SYSTEMATIC REVIEW AND META-ANALYSIS

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The Association between Periodontitis and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Background & Aims: Recent studies have suggested an association between periodontitis and nonalcoholic fatty liver disease (NAFLD) although the results were inconsistent. The current systematic review and meta-analysis was conducted with the aim to comprehensively investigate this possible association by identifying all relevant studies and combining their results together.

Methods: A comprehensive literature review was conducted utilizing the MEDLINE and EMBASE databases through December 2019 to identify all studies that compared the risk of NAFLD among patients with periodontitis to individuals without periodontitis. Effect estimates from each study were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird.

Results: A total of five studies with 27,703 participants fulfilled the eligibility criteria and were included in the meta-analysis. All five studies reported the magnitude of association between NAFLD and periodontitis that was diagnosed based on the periodontal pocket depth of > 3.5-4 mm. The pooled OR of unadjusted analysis was 1.48 (95%CI: 1.15-1.89; I^2 92%). However, when adjusted results from the primary studies were used, pooled OR decreased to 1.13 and lost its statistical significance (95%CI: 0.95–1.35; I^2 67%). Three studies reported the magnitude of association between NAFLD and periodontitis that was diagnosed based on a clinical attachment level of ≥ 3 mm. The pooled OR of unadjusted analysis was 1.13 (95%CI: 1.07-1.20; I^2 0%). However, when adjusted results from the primary studied were used, pooled OR decreased to 1.08 and lost its statistical significance (95%CI: 0.94–1.24; I^2 58%)

Conclusions: The study found a significant association between periodontitis and NAFLD. However, the association lost its significance when various metabolic parameters were adjusted, suggesting that those metabolic conditions, not periodontitis itself, were predisposing factors for NAFLD.

Key words: nonalcoholic fatty liver disease – nonalcoholic steatohepatitis – periodontitis – periodontal disease – dental caries.

Abbreviations: NAFLD: nonalcoholic fatty liver disease; NHANES: National Health and Nutrition Examination Survey.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common liver disease characterized by hepatic fat deposition that is not caused by excessive alcohol consumption or other etiologies [1]. It has been estimated that approximately twenty-five percent of adults in the world are affected by NAFLD [1, 2]. NAFLD has a bidirectional relationship with metabolic syndrome and its components, including obesity, hypertension, diabetes mellitus, which is believed to be mediated by oxidative stress and chronic inflammatory response [3, 4]. Interestingly, recent studies have suggested that alteration in gut microbiome may also play a role in the pathogenesis of NAFLD [5, 6].

Periodontitis is a chronic oral inflammatory condition caused by an exaggerated inflammatory response against polymicrobial colonization in the dental plaque. *Porphyromonas gingivalis* is the bacteria commonly responsible for biofilm formation around the gingival area [7]. A recent National Health and Nutrition Examination Survey (NHANES) found that almost 10% of Americans suffered from severe periodontitis [8]. Because of the chronic systemic inflammatory response generated by chronic periodontitis, patients with this

condition may be at a higher risk of NAFLD [9, 10] although results from epidemiological studies were inconsistent [11-15]. In fact, a previous systematic review has suggested this association although no statistical evaluation was performed through a meta-analysis [16]. The current systematic review and meta-analysis was conducted with the aim to compare the risk of NAFLD among patients with periodontitis versus individuals without periodontitis, by identifying all relevant studies and combining their results together.

METHODS

Information Sources and Search strategy

A systematic literature search of the Ovid MEDLINE and EMBASE databases was carried out from inception to December 2019 to identify all original studies that compared the risk of NAFLD between patients with periodontitis and individuals without periodontitis. Three investigators (K.W., P.P., and P.U.) independently screened and reviewed the literatures using the search strategy that included the terms for "nonalcoholic fatty liver disease", "steatohepatitis", "periodontitis", "periodontal diseases", "periodontal infection", and "dental caries" as described in Supplementary Data 1. No language, publication status or publication date limitation was applied. References cited in selected articles were reviewed for additional eligible studies. We conducted this systematic review and meta-analysis in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guideline [17], which is provided as Supplementary Data 2.

Selection criteria

To be eligible for this meta-analysis, studies had to compare the risk of NAFLD among patients with periodontitis versus individuals without periodontitis. The study design could be either a cohort study, a case-control study or a cross-sectional study. An eligible cohort study must recruit two groups of participants, patients with periodontitis and comparators without periodontitis, and follow them for incident NAFLD. Relative risk (RR) comparing the incidence of NAFLD between the two groups along with 95% confidence interval (CI) must be provided. An eligible case-control study must recruit cases with NAFLD and controls without NAFLD and explore their prior history of periodontitis. Odds (OR) comparing the prevalence of periodontitis between the two groups along with 95% CI must be provided. An eligible cross-sectional study must recruit participants and explore whether they have NAFLD and periodontitis at the same time. OR of this association along with 95% CI must be provided. Inclusion was not limited by study size. When more than one article utilizing the same database/cohort was available, only one study with the most comprehensive data/analyses was included.

Retrieved articles were reviewed for their eligibility independently by the same three investigators (K.W., P.P., and P.U.) with disagreements resolved by consensus. The Newcastle-Ottawa quality assessment scale was used to appraise the quality of cohort studies and case-control studies [18]. The modified version of this scale was used for the quality assessment of cross-sectional studies [19].

Data abstraction

The investigators used a structured information collection form to extract the following data from each study: title of the study, name of the first author, publication year, year of study, country where the study was conducted, number of participants, baseline characteristics of participants, methods used to identify and confirm diagnosis of NAFLD, definition of periodontitis, adjusted effect estimates with 95%CI and covariates that were adjusted in the multivariate analysis.

To ensure the accuracy, this data extraction process was independently performed by two investigators (K.W. and P.P.) and was reviewed by the senior investigator (P.U.).

Statistical analysis

Data analysis was performed using the Cochrane Collaboration's Review Manager 5.3 software (London, United Kingdom). Adjusted point estimates from each study were consolidated by the generic inverse variance method of DerSimonian and Laird, which assigned the weight of each study for the pooled analysis based on the magnitude of its variance [20]. The random-effect model was chosen over the fix-effect model because the basic assumption of the fixed-effect model that all studies should yield the same result is universally not true for observational studies. RR of cohort study was used as an estimate of OR to calculate pooled OR along with OR of case-control and cross-sectional study. Cochran's Q test and I^2 statistic were used to quantify the between-study heterogeneity. A value of I^2 of 0-25% represents insignificant heterogeneity, 26-50% represents low heterogeneity, 51-75% represents moderate heterogeneity, and more than 75% represents high heterogeneity [21]. A funnel plot was used for the assessment for the presence of publication bias.

RESULTS

A total of 266 potentially eligible articles were identified using the described search strategy (117 from MEDLINE and 149 from EMBASE). After the exclusion of 91 duplicated articles, titles and abstracts of 175 unique articles were reviewed. One hundred and fifty-six articles were excluded at this stage since they were case reports, case series, correspondence, review articles, in vitro studies, animal studies or interventional studies, leaving 19 articles for full-text review. Fourteen of them were excluded after the full-length review because they did not report the outcome of interest. Finally, a total of five studies [11-15] (one cohort study [12] and four cross-sectional studies [11, 13-15]) with 27,703 participants were included in the meta-analysis. All five studies reported the association between the two conditions using periodontal pocket depth to diagnose periodontitis. Three out of five studies [11-13] also reported the association using the clinical attachment level to diagnose periodontitis. The literature retrieval, review and selection process are demonstrated in Fig 1. The characteristics and quality appraisal of the included studies are presented in Table I. Inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistic of 0.75.

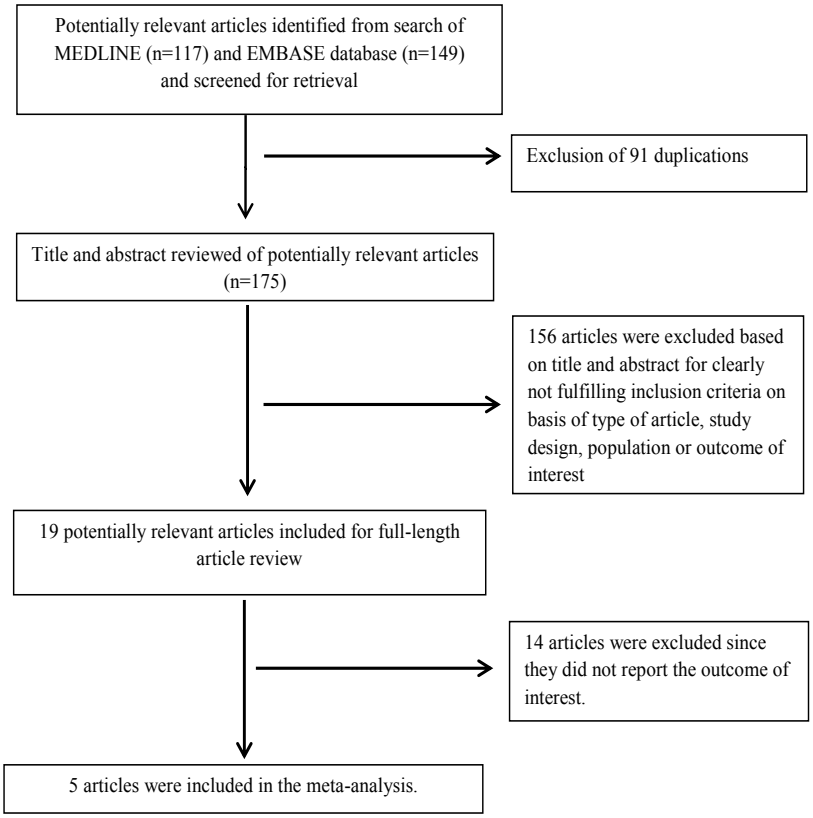

Fig. 1. Literature review process

Association between periodontitis and nonalcoholic fatty liver disease

All five studies reported the magnitude of the association between NAFLD and periodontitis that was diagnosed based on the periodontal pocket depth of > 3.5-4 mm. The pooled OR of unadjusted analysis was 1.48 (95%CI: 1.15-1.89; I^2 92%) (Fig. 2A). However, when adjusted results with insulin resistance and metabolic parameters from the primary studies were used, pooled OR decreased to 1.13 and lost its statistical significance (95%CI: 0.95–1.35; I^2 67%) (Fig. 2B).

Table I. Main characteristics of the studies included in this meta-analysis

Study	Akinkugbe et al [12]	Alazawi et al [13]	Akinkugbe et al [11]	Iwasaki et al [14]	Shin et al [15]
Country	Germany	USA	USA	Japan	South Korea
Study design	Retrospective cohort	Cross-sectional study	Cross-sectional study	Cross-sectional study	Cross-sectional study
Year	2017	2017	2018	2018	2019
Total number of participants	2,330	8,172	11,914	1,226	4,061
Recruitment of participants	Participants were residents of Western Pomerania, Germany, aged 20-79 years who were enrolled in a health survey study, The Study of Health in Pomerania. Enrollment was from 1996 to 2001 and participants were followed for the median duration of 7.7 years. Dental examination was performed at baseline. Abdominal sonography and liver chemistry tests were performed during follow-up visits (at 5 and 10 years after enrollment).	Participants were individuals aged 20-74 years who were enrolled in NHANES III study (conducted between1988 and 1994) and underwent both ultrasound and oral examination as a part of that study.	Participants were Hispanic/Latino individuals aged 18-74 years who were enrolled in a health survey study, Hispanic Community Health Study/Study of Latinos. Enrollment was from March 2008 to June 2011. Only participants who underwent dental examination and had serum transaminase measurement were included into this study.	Participants were individuals who underwent oral health check-ups at Asahi University Hospital in Gifu, Japan between January 2016 and December 2016. After enrollment, all participants underwent abdominal sonography and liver chemistry tests.	Participants were individuals aged 19 years and older who were enrolled in KNHANES 2010. Only participants who underwent dental examination and had serum transaminase measurement were included into this study.

Table I (continued)

Diagnosis of periodontitis	Periodontitis was diagnosed based on the presence of either CAL ≥ 3 mm or PD ≥ 4 mm.	Periodontitis was diagnosed based on the presence of either CAL ≥ 3 mm or PD ≥ 4 mm.	Periodontitis was diagnosed based on the presence of either CAL ≥ 3 mm or PD ≥ 4 mm.	Periodontitis was diagnosed based on the presence of PD ≥ 4 mm.	Periodontitis was defined as PD ≥ 3.5 mm.
Diagnosis of NAFLD	NAFLD was diagnosed based on ultrasound findings of hepatic steatosis without secondary causes of hepatic fat accumulation or elevated serum ALT (>34.2 U/l in men and >24.0 U/l in women) without other causes of liver injury.	NAFLD was diagnosed based on ultrasound findings of hepatic steatosis without secondary causes of hepatic fat accumulation.	NAFLD was diagnosed based on FLI score of ≥ 60%.	NAFLD was diagnosed based on ultrasound findings of hepatic steatosis without secondary causes of hepatic fat accumulation.	NAFLD was diagnosed based on FLI score of >60% and HSI >36%.
Average of participants in years	Overall 46.0	N/A	Overall 40.4	NAFLD: 53.0 No NAFLD 48.0	N/A
Percentage of female	Overall 59.0	NAFLD: 47.5 No NAFLD: 53.1	Overall 54.9	NAFLD: 17.1 No NAFLD 44.6	Overall 63.7
Baseline comorbidity	Overall Obesity: 17.0% Diabetes: 15.0%	NAFLD: Obesity: 38.3% Diabetes:10.7% Hypertension: 34.4% Hypercholesterolemia: 32.1% No NAFLD: Obesity: 14.0% Diabetes: 2.8% Hypertension: 18.7% Hypercholesterolemia: 25.0%	Overall Abdominal obesity: 52.2% Diabetes: 13.7%	N/A	Overall Obesity: 29.5% Diabetes: 9.9% Hypertension: 33.1% Hypercholesterolemia: 14.5%
Confounder adjusted in multivariate analysis	Age, waist circumference, BMI, alcohol, education, smoking, diabetes and physical activity	Gender, age groups, ethnicity, poverty income ratio, education, diet, smoking, diabetes, hypertension, cholesterol and BMI	Age, gender, abdominal obesity, smoking, diabetes, physical activity, education, and acculturation score	Gender, age, Brinkman index, BMI, present teeth, HbA1C, total cholesterol, triglyceride, HDL, LDL, SBP, DBP and CRP	Age group, income, education, smoking, alcohol consumption, International Physical Activity Questionnaire, diabetes, obesity, hypertension and hypercholesterolemia
Quality assessment (Newcastle-Ottawa scale)	Selection: 4 Comparability: 1 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3

Abbrev.: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CAL: clinical attachment level; CRP: C-reactive protein; DBP: diastolic blood pressure; FLI: fatty liver index: HbA1C: hemoglobin A1C; HDL: high-density lipoprotein; HIS: hepatic steatosis index; KNHANES: Korean National Health and Nutrition Examination Survey; LDL: low-density Lipoprotein; NAFLD: non-alcoholic fatty liver disease; NHANES: United States National Health and Nutrition Examination Survey; PD: probe pocket depth; SBP: systolic blood pressure; WC; waist circumference.

Three studies reported the magnitude of the association between NAFLD and periodontitis that was diagnosed based on the clinical attachment level of ≥ 3 mm. The pooled OR of unadjusted analysis was 1.13 (95% CI: 1.07-1.20; I^2 0%) (Fig. 3A). However, when adjusted results with insulin resistance and metabolic parameters from the primary studies were used, pooled OR decreased to 1.08 and lost the statistical significance (95%CI: 0.94–1.24; I^2 58%) (Fig. 3B).

Subgroup analysis

The subgroup analysis was performed based on the methods used to diagnose NAFLD, ultrasonography versus non-invasive markers. However, this subgroup analysis can be performed for only periodontitis that was diagnosed based on the periodontal pocket depth. It could not be done for periodontitis that was diagnosed based on the clinical attachment level because only three studies were available for that meta-analysis.

For the unadjusted analysis, the pooled OR of the ultrasonography subgroup was 1.34 (95%CI: 0.97–1.84; I^2 91%) and the pooled OR of the non-invasive marker subgroup was 1.92 (95% CI: 0.76 – 4.85; I^2 94%) (Fig. 2A).

For the adjusted analysis, the pooled OR of the ultrasonography subgroup was 1.24 (95%CI: 0.80–1.91; I^2 73%) and the pooled OR of the non-invasive marker subgroup was 1.27 (95%CI: 0.75–2.14; I^2 75%) (Fig. 2B).

Evaluation for publication bias

A funnel plot was constructed for the analysis based on the periodontal pocket depth but not the clinical attachment level as only three studies were available for the latter.

The plots for both unadjusted (Fig. 4) and adjusted analysis (Fig. 5) were relatively symmetric and, thus, were not indicative of publication bias.

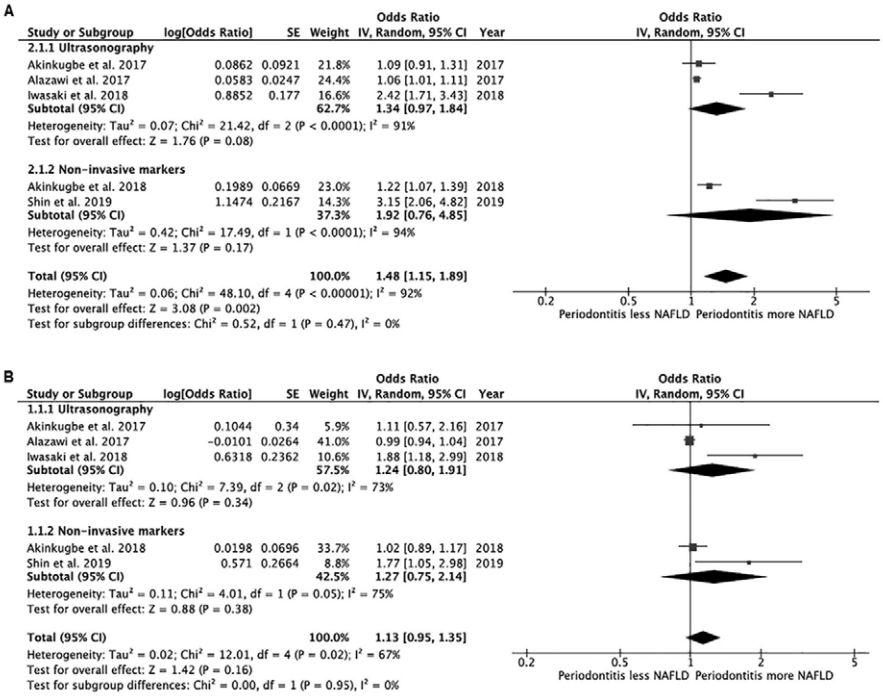

Fig. 2. A) Forest plot of the unadjusted meta-analysis on the association between periodontitis diagnosed based on the probe pocket depth and nonalcoholic fatty liver disease. B) Forest plot of the adjusted meta-analysis on the association between periodontitis diagnosed based on the probe pocket depth and nonalcoholic fatty liver disease.

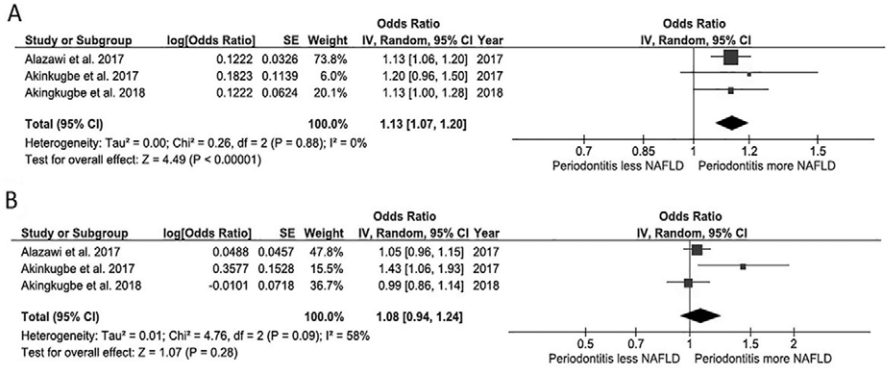

Fig. 3. A) Forest plot of the unadjusted meta-analysis on the association between periodontitis diagnosed based on the clinical attachment level and nonalcoholic fatty liver disease. B) Forest plot of the adjusted meta-analysis on the association between periodontitis diagnosed based on the clinical attachment level and nonalcoholic fatty liver disease.

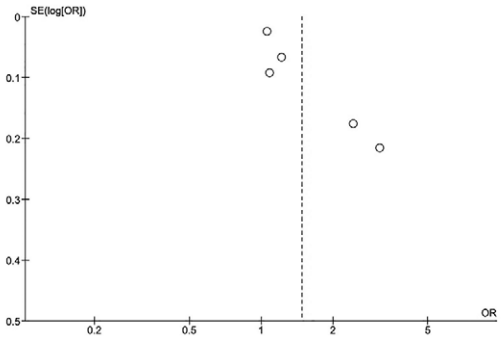

Fig. 4. Funnel plot of the unadjusted meta-analysis on the association between periodontitis diagnosed based on probe pocket depth and nonalcoholic fatty liver disease.

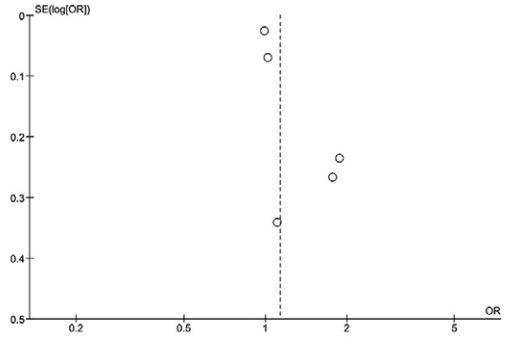

Fig. 5. Funnel plot of the adjusted meta-analysis on the association between periodontitis diagnosed based on the probe pocket depth and nonalcoholic fatty liver disease.

DISCUSSION

The multiple-hit theory is the widely accepted model of pathogenesis of NAFLD [22]. According to this model, systemic inflammation, in addition to insulin resistance and metabolic syndrome, also plays an important role in hepatic injury that leads to fatty accumulation [22]. Tumor necrosis factor-alpha and interleukin-6 are the two important inflammatory mediators that are known to be involved in this pathogenesis [23, 24]. Interestingly, both can be locally produced in the biofilm of the dental plaque of patients with periodontitis and can subsequently enter bloodstream causing systemic inflammation [25]. In addition, a study in fatty liver mice with dental *Porphyromonas gingivalis* infection found positive staining of the bacteria in both hepatocytes and liver macrophages [26], suggesting that the bacteria may enter bloodstream through exposed blood vessels of periodontitis, causing bacteremia and direct injury to the liver. Based on these observations, it is possible that periodontitis could be an independent risk factor for the development of NAFLD.

However, the results of the current systematic review and meta-analysis do not support this hypothesis as we only found a significantly increased risk of NAFLD in the unadjusted models for both diagnoses based on the periodontal pocket depth and the clinical attachment level. After adjustment for insulin resistance and metabolic parameters, the magnitude of association decreased to a non-significant level, suggesting that the apparent association was confounded by those metabolic conditions. This is unsurprising as it is known that patients with periodontitis have a higher prevalence of metabolic syndrome and diabetes than the general population [27, 28]. In fact, a systematic review and meta-analysis published in 2013 concluded that the current literature supports an association between metabolic syndrome and periodontitis [27].

Even though the current study took advantage of the systematic review and meta-analysis technique to ensure that all available data were accounted for, the study still had some limitations and the results should be interpreted with some caution. First, between-study heterogeneity was not low in most analyses. We suspect that the variation in the definition of NAFLD and characteristics of background population were responsible for this. Second, the meta-analysis included only five studies from four countries and, thus, the results may not be generalizable to the other parts of the world. Third, the prevalence of NAFLD in the included studies might be under or overestimated since the included studies did not use liver biopsy, which is the gold standard technique, to diagnose NAFLD. In fact, two studies [11, 15] included in this meta-analysis with more than half of the study population (15,975 out of 27,703 subjects) predicted the presence of NAFLD using non-invasive scores. Therefore, the prevalence of NAFLD can possibly be underestimated. We tried to minimize this bias by performing subgroup analysis based on the methods used to diagnose NAFLD (ultrasonography versus non-invasive markers). We were able to perform this subgroup analysis on periodontitis that was diagnosed based on periodontal pocket depth. Unfortunately, the analysis was severely underpowered as only a few studies were eligible, with none of the subgroup analysis reaching statistical significance. Lastly, we cannot be certain what confounders were responsible for this association as variables that were adjusted in the multivariate analysis varied across the included studies.

In conclusion, the current systematic review and meta-analysis found a significant association between periodontitis and NAFLD. However, the association lost its significance when various metabolic parameters were adjusted, suggesting that those metabolic conditions, not periodontitis itself, were the predisposing factors for NAFLD.

Conflicts of interest: None to declare.

Authors' contributions: K.W., P.P, W.C., P.U., S.P: conceived and designed the study. K.W., P.P, W.C., P.U., F.J.L., D.M. H. analysed the data and drafted the manuscript. S.P., P.U. critically revised the manuscript and supervised the study. All the authors approved the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-841

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