Six studies were case–control studies: Li[29]; Han[46]; Thanakun et al.[43]; Jaramillo et al.[50]; Koo and Hong[56]; and Pham,[57] and the remaining 31 studies were cross-sectional.

Only one study was carried out in adolescents in whom gingivitis was assessed.[65] The criteria of periodontitis ranged from radiographically as mentioned by Nesbitt et al.[33] to clinically reported by Page and Eke.[20] In some instances, arbitrary criteria of PPD or CAL were considered in this study. The periodontitis ranged from 6.3% to 80% among various studies. However, the percentage of subjects classified as having MetS across the included studies varied from 5.0% to 85%.

QUALITY ASSESSMENT

The Newcastle–Ottawa scale was utilized to evaluate the quality of the studies. The quality of the study was judged using the star system of rating adhering to the criteria based on the selection of the study groups, the comparability, and exposure or the outcome of interest. The results varied across the selected studies, which are shown in Table 2. The scale ranged from 0 to 9 stars for each article. More stars indicated a higher quality of the study.

SUBGROUP ANALYSIS

Many studies did not report data gender-wise, but studies that reported data based on gender showed a higher prevalence of females' MetS. So we performed a subgroup analysis based on the gender of the study participants.

The subgroup analysis by gender demonstrated a crude OR of 1.385 (95%: 1.043–1.839, $I^2 = 94.61\%$, $P < 0.001$) in females and 1.58 (95% CI: 1.42–1.77, $I^2 = 89.9\%$, $P < 0.001$) for both genders [Figure 2]. The subgroup analysis by directionality showed crude ORs of 1.28 (95% CI: 0.91–1.79, $I^2 = 96.44\%$, $P = 0.000$) for PD to MetS for females [Figure 3] and 1.60 (95% CI: 1.37–1.87, $I^2 = 90.87\%$, $P = 0.000$) for overall PD to MetS for both genders [Figure 4]. The subgroup analysis by directionality showed crude ORs of 2.12 (95% CI: 0.78–5.73, $I^2 = 88.31\%$, $P < 0.001$)

for MetS to PD for females [Figure 5] and 1.56 (95% CI: 1.35–1.80, $I^2 = 91.67\%$, $P < 0.001$) for MetS to PD for both genders [Figure 6].

DISCUSSION

In this study, relevant publications that described the prevalence of MetS and PDs and vice versa were selected regardless of the criteria used for defining periodontitis and MetS. Random-effects meta-analysis was used to pool the prevalence. Heterogeneity was explored using formal and subgroup analyses based on gender (females alone vs. both genders), directionality (overall PD to MetS vs. overall MetS to PD), and directionality among females (female PD to MetS vs. female MetS to PD). Study quality and publication bias were also explored.
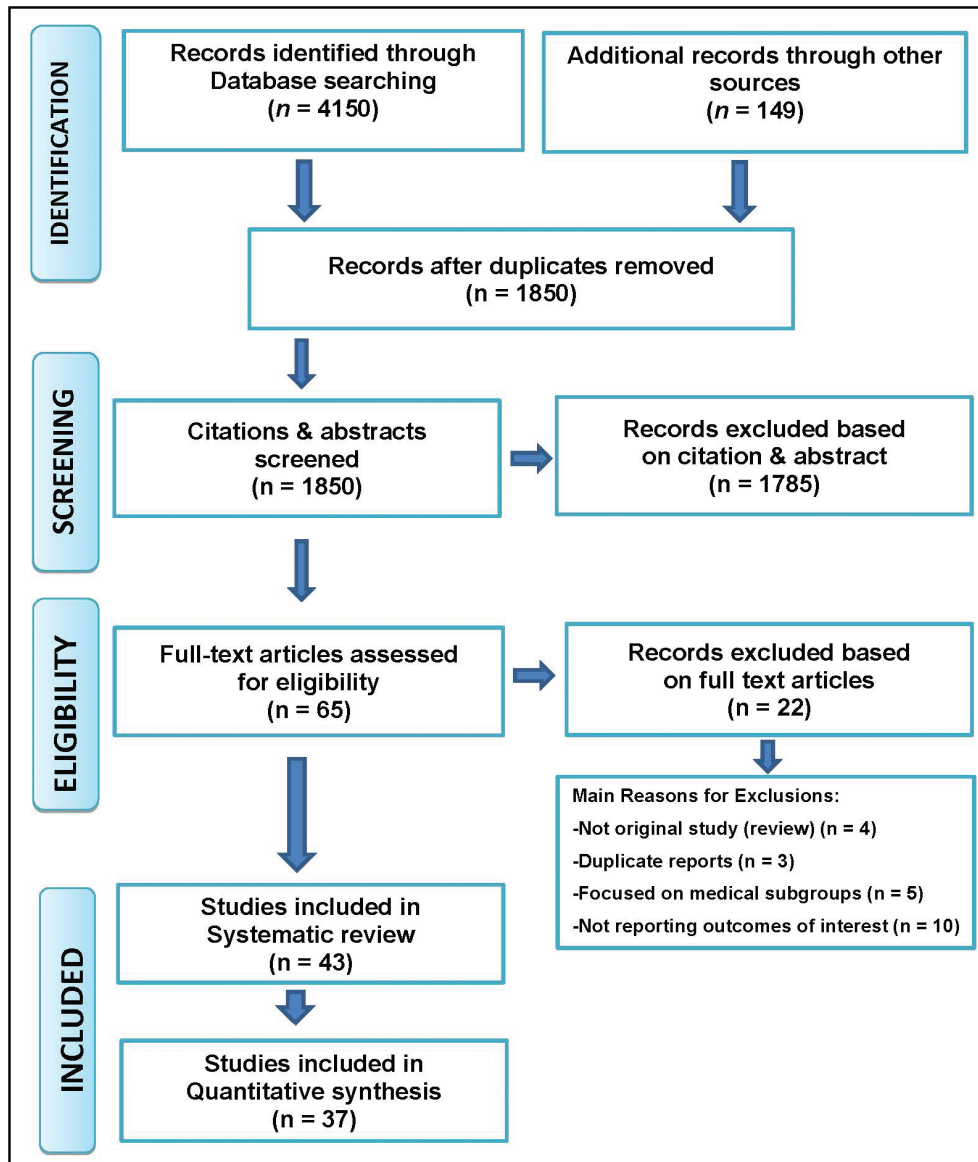

Figure 1: Flowchart of the search studies for systematic review

The study findings revealed no clear association between MetS and PD in females. However, gender predisposition can depend on multiple factors such as hormones, genetics, behavior, stress, to name a few. The changes in hormone levels occurring during puberty, pregnancy, menstruation, and menopause, and those that occur with the use of hormonal supplements, have long been associated with the development of gingivitis. One research carried out in Korea by Lee *et al.* in 2015[65] concluded that the probability of gingivitis is increased among those with three or more positive markers of the MetS, and HDL cholesterol levels are a significant risk factor.

To date, there has been no unified concept of MetS that can be extended to adolescents, and current adult-based meanings of MetS might not be sufficient to solve the issue in this age group; thus, the word "high risk of MetS" has been used instead of MetS. There were no indicators of any hormonal influences at the moment.

Three studies were conducted in females with the directionality of MetS to PD (Shimazaki *et al.*,[26] Furuta *et al.*,[38] and LaMonte *et al.*[41]). Shimazaki concluded that if participants have more components of MetS, PD's likelihood increased depending on their components. However, it was reported that the MetS components were not consistently associated with periodontal measures in older post-menopausal women.[41]

Estrogen insufficiency could affect oral soft and hard tissues. Women in their post-menopausal are likely to have osteoporosis, thereby increasing the risk of periodontal destruction.[66] Likewise, postmenopausal women have demonstrated altered lipid metabolism and increased risk for cardiovascular diseases.[67-70]

Tu *et al.*[40] explored the directionality of PD to MetS. A small but statistically significant association was found between MetS and PD among Taiwanese

Table 2: The Newcastle–Ottawa quality assessment scale			
Study (author, year, ref.)	Selection	Comparability	Outcome
Shimazaki *et al.*, 2007[26]	**	**	**
D'Aiuto *et al.*, 2008[11]	****	**	**
Khader *et al.*, 2008[27]	***	*	**
LI *et al.*, 2009[29]	**	*	**
Morita *et al.*, 2009[30]	**	*	**
Kushiyama *et al.*, 2009[28]	*	**	**
Andriankaja *et al.*, 2010[16]	***	**	**
Nesbitt *et al.*, 2010[33]	**	*	*
Benguigui *et al.*, 2010[31]	****	**	**
Han *et al.*, 2010[32]	***	**	**
Timonen *et al.*, 2010[34]	***	*	*
Bensley *et al.*, 2011[35]	**	*	**
Kwon *et al.*, 2011[13]	**	**	**
Chen *et al.*, 2011[36]	**	**	*
Han, 2012[46]	**	**	**
Fukui *et al.*, 2012[37]	***	**	***
Tu *et al.*, 2013[40]	**	*	*
Sora *et al.*, 2013[39]	***	**	***
Furuta *et al.*, 2013[38]	****	*	**
Lamonte *et al.*, 2014[41]	****	**	**
Thanakun *et al.*, 2014[43]	**	*	*
Alhabashneh *et al.*, 2015[44]	***	**	***
Minagawa *et al.*, 2015[47]	***	**	**
Iwasaki *et al.*, 2015[45]	**	**	**
Jaramillo *et al.*, 2017[50]	***	**	**
Kumar *et al.*, 2016[49]	***	**	***
Gomes-Filho *et al.*, 2016[48]	***	**	***
Musskopf *et al.*, 2017[52]	***	**	**
Kikui *et al.*, 2017[51]	***	**	**
Kim *et al.*, 2018[55]	***	**	**
Pham, 2018[57]	***	**	**
Koo and Hong, 2018[56]	**	**	**
Nascimento *et al.*, 2018[62]	***	**	***
Abdalla-Aslan *et al.*, 2019[60]	***	**	***
Kim *et al.*, 2019[61]	***	**	**

females, and a weaker association in Taiwanese males was observed. It could be due to relatively weaker influence of periodontal infection on MetS than stronger genetic and environmental risk factors. Moreover, the periodontal infections "compete" with these factors in their independent effects on MetS. These competing effects phenomenon may be larger in

men than in women as men tend to have a less healthy lifestyle; hence, smaller ORs were reported in men.[40]

Six longitudinal studies were included in this review. According to a 4-year longitudinal study by Morita in 2010, the presence of periodontal pockets was associated with increased risk of MetS components. Similarly, another longitudinal study observed that individuals
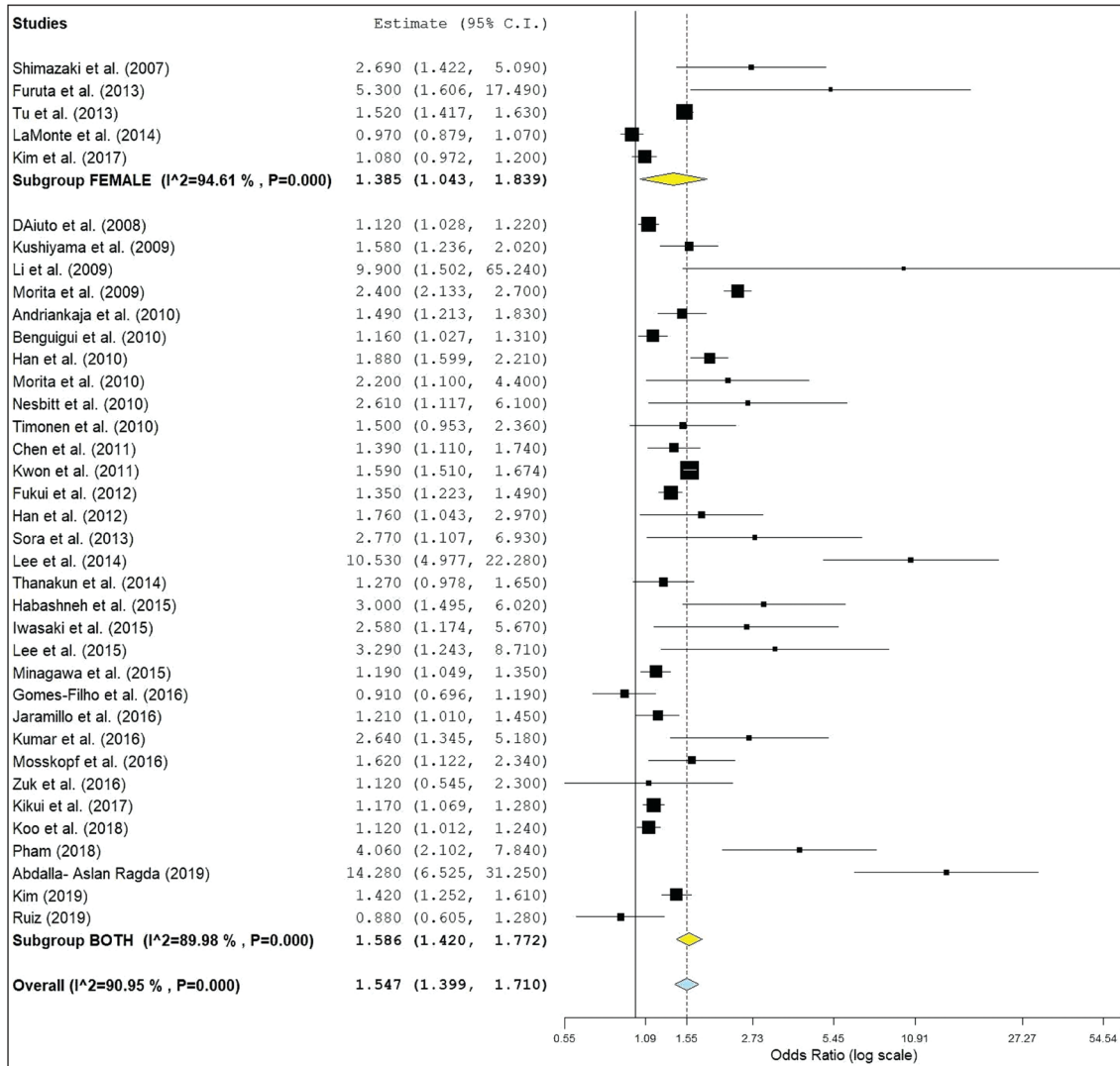

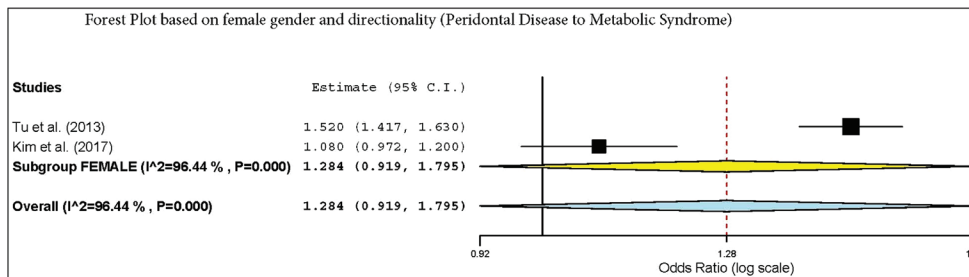**Figure 2:** Forest plot of gender and MetS

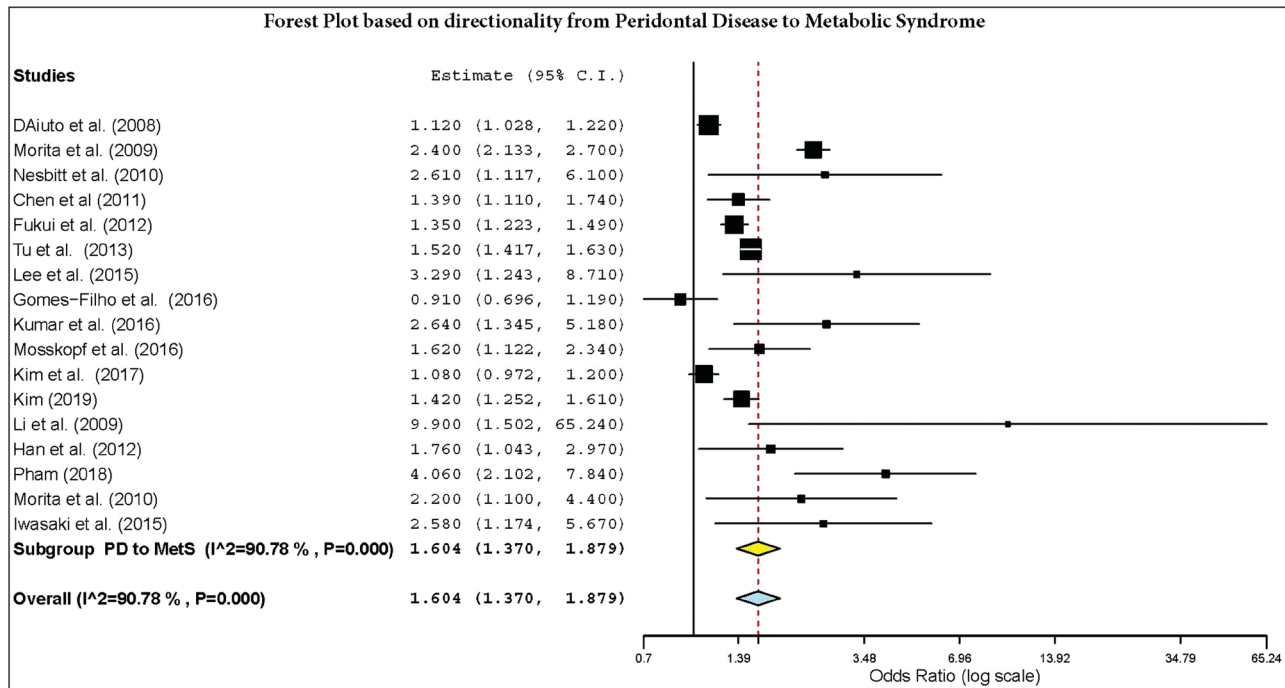**Figure 3:** Forest plot of PD to MetS in females

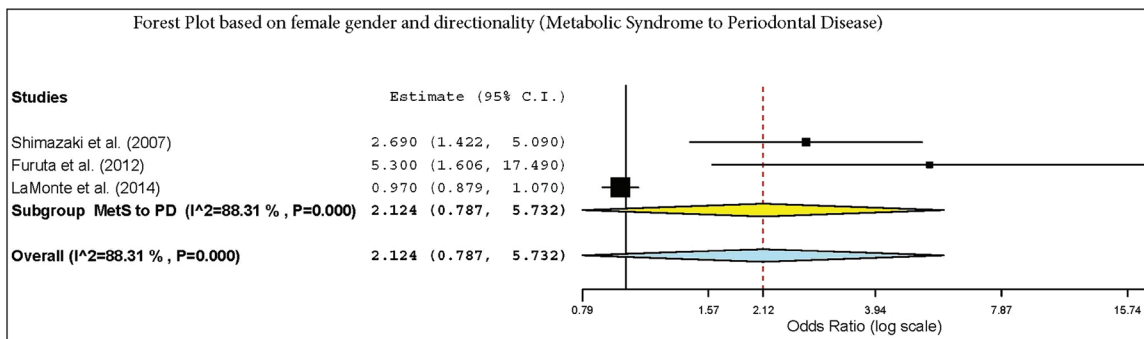**Figure 4:** Forest plot of overall PD to MetS

Figure 5: Forest plot of MetS to PD in females

with a more significant number of MetS components were more likely to have PD.[42] A 3-year follow-up study by Iwasaki *et al.*[45] reported that the participants with MetS had a significantly increased risk of PD, with a higher positive correlation in females. As the reported longitudinal trials are very minimal and inconclusive, further interventional studies on periodontal therapy-induced changes in the condition of MetS in patients with PD and MetS could be required to establish the causal relationship between PD and MetS.

In this review, 31 studies were cross-sectional, with the reported 24% prevalence of MetS. Although several studies investigated the relationship between MetS and PD, none has reviewed this relationship exclusively among females. The influence of gender on pathophysiology and clinical expression of MetS is of

great significance, given the alarming increase in the prevalence of MetS among females.

This review found 14 studies that reported a higher prevalence of association between PD and Mets in females, and 11 studies reported it to be higher in males. On the contrary, Thanakun *et al.*[43] reported no gender difference in the association between periodontitis and MetS.

The variability in results may be due to selection bias, differences in diagnostic criteria for PD and MetS, or the improper control of confounding factors. Moreover, high heterogeneity has been observed across reported studies. One of the likely causes of heterogeneity is the study area (urban/rural) from where study subjects were considered for examination. Moreover, MetS differed between males and females, with higher prevalence in females than that identified by the subgroup analysis. Within the male and female subgroups, a high
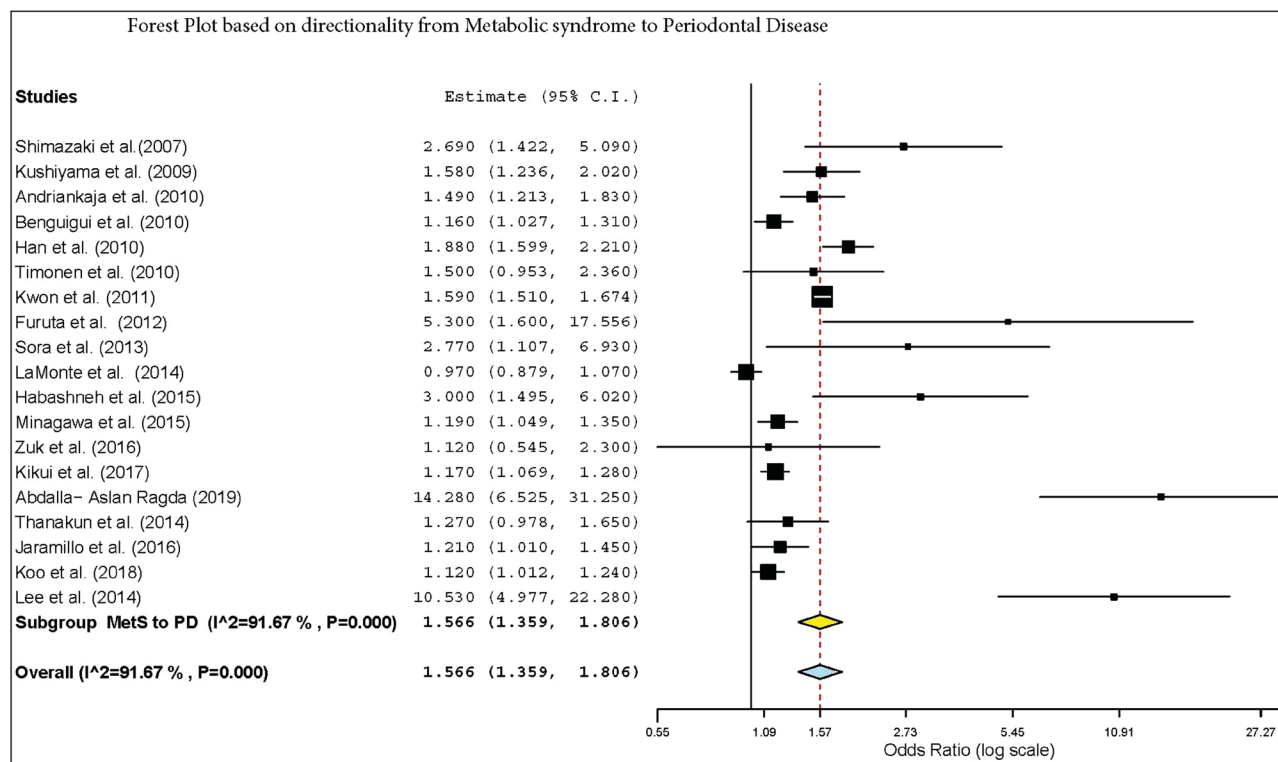
Figure 6: Forest plot of overall MetS to PD

between-study heterogeneity on the prevalence of MetS was observed. The quality evaluation review indicates that many studies do not meet the "adequate sample size" criteria. Another issue was that data collection was carried out in certain studies without sufficient coverage of the identified sample.

Strength and limitations

This review's strength is the comprehensiveness of the method, which involved looking for various databases, well-defined requirements for inclusion/exclusion, and thorough usage of reference lists. However, there are drawbacks to our systematic review and meta-analysis. This study did not consider non-English publications and local-level journals that are not accessible via large academic databases. In addition, there were difficulties in having a universally accepted clinical case definition of periodontitis. The definitions of MetS, age ranges, waist circumference, and research settings were not similar, resulting in a lack of homogeneity in the assessment of MetS. Moreover, longitudinal, cross-sectional, and case–control studies were taken together, which may have caused outcome bias. Hence, the outcome of this review is affected by many factors.

Conclusion

This study lacks convincing proof of a link between MetS and periodontitis in females when compared with an overall association between MetS and PD.

Directionality indicated higher odds of having MetS and PD than PD and MetS among females. Further longitudinal and treatment trials are needed to confirm these associations among females.

Conflicts of interest
There are no conflicts of interest.

Authors contributions
Not applicable.

Ethical policy and institutional review board statement
Not applicable.

Patient declaration of consent
Not applicable.

Data availability statement
Not applicable.

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