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SYSTEMATIC REVIEW

Periodontitis and risk of immune-mediated systemic conditions: A systematic review and meta-analysis

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Abstract

Introduction: The aim of this review is to examine and quantify the long-term risk of immune-mediated systemic conditions in people with periodontitis compared to people without periodontitis.

Methods: Medline, EMBASE and Cochrane databases were searched up to June 2022 using keywords and MeSH headings. The 'Risk of Bias in Non-Randomised Studies of Interventions' tool was used to assess bias. Cohort studies comparing incident metabolic/autoimmune/inflammatory diseases in periodontitis to healthy controls were included. Meta-analysis and meta-regression quantified risks and showed impact of periodontitis diagnosis type and severity.

Results: The search retrieved 3354 studies; 166 studies were eligible for full-text screening, and 30 studies were included for review. Twenty-seven studies were eligible for meta-analysis. The risks of diabetes, rheumatoid arthritis (RA) and osteoporosis were increased in people with periodontitis compared to without periodontitis (diabetes—relative risk [RR]: 1.22, 95% CI: 1.13–1.33; RA—RR: 1.27, 95% CI: 1.07–1.52; osteoporosis—RR: 1.40, 95% CI: 1.12–1.75). Risk of diabetes showed gradient increase by periodontitis severity (moderate—RR = 1.20, 95% CI = 1.11–1.31; severe—RR = 1.34, 95% CI = 1.10–1.63).

Conclusion: People with moderate-to-severe cases of periodontitis have the highest risk of developing diabetes, while the effect of periodontal severity on risk of other immune-mediated systemic conditions requires further investigation. More homologous evidence is required to form robust conclusions regarding periodontitis-multimorbidity associations.

KEYWORDS
arthritis, cohort studies, diabetes, immune response, periodontitis, systematic review, systemic disease

1 | INTRODUCTION

As the life expectancy increases globally, multimorbidity has become an increasing public health issue causing notable burden on healthcare services such as uncoordinated care and issues with polypharmacy.[1] Multimorbidity development is especially common in people with pre-existing conditions including diabetes mellitus (diabetes) and rheumatoid arthritis (RA).[2,3] A prior study has demonstrated that periodontitis is also linked with long-term multimorbidity development.[4] Identifying the risk factors to multimorbidity

development is vital in the pursuit to alleviating pressures on healthcare services.

Metabolic diseases such as diabetes, kidney and liver diseases and metabolic syndrome can be defined as such through their disturbances to the metabolic network, that is the homeostatic cycle of uptake of glucose, fatty acids and energy release.[5] Disruption to metabolic pathways, for example glucose handling in diabetes, can consequently impair immune function.[6,7] Alternatively, chronic inflammation mediates autoimmune disorders such as inflammatory bowel disease, RA, Sjogren's syndrome and psoriasis, as well as musculoskeletal conditions such as osteoporosis. Uncontrolled cytokine secretion through chronic systemic inflammation in these conditions can also disturb immune responses.[8–10] Dysregulated immune function via disrupted metabolic networks or uncontrolled inflammatory responses may advance multimorbidity progression and intensify subsequent healthcare burden.[11]

Periodontitis is a chronic oral condition that manifests as bleeding gums and loose teeth, as a result of localized inflammation.[12] The condition is diagnosed in clinic by indications of clinical attachment loss of the periodontal tissue.[13] It is hypothesized that periodontitis may cause systemic inflammation via upregulation of shared inflammatory pathways.[14] As such, periodontitis has been linked to development of systemic conditions including cardiovascular disease (CVD),[15] hypertension,[16] cognitive decline,[17,18] all-cause mortality[19] and COVID-19 prognosis.[20,21] Other cross-sectional evidence suggests that people with periodontitis are more likely to have co-morbidities, for example diabetes, obesity[22,23] and rheumatoid arthritis (RA).[24] There is growing literature that suggests periodontitis may be associated with subsequent development of immune-mediated systemic conditions[25,26]; however, this has not yet been systematically researched. Hitherto, no systematic review has summarized the longitudinal evidence for the associations of periodontitis with development of immune-mediated systemic conditions and assessed the impact of study factors. Exploration of risk factors and associations with oral health is integral to understanding multimorbidity development and driving appropriate interventions.

Therefore, the aims of this systematic review were as follows:

1. To examine and quantify the long-term risk of immune-mediated systemic conditions in people with periodontitis compared to people without periodontitis.
2. To conduct a meta-regression to evaluate the impact of study factors.

2 | METHODS

Study design—a systematic review and meta-analysis of longitudinal cohort studies that examine the risk of immune-mediated diseases in people with periodontitis compared to people without periodontitis.

This systematic review was registered to PROSPERO (registration number: CRD42019154897).

2.1 | Search strategy

The search string considered alternate terms and several conditions via inclusion of key words and appropriate Medical Subject Headings (MeSH) terms. The final search string was as follows: (periodon* OR tooth loss OR missing teeth) AND (systemic disease OR diabetes mellitus OR kidney disease OR liver disease OR metabolic syndrome OR metabolic disease OR osteoporosis OR rheumatoid arthritis OR psoriasis OR inflammatory disease) AND (incidence OR cohort OR longitudinal OR randomi*ed controlled trial [RCT]) (Table S1).

The search string was applied from database conception until 6 June 2022 to EMBASE, Medline and Cochrane databases. Additional reference checking and 'citation snowballing', or iterative citation searches, of eligible studies were undertaken to maximize the scope of literature retrieval.

2.2 | Study selection

Studies retrieved from the search databases were imported into a citation manager and screened for duplicates using an automated system. One author screened the title and abstract for eligibility, with validation by a second author. Whole articles were inspected for data extraction and quality assessment. Prior to the search, a data extraction form was developed to consistently collect data including: demographics, data source, exclusion/inclusion criteria, total follow-up duration, disease outcome and study limitations. A second author monitored data extraction and supported resolving queries thereby ensuring adherence to the protocol (registration number: CRD42019154897). Two authors analysed the risk of bias.

2.3 | Eligibility criteria

Strict eligibility criteria guided the search. The inclusion criteria of the present systematic review are outlined below:

- Longitudinal retrospective/prospective cohort and randomized controlled trials.
- Minimum of 1-year follow-up.
- Explicit mention of clinically or self-reported diagnosis or signs of periodontitis.
- Clearly defined classification of metabolic, autoimmune or inflammatory diseases.
- Subjected to peer-review.

Studies were excluded if they met any of the following points within the exclusion criteria:

- Cross-sectional, case series, case–control or experimental studies.
- Populations with predefined systemic disease.
- Protocols, abstracts, reviews or conference proceedings.

- Lack of validated or clearly defined diagnosis of periodontitis.
- Absent or unclear definition disease.
- Estimates of risk not attainable.

In addition, populations with pre-diagnosed immune-mediated systemic conditions were not eligible to ensure accurate incident risk quantification, rather than prevalence of concurrent diagnoses. Clinical classification of periodontitis comprised clinical examination or the identification of appropriate codes within electronic health records and/or insurance databases. To maximize the number of eligible studies, we also included those that utilized self-reported periodontitis case definition. Self-reported periodontitis was denoted through questionnaire or interview responses. As per recommendations, oral complaints or diagnoses such as caries, cysts/lesions, peri-implantitis and odontogenic infection were not accepted as case definitions as they are not directly attributed to a clinical diagnosis of periodontitis.[12] In the case of absent raw data, corresponding authors were contacted for further information.

2.4 | Quality assessment

This review utilized the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) as no RCTs were retrieved, and to ascertain certain controversies such as selection and confounder bias associated with observational studies.[27] The ROBINS-I tool is recommended by Cochrane to determine risk of bias in cohort and longitudinal observational studies.[28] The ROBINS-I tool measures across seven domains; the highest level of bias across a single domain classifies the study's overall level of bias. The findings of bias assessment were adjudicated by a second author before incorporation to the final ROBINS-I assessment table. To supplement the risk of bias assessment, the quality of reporting for each study was assessed using the CONSORT-ROUTINE extension.[29] This tool has previously shown its utility in assessing quality of reporting in observational studies which utilize routinely collected data.[30] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach determined overall quality, certainty and applicability of the evidence. Given the recommendation by Cochrane for studies assessed using the ROBINS-I tool, all studies start with high certainty of evidence. The GRADE pro GDT 2015 programme generated a certainty of evidence table (supplement table xx).The review protocol was pre-registered to the PROSPERO database in October 2019 (registration number: CRD42019154897). This systematic review adhered PRISMA guidelines.[31]

2.5 | Statistical analysis

Estimates for relative risks (RR), odds ratios (OR) and hazard ratios (HR) were extracted to quantify the risk of developing the disease outcome. To ensure viable meta-analysis and pooling, non-RR estimates were converted using equations.[32] For the purposes of illustration and tabulation, conditions were noted as immune-mediated via disrupted metabolic networks (diabetes, kidney disease, liver disease, metabolic syndrome) or chronic inflammation (inflammatory bowel disease, osteoporosis, RA, psoriasis, Sjogren's syndrome), and as such were recognized as metabolic or autoimmune/inflammatory diseases, respectively. Random effect meta-analysis was performed to synthesize the risk of developing each disease where study numbers allowed. For further viability within the meta-analysis, included studies must have reported separate population sizes for periodontitis and healthy controls. Where risk estimates were stratified by sex and periodontitis severity within studies and no overall estimate was available, values were pooled for an overall RR for the given study. Subgroup analysis was performed for periodontitis diagnosis type (self-report/clinically diagnosed) and severity; meta-regression compared the risks between subgroups and individual conditions. To account for statistical heterogeneity, I^2 was calculated with synthesized pooled estimates.

Egger's test and funnel plots were used to demonstrate potential publication bias. Forest plots illustrated the pooled results for the overall RRs where appropriate. We conducted a sensitivity analysis to assess the effect of removing studies that did not adjust for smoking status. Studies that were not eligible for meta-analysis were outlined as part of the narrative review.

The analysis was performed using R (version 4.0.2). Statistical significance was set as $p < .05$.

3 | RESULTS

In total, 3354 studies were retrieved from the search. Following first stage screening of titles and abstracts, the full texts of 166 studies were reviewed. In total, there were 30 studies eligible for review. Two studies did not report raw sample size data and therefore were excluded in the meta-analysis.[25,26] One study reported risks for both metabolic and inflammatory diseases as collective disease groups and was also not eligible for meta-analysis.[4] Of studies eligible for meta-analysis ($n = 27$), fourteen studies quantified risk for metabolic diseases including diabetes ($n = 9$), kidney disease, ($n = 2$), liver disease ($n = 3$) and metabolic syndrome ($n = 1$) (Figure S1). Twelve further studies assessed the risk of autoimmune/inflammatory diseases such as osteoporosis ($n = 4$), RA ($n = 4$), inflammatory bowel disease ($n = 1$), psoriasis ($n = 2$) and Sjogren's syndrome ($n = 1$; Figure S1).

The included studies were published between 2008 and 2022. Fifteen studies used retrospective data and three studies used a self-reported responses of periodontitis as the exposure[4,33,34]; the remaining studies utilized clinical classification ($n = 27$). Most studies utilized data from Asian populations ($n = 18$); the remaining studies were based in the United States and Europe, including two studies from the UK.[4,35] The median follow-up period was 10 years (interquartile range [IQR]: 5–12 years) (Table 1). Seventeen studies stratified risk estimates by periodontitis severity. Eight studies did not adjust for smoking status[4,36–42] (Table S2).

TABLE 1 Summary of included studies.

Study	Cohort	Total population	Location	Periodontitis classification	Periodontitis diagnosis	Outcome	Total follow-up (years)	Risk of bias[b]
Metabolic diseases								
Alshihayb 2021[75]	Prospective	672	USA	Clinical	PPD at multiple sites per tooth	Diabetes	28	Critical
Akinkugbe 2017[79]	Prospective	2333	Germany	Clinical	PPD and CAL at 4 sites per tooth	Liver disease	9	Serious
Demmer 2008[43]	Retrospective	9296	USA	Clinical	Periodontal pockets and tooth mobility	Diabetes	20	Serious
Grubbs 2016[80]	Retrospective	761	USA	Clinical	PPD and CAL at 6 sites per tooth; half mouth	Kidney disease	5	Critical
Helenius-Hietala 2019[81]	Prospective	6165	Finland	Clinical	PPD at four sites per tooth.	Liver disease	13	Critical
Ide 2011[82]	Prospective	5848	Japan	Clinical	CPI	Diabetes	7	Serious
Iwasaki 2012[83]	Retrospective	317	Japan	Clinical	PPD, CAL and BOP at six sites per tooth	Kidney disease	2	Critical
Kebede 2018[32a]	Prospective	2034	Germany	Clinical	CAL and PPD, four sites per tooth	Diabetes	11	Critical
Larvin 2021[84a]	Retrospective	188863	UK	Self-report	Responses of bleeding gums, painful gums, loose teeth	Metabolic diseases	15	Serious
Lee 2017[85]	Retrospective	354850	South Korea	Clinical	KCD codes	Diabetes	12	Critical
Lin 2014[86]	Retrospective	44601	Taiwan	Clinical	ICD-9 claims codes	Diabetes	5	Critical
Miyawaki 2016[33]	Prospective	2469	Japan	Self-report	Responses of gingival bleeding or loose teeth	Diabetes	5	Serious
Morita 2010[44]	Prospective	1023	Japan	Clinical	CPI of 10 representative teeth in sextants	Metabolic syndrome	4	Serious
Morita 2012[87]	Prospective	21355	Japan	Clinical	CPI of 10 representative teeth in sextants	Diabetes	5	Serious
Myllymak 2018[88]	Prospective	395	Finland	Clinical	PPD	Diabetes	15	Serious
Shin 2022[89]	Retrospective	165032	South Korea	Clinical	ICD-10 codes	Liver disease	11	Serious
Winning 2017[35]	Prospective	1400	UK	Clinical	PPD and CAL at four sites per tooth	Diabetes	9	Critical
Inflammatory diseases								
Arkema 2010[25a]	Prospective	81132	USA	Self-report	Reported history of periodontal surgery	RA	11	Critical
Choi 2017[90]	Retrospective	13464	South Korea	Clinical	KCD codes	Osteoporosis	11	Serious
Choi 2021[91]	Prospective	691506	South Korea	Clinical	KCD codes	RA	12	Critical
Chou 2015[36]	Retrospective	894013	Taiwan	Clinical	ICD-9 claims codes	RA	10	Serious
Demmer 2011[45]	Prospective	9564	USA	Clinical	Periodontal index, full mouth examination, 6 sites per tooth	RA	20	Serious

TABLE 1 (Continued)

Study	Cohort	Total population	Location	Periodontitis classification	Periodontitis diagnosis	Outcome	Total follow-up (years)	Risk of bias[b]
Huayoung 2021[37]	Retrospective	23032	South Korea	Clinical	KCD codes	RA	5	Critical
Keller 2012[38]	Retrospective	230730	Taiwan	Clinical	ICD-9 claims codes	Psoriasis	5	Critical
Larvin 2021[84a]	Retrospective	188863	UK	Self-report	Responses of bleeding gums, painful gums, loose teeth	Inflammatory diseases	15	Serious
Lee 2017[85]	Retrospective	354850	South Korea	Clinical	KCD codes	Osteoporosis	12	Critical
Lin 2015[41]	Retrospective	1878401	Taiwan	Clinical	ICD-9 claims codes	Osteoporosis	9	Critical
Lin 2018[46]	Retrospective	135190	Taiwan	Clinical	ICD-9 claims codes	IBD	13	Critical
Lin 2018[40]	Retrospective	135190	Taiwan	Clinical	ICD-9 claims codes	pSS	13	Critical
Mau 2017[42]	Retrospective	88389	Taiwan	Clinical	ICD-9 claims codes	Osteoporosis	9	Critical
Nakib 2013[34]	Prospective	60457	USA	Self-report	Reported history of periodontal bone loss	Psoriasis	10	Critical

Abbreviations: BOP, bleeding on probing; CAL, clinical attachment level; CPI, community periodontal index; IBD, inflammatory bowel disease; ICD, international classification of diseases; KCD, Korean classification of diseases; PPD, probing pocket depth; RA, rheumatoid arthritis; pSS, Sjogren's syndrome; UK, United Kingdom; USA, United States of America.

[a]Not eligible for meta-analysis due to unavailable raw data/grouped disease outcomes.

[b]Further details of ROBINS-I assessment for risk of bias can be found in Table S3.

ROBINS-I assessment revealed that eighteen studies were at critical risk of bias with the remaining 12 studies at serious risk (Table S3). Confounding was the domain in which the most studies were at critical risk of bias ($n = 17$) due presence of unobserved confounders and residual bias. The quality of reporting across studies according to CONSORT-ROUTINE was good (Table S4). Funnel plots suggest that there was significant risk of publication bias in studies that examined metabolic disease outcomes (Egger's test: $\beta = 5.67$, $p < .05$; Figure S2); this was marginally reduced but still prevalent in autoimmune/inflammatory diseases (Egger's test: $\beta = 2.04$, $p < .05$; Figure S3). The certainty of the evidence was low to very low for the outcomes explored in this systematic review assessed according to GRADE criteria (Table S5). This was due to the high risk of confounding and selection biases associated with observational studies.

3.1 | Periodontitis and risk of diabetes

Random effects meta-analysis revealed a 22% higher risk of incident diabetes in people with periodontitis compared to healthy controls (relative risk [RR] = 1.22, 95% confidence interval [CI] = 1.13–1.33). This was marginally reduced in studies using a clinical periodontitis definition (RR = 1.16, 95% CI = 1.10–1.22). Heterogeneity was low amongst studies reporting diabetes risk using a clinical periodontitis definition ($I^2 = 20.3\%$; Figure 1). Kebede et al[32] was not eligible for meta-analysis due to absence of raw data; however, their findings showed a twofold greater risk of diabetes in people with severe periodontitis compared to healthy controls[26] (Table S2). Compared to Demmer et al[43] who reported risk of diabetes in people with mild periodontitis (RR = 1.01; 95% CI = 0.81–1.26),[43] there was an incremental increased risk of diabetes in people with moderate-to-severe periodontitis (RR = 1.20, 95% CI = 1.11–1.31; RR = 1.34, 95% CI = 1.10–1.63). Heterogeneity was low in studies that reported risk of diabetes in moderate and severe periodontitis ($I^2 = 0\%$; $I^2 = 20.1\%$; Figure 2).

3.2 | Periodontitis and risk of other metabolic diseases

The risk of kidney disease was around twofold higher in people with periodontitis (RR = 2.01, 95% CI = 1.36–2.97) while risk of liver disease was increased by 50% (RR = 1.53, 95% CI = 0.86–2.73; Figure 1). The risk for liver disease in severe PD was 112% higher (RR = 2.12, 95% CI = 1.09–4.13; Table S6). Heterogeneity varies in these studies (kidney disease: $I^2 = 0.0\%$; liver disease: $I^2 = 91.6\%$; Figure 3). One study not eligible for meta-analysis reported 13% increased risk of diabetes, liver disease, kidney disease and metabolic syndrome as a combined metabolic diseases outcome in people with self-reported periodontitis (RR = 1.13, 95% CI = 1.01–1.27).[4] Morita et al[44] also found 43% increased risk of metabolic syndrome (manifestation of blood glucose and blood pressure disturbances, and obesity) in people with periodontitis[44] (Table S2).

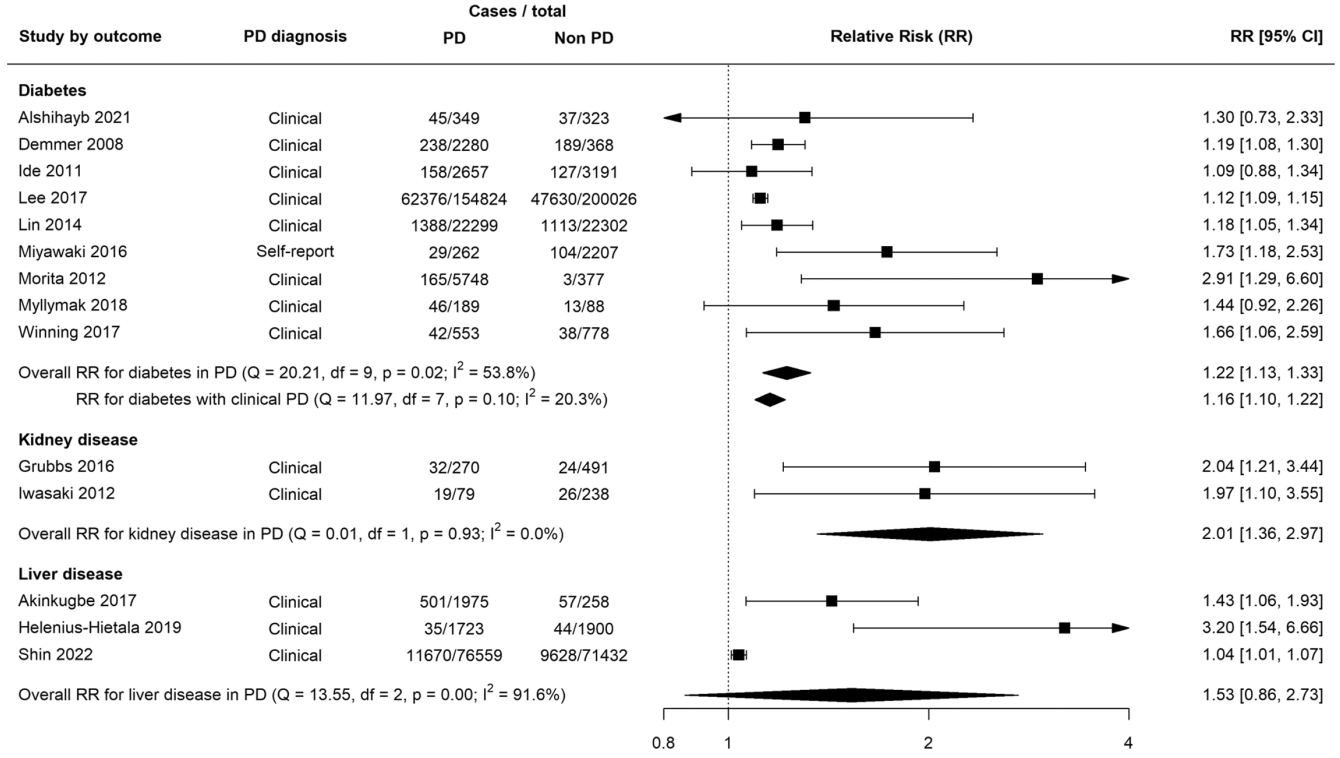

FIGURE 1 Forest plot illustrating results from random effect meta-analysis for the incident risk of diabetes, kidney disease and liver disease, stratified by self-reported or clinical periodontitis diagnosis. CI, confidence interval, df, degrees of freedom, PD, periodontitis, RR, relative risk.

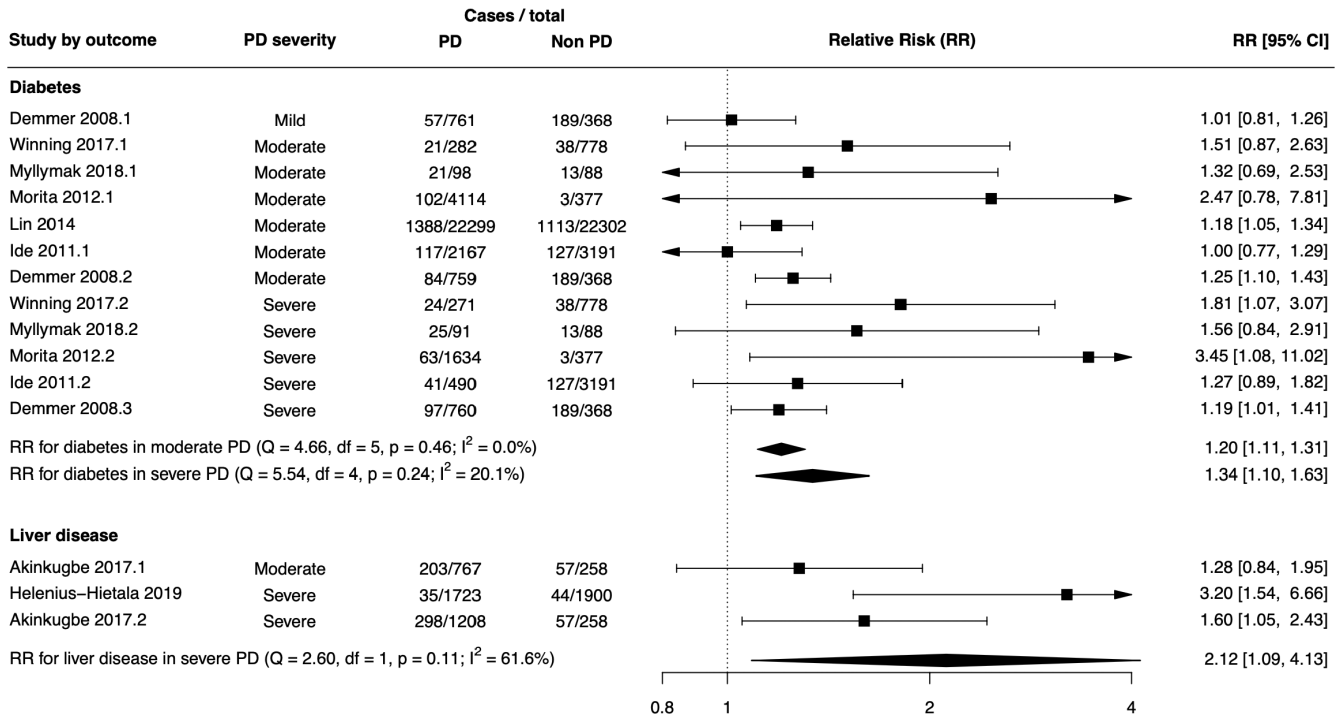

FIGURE 2 Forest plot illustrating results from random effect meta-analysis for the incident risk of diabetes and liver disease, stratified by periodontitis severity. CI, confidence interval, df, degrees of freedom, PD, periodontitis, RR, relative risk.

Meta-regression revealed increased risk of metabolic diseases collectively in studies that utilized self-reported periodontitis compared to clinical classification (RR = 1.57; 95% CI = 0.76–3.28). Risks of kidney disease, liver disease and metabolic syndrome were higher than of diabetes (RR = 1.19, 95% CI = 0.56–2.56; RR = 1.12, 95% CI = 0.77–1.64; RR = 1.10, 95% CI = 0.63–1.95; Table 2), though

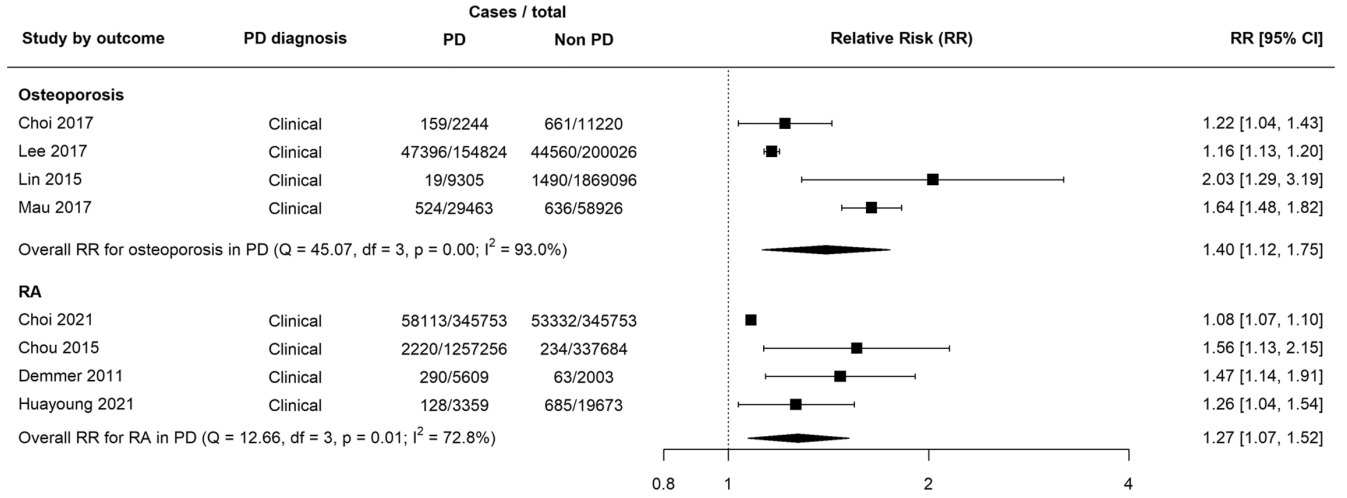

FIGURE 3 Forest plot illustrating results from random effect meta-analysis for the incident risk of osteoporosis and rheumatoid arthritis in people with periodontitis. CI, confidence interval, df, degrees of freedom, PD, periodontitis, RR, relative risk.

these estimates were limited by small study numbers. Sensitivity analysis revealed that removing studies that did not adjust for smoking status did not significantly impact heterogeneity of metabolic diseases collectively (I^2 = 80.6%) (Figure S4). The risk of metabolic diseases in studies with total follow-up length of less than 10 years was higher than those of 10 or more years (RR = 1.45, 95% CI = 1.23–1.71; RR = 1.12, 95% CI = 1.05–1.20, respectively; Figure S5).

3.3 | Periodontitis and risk of osteoporosis

Random effects meta-analysis demonstrated a 40% increased risk of osteoporosis in people with periodontitis compared to healthy controls (RR = 1.40, 95% CI = 1.12–1.75). Heterogeneity was high in studies reporting incidence of osteoporosis (I^2 = 93.0%; Figure 3). One study reported risk of osteoporosis by periodontitis severity.[42,43] The risk for osteoporosis was 56% higher in people with mild periodontitis (RR = 1.56, 95% CI = 1.38–1.75), rising to more than two-fold in moderate and severe cases (RR = 2.08, 95% CI = 1.60–2.70; RR = 2.07, 95% CI = 1.08–3.96; Table S6).

3.4 | Periodontitis and risk of rheumatoid arthritis

The risk RA was increased by 27% in periodontitis compared to healthy controls (RR = 1.27, 95% CI = 1.07–1.52). Heterogeneity was moderately high in studies reporting incidence of RA (I^2 = 72.8%; Figure 3). One study quantified risk of RA in mild, moderate and severe cases of periodontitis compared to healthy controls and found they were similarly increased (RR = 1.67, 95% CI = 1.14–2.45; RR = 1.43, 95% CI = 0.88–2.33; RR = 1.22, 95% CI = 0.74–2.01; Table S6).[45] Arkema et al[25] was not eligible for meta-analysis due to absent raw data also noted 2% and 18% greater risk of RA in nurses with mild to moderate PD, compared to healthy controls[25] (Table S2).

3.5 | Periodontitis and risk of other autoimmune/inflammatory diseases

Two studies reported increased risks of psoriasis of 52% and 40%, respectively (RR = 1.52, 95% CI = 1.38–1.70; RR = 1.40, 95% CI = 1.13–1.73).[34,38] Another study found 46% increased risk of Sjogren's syndrome in people with periodontitis, while risk of inflammatory bowel disease in the same population was not significantly increased (RR = 1.46, 95% CI = 1.35–1.58; RR = 1.01, 95% CI = 0.94–1.08).[46] Larvin et al. (2021) reported a 12% increased risk of grouped autoimmune/inflammatory diseases (comprising osteoporosis and autoimmune diseases) in people with self-reported periodontitis compared to healthy controls (RR = 1.12, 95% CI = 0.93–1.36; Table S2).

There was higher risk for autoimmune/inflammatory diseases in self-reported compared to clinically diagnosed periodontitis (RR = 1.83, 95% CI = 0.56–5.99). Sensitivity analysis revealed that removing studies that did not adjust for smoking status reduced the risk of inflammatory diseases in people with PD to 20% (RR = 1.20, 95% CI = 1.09–1.32; Figure S6). The risk of autoimmune/inflammatory diseases was higher in studies with shorter follow-up than those of 10 years or more (RR = 1.41, 95% CI = 1.18–1.67; RR = 1.21, 95% CI = 1.11–1.32, respectively; Figure S7).

4 | DISCUSSION

This systematic review and meta-analysis of 27 longitudinal cohort studies examined the risk of immune-mediated systemic diseases in people with periodontitis. Diabetes was the most reported disease outcome, and the risk of diabetes is 22% higher in people with periodontitis compared to healthy controls. The risks of developing subsequent kidney and liver diseases, and the risks of osteoporosis and RA are also significantly increased, though the evidence for these associations is scarce. The study showed gradient effect on risk of diabetes in moderate-to-severe periodontitis, though this did not

TABLE 2 Meta-regression demonstrating between-group differences of periodontitis diagnosis, periodontitis severity and disease outcome as covariates to risk of overall metabolic and inflammatory diseases meta-analysis.

	Studies (*n*)	Relative risk (95% CI)
Metabolic diseases		
Periodontitis diagnosis type		
Clinical	14	1.00 (ref)
Self-report	2	1.57 (0.76–3.28)
Periodontitis severity		
Mild	1	1.00 (ref)
Moderate	8	1.17 (0.77–1.79)
Severe	10	1.52 (0.96–2.41)
Disease outcome		
Diabetes	9	1.00 (ref)
Kidney disease	2	1.19 (0.56–2.56)
Liver disease	3	1.12 (0.77–1.64)
Metabolic syndrome	1	1.10 (0.63–1.95)
Inflammatory diseases		
Periodontitis diagnosis type		
Clinical	11	1.00 (ref)
Self-report	2	1.83 (0.56–5.99)
Periodontitis severity		
Mild	2	1.00 (ref)
Moderate	2	1.19 (0.80–1.78)
Severe	4	1.69 (0.76–3.78)
Disease outcome		
Osteoporosis	4	1.00 (ref)
Psoriasis	2	0.57 (0.17–1.92)
RA	4	1.04 (0.69–1.57)

Abbreviations: CI, confidence interval; IBD, inflammatory bowel disease; *n*, number of studies; RA, rheumatoid arthritis; ref, reference group.

have a consistent effect on risk of other immune-mediated systemic conditions.

In this study, we quantified the risk of development for conditions that cause immune response dysregulation in people with periodontitis. Previous reviews have not summarized the evidence of multiple immune-mediated systemic conditions. A systematic review recently calculated the longitudinal risk of diabetes to be 26% higher in people with periodontitis compared to those without.[47] This is consistent with our findings that the risk of diabetes was 22% higher in people with periodontitis; the marginal difference is likely due to exclusion of one study in our meta-analysis due to non-availability of raw data.[26] As reflected in the current findings, previous evidence has demonstrated significantly increased odds of kidney and liver conditions in populations with periodontitis.[48,49] The risks for kidney and liver diseases in the present study were much higher than any other condition, though this value is likely influenced by the small number of studies. Other systematic reviews have quantified the odds of autoimmune diseases such as RA[50,51] and inflammatory bowel disease,[52] and inflammatory conditions such as osteoporosis.[53] One systematic review concluded that there is no significant difference in prevalence of periodontitis in people with RA.[54] It is worth noting that previous systematic reviews have incorporated cross-sectional studies that can only demonstrate correlation and therefore prevent conclusions on the direction of association. Until now, there has been no comparable study to use longitudinal studies exclusively to account for the risk of periodontitis on diseases characterized by chronic inflammation.

A plausible mechanism for the observed associations between periodontitis and higher risks of diabetes, RA and osteoporosis is via upregulation of shared inflammatory pathways and uncontrolled cytokine secretion.[55,56] For example, periodontal pathogens such as *P. gingivalis* are linked to augmented levels of pro-inflammatory mediators such as C-reactive protein and IL-6.[57] These markers upregulate inflammatory pathways, and the hyperinflammation that ensues can become systemic. This can also cause disturbances to homeostatic metabolic networks via dyslipidaemia and insulin resistance,[58,59] and effects to the autoimmune system through amplified burden of citrullinated peptides.[60] Other findings suggest that systemic inflammation is not a mediator in the relationship between periodontitis and subsequent all-cause mortality.[19] While this outcome is broader than the scope of the present review, the inference that associations are and multifactorial and more complex than upregulation of single pathways is paramount to interpreting oral-systemic associations. Nonetheless, the pathogenicity of localized *P. gingivalis* infection and the chronic inflammation the periodontitis condition causes can have a profound effect on overall systemic health and subsequent disease development.

The focus of this review unites the systemic effects of metabolic network disruption and uncontrolled chronic inflammation as preluding steps towards further multimorbidity development. Conditions such as diabetes and kidney and liver diseases induce hyperglycaemia and hyperlipidaemia. These disorders interact with, and reduce, leukocyte and macrophage activity of removing pathogens, thereby dysregulating immune responses.[61] Furthermore, the uncontrolled upregulation of pro-inflammatory mediators and cytokines as a result of chronic diseases, such as RA or osteoporosis, have deleterious effect on immune response and other tissues.[62] The subsequent dysfunctional immune responses result in inefficient eradication of invading pathogens and infections. This puts individuals with pre-existing conditions at risk for further multimorbidity development and healthcare burden. As such, people with periodontitis with systemic inflammation as a co-morbidity are at heightened risk of systemic multimorbidity development.[63]

Our results illustrate a dose–response relationship between periodontitis severity and risk of diabetes, which reflects a recent study that showed a non-linear trend between community periodontal index scores and diabetes incidence.[47] A dose–response relationship has also been observed in periodontitis and subsequent risk of cardiovascular disease.[15] Although we did not observe the

dose–response relationship for other conditions, this was likely due to the reduced number of studies that reported periodontitis severity and the subsequent impact of heterogeneity.

The findings of the present review and meta-analysis found 22%, 40% and 27% increased risks for diabetes, RA and osteoporosis in people with periodontitis. We previously found a 20% higher risk of CVD in people with periodontitis compared to healthy controls.[15] Other reviews have suggested that people with periodontitis have a 20% higher risk of cognitive decline[64] and 46% higher risk of all-cause mortality.[65] It could be surmised that periodontitis may not augment one's risk of an individual condition, but rather increases an individual's susceptibility to further multimorbidity development in general.[57] In this case, a holistic approach may be more appropriate in exploring associations of multimorbidity development in people with periodontitis. We previously utilized the novel process mining method to identify multimorbid disease trajectories of periodontitis within the UK Biobank population who were free from systemic disease at baseline.[4] Process mining differs from traditional epidemiologic methods which usually examine risks of single diseases and do not account for temporal progression of multiple outcomes. Future studies using process mining methods on routinely collected data could illustrate the effect of periodontal treatment on multimorbid disease progression pathways. This would identify whether periodontal treatment can be a candidate as a non-drug treatment alternative to multimorbidity prevention.

Until now previous reviews have not assessed the effect of periodontitis classification type on risk of metabolic/inflammatory diseases, with the concern that the use of self-reported classifications of periodontitis should be limited to validated tools only.[66,67] Conversely, previous literature suggests that the use of self-reported measures such as 'bleeding gums' and 'loose teeth' may be viable proxies when clinical periodontal examination is unavailable only.[66,67] We recently showed that there was no difference in risk of CVD in people with periodontitis using a clinical vs self-reported classification,[15] while the present study suggested an increased risk of immune-mediated systemic disease in self-reported periodontitis compared to clinical diagnosis. These findings suggest that there is a strong potential for type II error and validation studies are required to substantiate the use of self-reported periodontitis indicators in the general population. Additionally, our subgroup analysis revealed higher risks of immune-mediated systemic diseases in studies with shorter follow-up length; this could be reflective of pre-existing, undiagnosed conditions circulating in populations. The estimates from studies of shorter follow-up period could report co-prevalence of conditions, rather than the incident risk also leading to type II errors. Future studies should aim for longer follow-up periods to improve accuracy of risk estimates.

This review is timely given the emerging evidence showing links periodontitis and subsequent systemic disease progression and will demonstrate the importance for research into oral-systemic associations in alleviating the overall burden of multimorbidity. The strengths of our systematic review are largely reflective of the robust search strategy and statistical methodology used. Given that only longitudinal cohort studies were included, we can draw a degree of causal inference between the association of periodontitis and subsequent development of metabolic and inflammatory diseases. Through subgrouping and meta-regression, we explored the effect of periodontitis on subsequent risk of all-incident metabolic/inflammatory diseases, plus individual diagnoses. This not only enabled inclusion of more studies than before in a systematic review of this topic, but also allowed for investigation of the impact periodontitis classification type and severity on development of metabolic and inflammatory diseases which has not previously been done before. The reliability of the report is strengthened through strict adherence to the PRISMA guidelines.[31]

Though reporting quality of studies was overall good according to the CONSORT-ROUTINE specification, the results from ROBINS-I assessment revealed confounding and selection bias were significant limiters of all included studies through their use of electronic health records, non-generalisable cohorts or non-random sampling methods. The certainty of the evidence was also low for the outcomes explored in this systematic review. This reflects the high risk of confounding and selection biases which are not unexpected in observational studies. In some research datasets, there may also be an element of 'healthy volunteer' bias.[68] Other factors such as disease history are confounders to the association and can significantly impact development of periodontitis and other systemic diseases; residual bias remains even when confounders are adjusted for in the risk models. Residual bias can also limit findings due to unmeasured confounders, such as socioeconomic status, which is difficult to accurately measure in routine data yet is an important risk factor to both periodontitis and systemic disease.[69] Studies were also not able to account for undiagnosed conditions prior to periodontitis that could also interact with inflammatory pathways and may limit inferences on the direction of association. Accordingly, a limitation to the findings of this systematic review is the small number of eligible studies and large proportion of statistical heterogeneity which limits the certainty of pooled estimates. We were able to account for some of this through subgrouping by periodontitis severity in the meta-analysis of risk for metabolic diseases; however, this reduced the sample sizes and limits statistical power of these pooled estimates. Subgrouping had reduced effect for inflammatory diseases which could be due to the limited number of studies that reported periodontitis severity and risk of inflammatory diseases. As such, there is a need for further analogous research is needed in this field before robust conclusions can be made. While self-reported versus clinical classifications of periodontitis did not show significant differences in risk estimates, significant heterogeneity remained after subgrouping suggesting unaccounted for differences. This could be due differing medical classification guidelines, diagnostic inconsistencies in partial and whole mouth periodontal examinations,[70] and discrepancies in case definition used to define periodontitis.[71] For example, studies can grossly underreport prevalence of periodontitis if the case definition does not account for mild cases[13]; this may subsequently confound the reliability of risk estimates for these outcomes. There is also evidence to suggest that self-reported signs

of periodontal disease can accurately identify patients,[72] though accuracy may be reduced in less severe cases.[73] A universally accepted and validated case definition for periodontitis research should be agreed to alleviate potential measurement bias. The meta-analysis was restricted by the limited available data for further subgrouping and meta-regression. More studies are required to enable exploration of additional risk factors such as sex and age in the future. Several included studies did not adjust for smoking which may have had further unobserved confounding effect on risk estimates. While the sensitivity analysis showed that this had minimal impact to heterogeneity, it is widely accepted that smoking is a significant risk factor to periodontitis and systemic disease and future observational cohorts that include these data should be favoured.[74] One study used quantitative bias analysis to account for the risk of unmeasured confounding and found that the association between periodontitis and diabetes remained.[75] Incorporating causal inference methods such as quantitative bias analysis and propensity score matching alleviates the risk of selection bias and are a necessity for robust observational studies.[76]

The present systematic review advocates the association between periodontitis and higher risk for developing further multimorbidity; this has clinical implications. For example, dental professionals need to be aware of the risks of multimorbidity and prioritize effective prevention and management of periodontitis so that risks of subsequent systemic diseases may be minimized.[77] Researchers should also consider periodontitis as a possible risk factor when exploring incidence of systemic diseases. Additionally, the low certainty of evidence advocates for better quality studies in the future which navigate the risks of confounding and selection biases. The findings are also timely in the wake of the COVID-19 pandemic, which has shown that both periodontitis and multimorbidity greatly increases risk of adverse outcomes[20,78]; oral health self-management should be stressed as public health initiative to reduce further burden of multimorbidity on healthcare services.

5 | CONCLUSION

In conclusion, people with moderate-to-severe cases of periodontitis have higher risk of developing diabetes, while the effect of periodontal severity on risk of other immune-mediated systemic conditions requires further investigation. The certainty of evidence in this field is low. More longitudinal evidence with careful population selection and study design is required to form robust conclusions on the association of periodontitis and subsequent immune-mediated systemic diseases.

AUTHOR CONTRIBUTIONS

HL contributed to conception, study screening, data analysis and interpretation, and drafted the manuscript. JK contributed to interpretation, and critically revised the manuscript. VRA contributed to interpretation, and critically revised the manuscript. SP contributed to interpretation, and critically revised the manuscript. JW contributed to conception, study screening, study design, data acquisition and interpretation, and critically revised the manuscript. All authors gave their final approval and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article are available in this published article and supplement materials.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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