Title: Periodontal health and the frequency of COPD exacerbations: a systematic review and meta-analysis

Running title: Periodontitis and COPD exacerbations

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Abstract

Objectives

The primary objective of this systematic review was to analyse the association between poor periodontal health and the frequency of chronic obstructive pulmonary disease (COPD) exacerbations.

Sources

Pubmed; Embase; Web of Science; CINAHL and Medline were searched for studies published until May 2020, with no language restriction.

Study selection

Studies reporting periodontal condition, or periodontal treatment outcomes, with data on the frequency of exacerbations of COPD were identified. Secondary outcomes included quality of life and hospitalisation. Studies were assessed for eligibility and quality by two assessors independently.

Data

Searches identified 532 records and 8 papers met the inclusion criteria. The data from clinical trials showed a significant reduction in the frequency of exacerbations over one year following periodontal treatment (Relative risk = 0.28; 95% confidence interval (CI) 0.09-0.83, *p*=0.02). Based on the random-effects model of pooled studies, poor periodontal status as quantified by; high plaque index (Odds ratio (OR) 1.63; 95% CI 1.15 - 2.31, *p*=0.01), deep probing pocket depths (OR=2.03; 95% CI 1.46 - 2.82, *p*<0.001) and increased clinical attachment level (OR=1.68; 95% CI 1.17

- 2.42, *p*=0.01) were associated with increased frequency of COPD exacerbations. Qualitative analysis revealed that better periodontal health was associated with reduced hospitalisations and improved quality of life in COPD patients. The quality of some of the included studies was low and there was evidence of heterogeneity.

Conclusion

The data supports an association between poor periodontal health and the frequency of COPD exacerbations. A limitation was the high risk of bias and the poor quality of some of the included studies.

Clinical Significance

Severe COPD exacerbations frequently lead to hospitalisation, with significant healthcare costs, and are associated with an increased risk of mortality. Emerging evidence suggests good periodontal health, including improvements as a result of periodontal treatment, can reduce the frequency of COPD exacerbations, hospitalisation and improve the quality of life for COPD patients.

Introduction

The global initiative for chronic obstructive lung disease (GOLD) defines COPD as 'a common preventable and treatable disease characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases[1]. It has a worldwide prevalence of 9–10% in adults >40 years of age and is responsible for an estimated global annual death toll of 3 million [2].

It is well recognised that smoking is the primary risk factor for COPD[2], but emerging evidence suggests that periodontitis may contribute to the risk of COPD[3]. Periodontitis is a chronic inflammatory disease, caused by anaerobic bacteria and characterised by destruction of tooth-supporting structures [4]. COPD and periodontitis share several risk factors such as age, smoking, stress and ethnicity[5]. The diseases also have similar pathophysiology, characterised by inflammation, recruitment of neutrophils and release of proteolytic enzymes, resulting in the destruction of the pulmonary alveolus or destruction of the periodontal tissues[6]. Patients with confirmed COPD have lower tooth brushing frequency and poorer periodontal health than comparable control groups[7][8]. The association between periodontitis and COPD has been the subject of several observational longitudinal studies. In a meta-analysis of 14 observational studies, periodontal disease was found to be a significant and independent risk factor for COPD, however, whether a causal relationship exists remains uncertain[9].

Progressive lung function decline may be accelerated by acute exacerbations of COPD (AE-COPD)[2]. These acute episodes frequently necessitate additional therapy

and may also lead to hospitalisation incurring substantial healthcare costs. Factors that contribute to AE-COPD include co-morbidities, smoking, airway infections (bacterial and viral) and environmental pollution. Studies have shown that bacterial lung infections are the cause of 50% of COPD exacerbations[10]. The majority of AE-COPD respond to antibiotic treatment, providing further evidence that infection is an important factor[11]. Increased microbial diversity in COPD patients has been demonstrated with the identification of oral bacteria in their lung microbiome and tissue[12][13]. In COPD patients, it is possible that reduced laryngotracheal mechanosensitivity and decreased airway clearance due to impaired mucociliary function[14][15], increases the risk of aspiration of oral secretions and bacteria.

One of the suggested mechanisms through which poor oral health and periodontal disease contribute to the development and progression of COPD is by aspiration of pathogenic bacteria[16][17]. The dental plaque biofilm, particularly that associated with the tissue changes in periodontal disease, incorporates pathogenic bacterial species that may be disseminated to cause infection in extra oral sites[18][19]. Poor oral hygiene may contribute to the colonisation of dental plaque by respiratory pathogens[20]. Elevated antibody levels against key periodontal pathogens including *Fusobacterium nucleatum* and *Prevotella intermedia* have also been found in the sputum of patients with an acute exacerbation of chronic bronchitis, further supporting a role for oral bacteria in lung infections[21].

Frequent AE-COPD are associated with accelerated lung function decline, decreased quality of life, increased mortality rates and poorer survival outcomes, thereby placing a significant burden on health care services[22][23]. Therefore, strategies to prevent or reduce the frequency of COPD exacerbations are required. We hypothesise that

improvement in periodontal health could reduce the frequency of AE-COPD. While there are suggestions of an association[24] there is currently no clear evidence on the strength of any association between periodontal disease and COPD exacerbations to inform clinical practice. The aim of this systemic review, therefore, is to critically appraise the emerging literature and to synthesise evidence on a putative link between poor periodontal health and COPD exacerbations to inform research and clinical practice.

Materials and Methods

This systematic review is reported using the PRISMA guidelines and the PICO framework to address the following clinical question: “Does poor periodontal health increase the frequency of exacerbations in patients with COPD? The following PICO model was used for selection of studies: **Population:** Adult patients with COPD; **Exposure**: poor periodontal health **Comparison:** good periodontal health; **Outcomes:** reduced frequency of COPD exacerbations. The PROSPERO registration number CRD42020180328.

Information sources and search strategy

Electronic database searches were undertaken using a combination of key search words (chronic obstructive pulmonary disease, exacerbation, reduced lung function, hospitalisation(s), quality of life, oral hygiene, periodontitis, gingivitis). These MESH search items and search strategy (Supplementary Table 1) were developed for the MEDLINE search and adopted for other electronic databases. Medline, Embase, Web of Science and CINAHL were searched in May 2020 with no language

restriction. To ensure literature saturation, reference lists of included studies were checked for eligible studies.

Study Selection Process

The studies eligible for inclusion were randomised clinical trials, cross-sectional studies, retrospective case control studies and cohort studies. Studies were considered if they included adult participants (≥ 18yrs) diagnosed with COPD, provided details of acute exacerbations of COPD, and included an assessment of the periodontal condition including oral hygiene (plaque index) and periodontal disease indices. Animal studies, non-clinical research, expert opinion, reviews, and studies not available in full text version were excluded.

The primary outcome was reduced frequency of COPD exacerbations associated with periodontal health or as a result of improved periodontal health in response to treatment. Secondary outcomes included quality of life, reduction in hospital admissions and treatment costs. The PRISMA flow chart (Figure 1) illustrates the selection process. For screening and assessment of eligibility criteria, titles and abstracts were screened by two assessors independently (NK, IEK). Full texts were obtained for all studies that met the inclusion criteria or when the abstract did not contain sufficient information to decide on the selection criteria. Full text articles were assessed independently for inclusion in the review by three assessors (NK, LW, IEK).

Quality assessment of included studies

The methodological quality of non-randomised studies was assessed using the Newcastle-Ottawa scale for case control studies and an adaptation of this scale[25] for cross sectional studies. The quality of randomised controlled trials was assessed using the criteria outlined in the Cochrane handbook for systematic reviews of interventions[26]. A high or low risk of bias was assigned to an individual study when there was evidence or absence of the following variables; selection bias, detailed allocation information, performance bias, detection details, attrition details, selective reporting bias or "other bias" that did not fall into any of the listed categories. Unclear risk of bias was assigned when there was insufficient information to permit judgment of 'high' or 'low' risk; when the risk of bias is genuinely unknown despite sufficient information about the conduct or when an entry is not relevant to a study. The risk of bias and quality of studies was assessed independently by three assessors (NK, LW, IEK). Furthermore, the evidence level for each of the included studies was graded using the Oxford Centre for Evidence-Based Medicine recommendations (http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidencemarch-2009/).

Data extraction

Data were extracted using custom designed forms (adopted from the Cochrane library). Extracted data included; the type of study, number and demographics of participants, COPD diagnosis, periodontal health parameters, respiratory outcomes, intervention/exposure, funding source, duration of follow-up, location of the study and quality of life assessment. The final data included for analysis were agreed by three

authors (NK, LW, IEK) and any differences of opinion were resolved by further discussion.

Data Synthesis

Data from randomised controlled trials were analysed using Review Manager, Version 5.3.5 (The Nordic Cochrane Centre, Copenhagen, Denmark) to calculate risk ratios and 95% CI. Data from case control and cohort studies were analysed using STATA Version 15 for Windows (StataCorp., Lake Station, TX, USA). We did assume that all studies shared a common effect, thus a random-effects model was determined for all quantitative syntheses. We estimated unadjusted pooled ORs and corresponding 95% CIs to measure associations between plaque index, periodontal pocket depth and clinical attachment loss with COPD exacerbation frequency. Heterogeneity was assessed by calculating the I^2 statistic and defined in accordance with the Cochrane Handbook as I^2<30%: acceptable heterogeneity, I^2 of 30–60%: moderate heterogeneity, I^2>60%: substantial heterogeneity.

Results

The search strategy identified 532 original titles and abstracts that were screened for potential eligibility, from which 45 full-texts were screened for inclusion (Figure 1). Eight articles met the inclusion criteria for the review and the study characteristics and descriptions are outlined in Tables 1 and 2. The excluded studies and reason for exclusion were outlined in Supplementary Table 2.

Periodontal health and frequency of COPD exacerbations

Three observational studies assessed the frequency of COPD exacerbations related to measures of periodontal health. Two of the studies **(**Liu *et al.* 2012)[27] and (Baldemero *et al.* 2019)[28] were assessed to be of good quality while that of AbdelHalim *et al.* 2018[29] was graded as poor (Supplementary Table 3). As shown in Figure 2 a meta-analysis found that the odds of frequent exacerbations were higher if the plaque index (PI) was >2 (n=3 studies, pooled OR=1.63, 95% CI 1.15 to 2.31, *p*=0.01, with moderate heterogeneity, I^2= 37.3%). The combined odds ratio for frequent exacerbations if mean clinical attachment loss (CAL) was ≥5mm was 1.68, 95% CI 1.17 to 2.42, *p*=0.01 and for mean probing pocket depth (PPD) >3mm was 2.03, 95% CI 1.46 to 2.82, *p*<0.001, but there was significant heterogeneity, I^2= 95% and 97% respectively**.**

Periodontal treatment and frequency of COPD exacerbations

Two randomised controlled trials (RCTs) that investigated the effect of periodontal treatment on the frequency of exacerbations in patients with COPD were identified. As shown in Figure 3 risk of bias assessment showed evidence of high risk of selection bias in one RCT (Kucukcoskun *et al*. 2013)[30]. There was unclear risk of bias for participant blinding in both RCTs (Kucukcoskun *et al*. 2013 [30] , Zhou *et al*. 2014[31] and also insufficient information to assess whether other risks of bias existed (e.g. bias towards specific study design) in both RCTs. The meta-analysis (Figure 3) showed a significant reduction in the number of exacerbations in COPD patients who received periodontal treatment at one year follow-up with risk ratio (RR)=0.28; 95% CI 0.09-0.83, with moderate heterogeneity I^2 = 46%.

Periodontal health and quality of life in COPD patients

Two studies (Zhou *et al.* 2011[32], Baldomero *et al.* 2019[28]) concluded that there was an association between better periodontal health and the quality of life of COPD patients. Baldomero *et al.* 2019[28] showed that worse Oral Health Impact Profile-5 (OHIP-5) scores were strongly associated with worse St George's respiratory questionnaire (SGRQ) scores, used to assess quality of life related to respiratory health status. Zhou et al. (2011)[32] found that poor periodontal health was significantly associated with poorer quality of life, assessed by SGRQ, in COPD patients. However, Agado *et al.* 2012[33] found that periodontal debridement for chronic periodontitis had no effect on the quality of life and illness in patients with COPD. Details of these studies are summarised as narrative synthesis (Table 3).

Periodontal health and risk of hospitalisation in COPD patients

Four studies included an assessment of hospitalisation frequency as a result of COPD exacerbations (Table 3). Two studies concluded better oral health/providing periodontal treatment reduced hospital admissions, AbdelHalim *et al.* 2018, [29]Barros *et al.* 2013[34]. Baldomero *et al.* 2019[28] concluded that while those affected by COPD with poorer periodontal examination outcomes had an increased risk of hospitalisation or emergency department visits, compared to those with better periodontal status, this did not reach statistical significance. Kucukcoskun *et al.* 2013[30] concluded that periodontal treatment reduced the frequency of COPD exacerbations, however, the number of hospitalisations increased in both the test and

control group during follow-up. No study reported on the cost of treatment provided for COPD exacerbations.

Discussion

Acute exacerbations are a key risk factor for the progression of COPD[35] and severe exacerbations that result in hospital admission are associated with high mortality levels[36][37]. Therefore, identifying modifiable risk factors is important to help reduce the frequency of exacerbations and improve COPD treatment outcomes. The findings of this systematic review showed poor periodontal health and poor oral hygiene could be potential risk factors for COPD exacerbations. The review also found that periodontal treatment was associated with a reduction in the frequency of COPD exacerbations. The findings are in agreement with previous studies which highlighted a potential relationship between periodontitis and respiratory function[9][3][38]. COPD and periodontitis are believed to have similar pathophysiology, as both diseases are characterised by chronic inflammation and shared risk factors[39]. Given the previously demonstrated role for oral bacteria in lung infections and pneumonia[20][19] it is reasonable to suggest that improved oral health will have a positive impact on COPD patients.

Many studies have suggested a putative link between oral health and COPD exacerbations, but to answer the research question “Does poor periodontal health increase the risk of frequent exacerbations in patients with COPD?” we limited studies to those with a clinical diagnosis of COPD and clear, measurable indicators of periodontal health. The studies identified were, however, heterogeneous in terms of designs and measures of outcomes, in particular for secondary outcomes such as

quality of life and hospitalisation, which necessitated a narrative synthesis for these outcomes.

Results of the meta-analysis showed a significant association between plaque scores and the frequency of COPD exacerbations. Although the odds ratio was modest, the level of the heterogeneity was moderate and results across the studies were consistent. Improving oral health by treating periodontal disease, which in turn improved plaque scores, also showed a similar trend. This result was not unexpected as evidence for a link between oral bacteria and pneumonia is strong[20][40]. The dental plaque biofilm may be a source of microorganisms associated with lung infections[18] and it is possible that in COPD patients with poor oral hygiene and high plaque scores, bacteria will be aspirated into the lungs leading to exacerbations[16]. Although the association of exacerbations with other measures of periodontal disease such as increased pocket depths and clinical periodontal attachment levels was statistically significant, the high heterogeneity and inconsistency across studies suggest that these results should be interpreted with caution. Data from the only two intervention studies available Kucukcoskun *et al*. 2013[30] and Zhou *et al*. 2014[31] supported an association between improvements in periodontal health resulting from treatment and a reduction in exacerbations during at least one year of follow-up. However, these studies were underpowered, and some aspects of their design were judged to have had a high risk of bias.

Other important outcomes investigated in this review were quality of life and the frequency of hospitalisation related to exacerbations. The format in which the data for these outcomes was reported prevented further meta-analysis, but generally, most studies suggested that poor periodontal health was associated with reduced quality of

life and increased hospitalisation rate for COPD patients. The narrative synthesis also concluded that providing periodontal treatment/improving periodontal health reduced the frequency of hospitalisations and improved the quality of life for COPD patients in studies analysing these outcomes.

To our knowledge, this is the first systematic review to analyse the link between periodontal status and the frequency of COPD exacerbations. The review was set to answer a specific question and followed standard systematic review methodology with clear inclusion and exclusion criteria. One of the limitations of the review, however, is the small number of included studies and aspects of the quality
particularly for the intervention studies. Additional limitations included the variability in COPD diagnostic criteria and the methods used to assess periodontal disease. In addition, due to the small number of studies included, it was not possible to detect publication bias. Nevertheless, the review enhances the current body of knowledge and provides evidence that further research is required in this area.

Conclusion

In conclusion, the findings of this systematic review suggest a potential link between poor periodontal status as indicated by high plaque levels, deep pocket depths, increased clinical attachment loss and the frequency of COPD exacerbations.
Qualitative evidence also highlights a potential positive correlation between improved periodontal health and a reduction in hospitalisation and improved quality of life in COPD patients. However, questions remain due to the high risk of bias and the poor quality of some of the included studies. Well designed, adequately powered

randomised controlled trials are needed to establish whether the periodontal condition influences the frequency of COPD exacerbations.

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Table1

Author (Year)	Study Design	Location	Duration of follow up	Intervention/ Exposure *	COPD Diagnosis	Funding	Level of Evidence *
Baldomero *et al*. (2019)	Case-control	USA	None	Poor periodontal health	ACP, ACCP & ATS	NHLBI VACDA	3b
Abdelhalim *et al.* (2018)	Crosssectional	Egypt	None	Poor periodontal health	GOLD Diagnostic Criteria	NS	4
Kucukcoskun *et al.* (2013)	Clinical trial	Turkey	1 Year	Periodontal treatment	GOLD Diagnostic Criteria.	NS	2b
Liu *et al.* (2012)	Crosssectional	China	None	Poor periodontal health	GOLD Diagnostic Criteria	NNSFC NSFB BSTPF	4
Zhou *et al.* (2014)	Randomised Clinical Trial	China	2 Years	Periodontal treatment	GOLD Diagnostic Criteria	NNSFC	2b
Zhou *et al.* (2011)	Crosssectional	China	None	Poor periodontal health	GOLD Diagnostic Criteria	ISTCRG NNSFC	3b
Brooke *et al.* (2012)	Randomised clinical trial	USA	None	Periodontal treatment	Not stated	ISUIM	2b
Barros *et al.* (2013)	Crosssectional	USA	5 Years	Poor periodontal health	GOLD Diagnostic Criteria	GlaxoSmith Kline Grant	2b

Table 1: Characteristics of studies that were included.

Abbreviations: ACP-American College of Physicians; ACCP- American College of Chest Physicians and ATS- American Thoracic Society criteria. NHLBI -National Heart, Lung and Blood Institute; VACDA -Veterans Affairs Career Development Award; NNSFC -National Natural Science Foundation of China; NSFB -Natural Science Foundation of Beijing; BSTPF -Beijing Science and Technology Programme Fund; NSnot

Table2

stated; ISTCRG -International Science and Technology Cooperation Research Grant, Beijing Municipal Science and Technology Commission, ISUIM (Idaho State University Intra Mural). * Oxford Centre for Evidence-Based Medicine; 2009.

Table3

Author (Year)	Number (Gender)	Age (Years)	Periodontal status	Respiratory outcomes	QOL
Baldomero *et al*. (2019)	136 (136 M/ 0 F)	Cases: 66.8 Controls: 67.5	Oral health questionnaire; Periodontal examination (PI, BOP, GI, PPD and CAL)	Self-reported COPD exacerbations; Hospitalisation frequency	SGRQ OHIP-5
Abdelhalim *et al*.(2018)	250 (250 M/ 0 F)	Cases: 56.75 ±10.42 Controls: 55.28 ±9.12	Periodontal examination (PI, BOP, GI, PPD and CAL)	COPD exacerbations; spirometry; CRP; Hospitalisation frequency	N/a
Kucukcokun *et al.* (2013)	40 (35 M/ 5 F)	Test: 61.8 ±7.57 Control: 57.85 ±12.09	Periodontal examination (PI, GI, PPD, BOP and CAL)	COPD exacerbations (physician confirmed); Hospitalisation frequency	N/a
Liu *et al.* (2012)	392 (287M/ 105 F)	Cases: 64.3 ± 10.1 Controls: 63.6 ± 9.7	Periodontal examination (PI, BI, PPD, CAL) Interview re oral hygiene behaviours	COPD exacerbations	N/a
Zhou *et al.* (2014)	60 (47 M/ 13 F)	Test: 63.9 ± 9.44 Control: 68.0 ± 7.64	Periodontal examination (PI, BOP, PPD, CAL)	COPD exacerbations at baseline, 6, 12 and 24 months	N/a
Zhou *et al.* (2011)	306 (210 M/ 6 F)	63.8	Periodontal examination (PI, BI, PPD, CAL); Number of teeth	Spirometry	SGRQ
Brooke *et al.* (2012)	30 (20 M/10 F)	64	Periodontal examination (PI, CAL)	Self-assessment of overall current health	SGRQ
Barros *et al.* (2013)	1635 (930 M/ 705F)	65	Periodontal examination (PPD, CAL)	Spirometry; COPD-related events frequency; Hospitalisation frequency; death	N/a

Table 2: Population characteristics. SGRQ-St George's Respiratory Questionnaire; Periodontal status (PI-plaque index, BI-bleeding index, BOP-bleeding on probing, GI-gingival index, PPD-probing pocket depth, CAL-clinical attachment level); N/a: Not applicable.

Table4

Supplementary Table 4. Narrative synthesis of secondary outcomes (Hospitalisations and Quality of Life).

Study	Outcome Measures	Results	Author Conclusion	Quality of Evidence	Critical Appraisal
Brooke et al, 2012, USA **(QOL)**	SGRQ-A scores to assess quality of life and self-assessment of overall current health in COPD patients receiving periodontal treatment and control group with no treatment	SGRQ–A and Illness Questionnaire scores showed no significant differences between groups in quality of life or illness following periodontal treatment. Total SGRQ scores decreased among groups but not significantly.	Periodontal debridement for chronic periodontitis has no effect on quality of life and illness in patients with COPD.	2b	Small sample size. The study does not state how COPD was defined. Participants were randomly assigned to groups. The findings cannot be applied to other patients with COPD as a non-probability sample was used, reducing external validity of the study. High risk of selection and performance bias
Kucukcoskun et al, 2013, Turkey **(Hospitalisations)**	Self-reported COPD exacerbations and hospitalisation confirmed by physician. Cases received periodontal treatment and control no treatment	Periodontal parameters were significantly correlated with most of the spirometry data. There were 7 hospitalisations in the test group and 12 in the control group over 12 months followup.	Periodontal health variables were associated with the frequency of COPD exacerbations and hospitalisations. .	2b	Small number of participants, all male participants. High risk of selection bias. No randomisation. COPD exacerbations were confirmed by physicians improving the validity of results. Periodontal examinations were carried out by dentists who were masked to the study participants and severity of COPD.

Barros et al 2013, USA ***(Hospitalisations)***	Frequency ofCOPDrelated events, hospitalisation for COPD exacerbation or death.	A statistically significant association was found between COPD- related events and oral health status.	Edentulism as a result of oral disease may predict the risk of COPD-related events and hospitalisation.	2b	Large sample, edentate (n=440) and dentate participants (n= 1195). Hospital coding was used to identify study participants,

		No teeth and poor oral hygiene, increase risk of hospitalisation or death as a result of COPD. (HR=2.28 and 95% CI 1.46-3.56). Participants with severe periodontal disease had the highest rate of COPD events, adjusted hazard ratios 1.37, for mild periodontitis, 1.34 for severe and 2.28 for edentulous cases			increasing reliability and reducing selection bias. Five-year follow-up of participants. Controls for confounding variables.
Zhou et al 2011, China ***(QOL)***	Quality of life assessed by SGRQ scores	After adjusting for age, gender, body mass index, and smoking status, missing teeth remained significantly associated with symptom score (p = 0.030) and activity score (p = 0.033) while plaque index was significantly associated with symptom score (p = 0.007).	Poor periodontal health as reflected by missing teeth and plaque index is significantly associated with lower quality of life in COPD patients.	3b	Retrospective study, recall bias. There are potential confounding effects of oral health behaviour factors and other lifestyle variables. Confounding accounted for by linear regression analysis. Questionnaires, possible recall bias, however replicate measurements were conducted and there were high levels of reproducibility.

Baldomero et al 2019, USA ***(QOL and Hospitalisations)***	St. George's Worse Questionnaire (SGRQ) and OHIP-5)	OHIP-5 was strongly associated with worse SGRQ scores. There was a non-significant trend towards more severe COPD exacerbations requiring emergency room visits and/or hospitalizations in those with worse periodontal health indices.	Respiratory	Patients suffering from severe COPD exacerbations were more likely to require hospitalisation and/or emergency department visits, when have poorer dental exam measurements.	3b	Small size unrepresentative sample, predominately white males. Does not control for smoking. COPD exacerbations were self-reported using questionnaire. Clear inclusions and exclusion criteria, with clear diagnostic criteria for COPD and oral health. Blinding of dental examiners
AbdelHalim et al, 2018, Egypt ***(Hospitalisations)***	Self-reported COPD exacerbation, number of hospitalisations	All periodontal health parameters were significantly associated with frequency of COPD exacerbations and hospitalisations (p <0.001). (OR 1.29 (0.30-5.57) (p =0.73).		Poor periodontal health is associated with frequency of exacerbations and hospitalisations per year	4	All male participants. Oral health and exacerbation frequency information was self-reported. The study does not control for smoking as confounding factor. Classification of COPD and periodontal disease was clearly stated. Blinded assessors for dental examination.

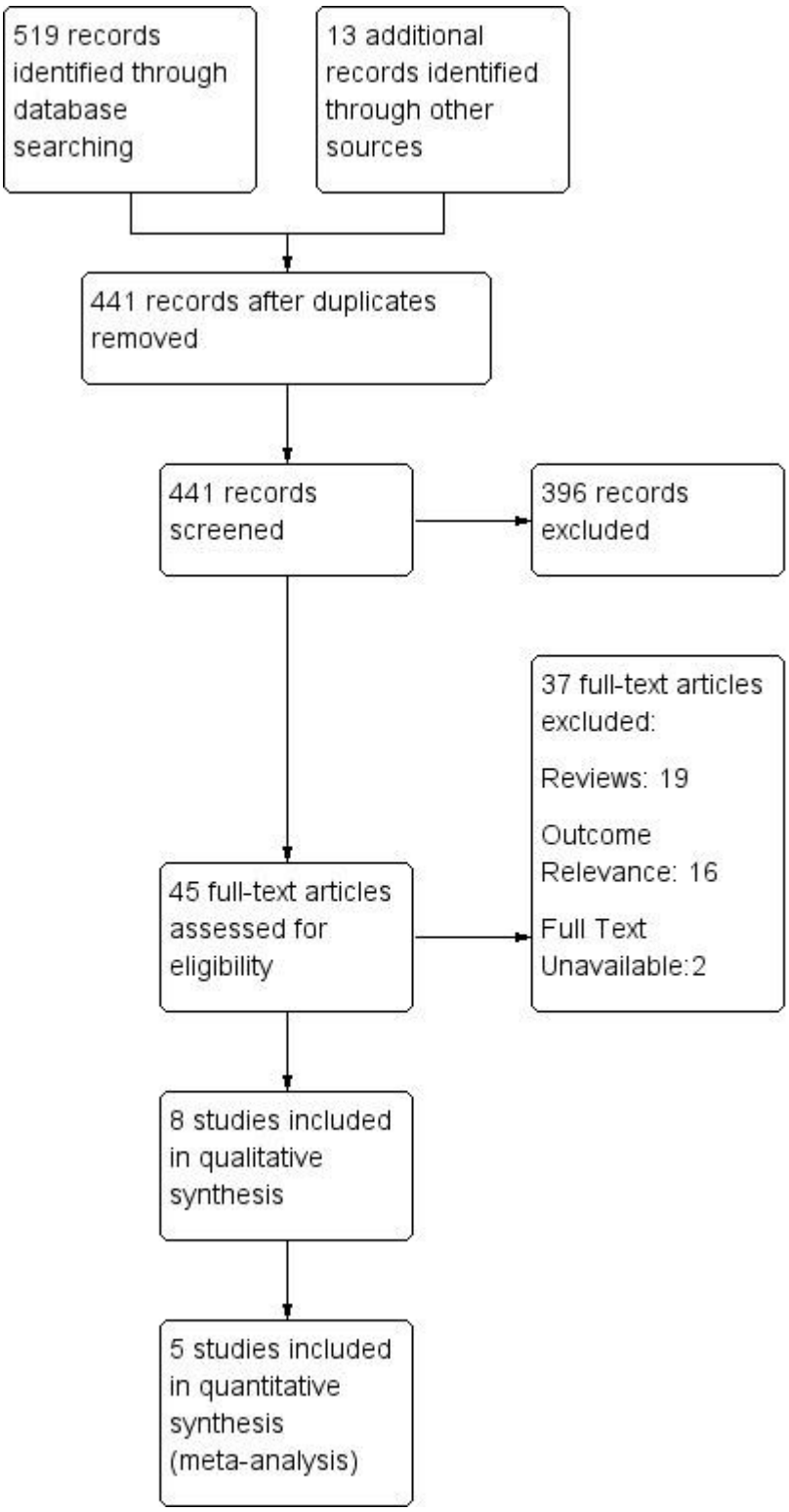
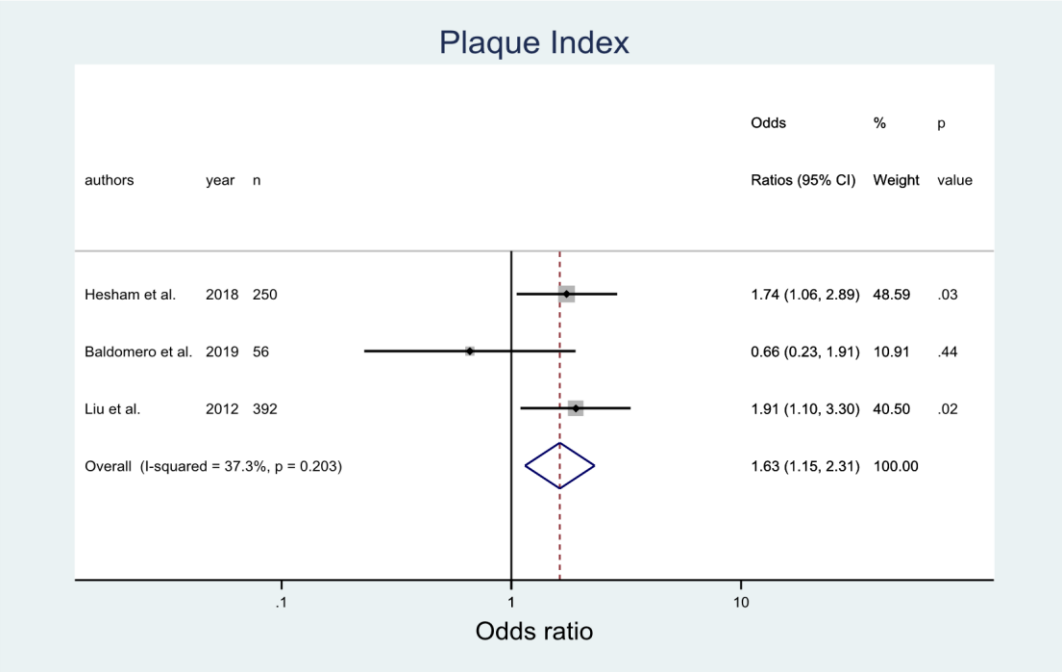
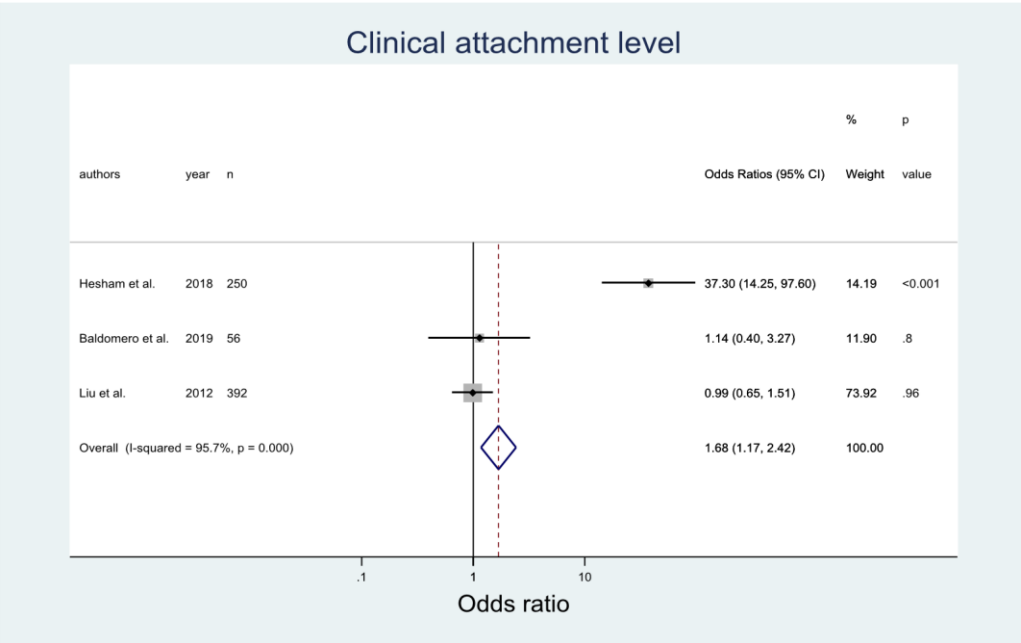


Figure 1: PRISMA Flow Diagram Figure 1

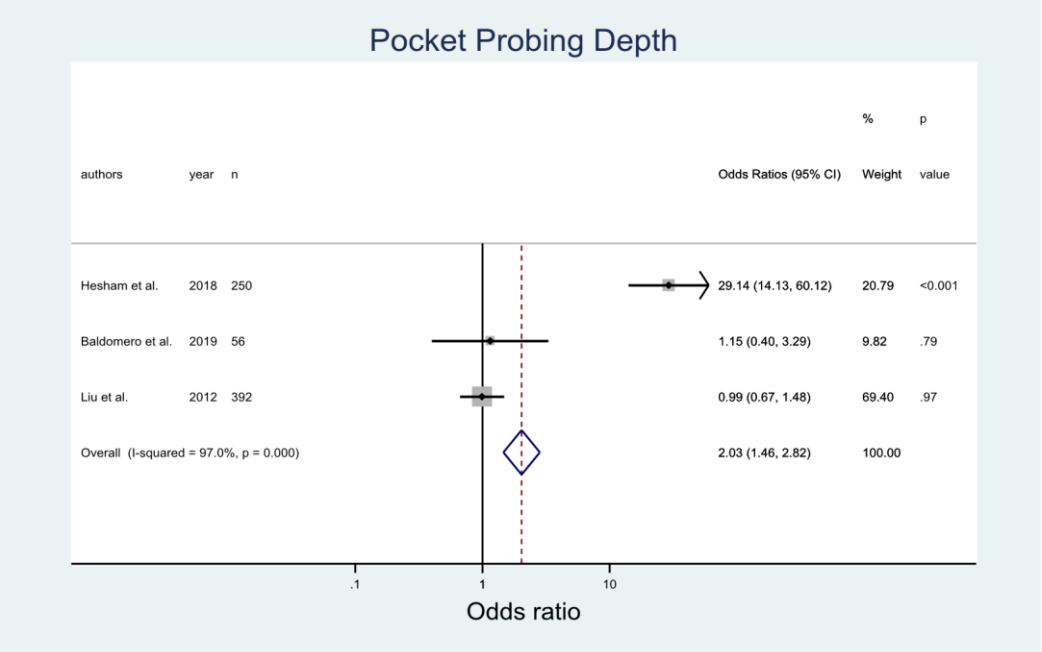
Figure 2


Plaque Index
authors
year
n
Odds Ratios (95% CI)
%
Weight
p
value
Hesham et al. 2018 250
1.74 (1.06, 2.89) 48.59 .03
Baldomero et al. 2019 56
0.66 (0.23, 1.91) 10.91 .44
Liu et al. 2012 392
1.91 (1.10, 3.30) 40.50 .02
Overall (I-squared = 37.3%, p = 0.203)
1.63 (1.15, 2.31) 100.00
.1
1
10
Odds ratio

(A)


Clinical attachment level
authors
year
n
Odds Ratios (95% CI)
%
Weight
p
value
Hesham et al. 2018 250
37.30 (14.25, 97.60) 14.19 <0.001
Baldomero et al. 2019 56
1.14 (0.40, 3.27) 11.90 .8
Liu et al. 2012 392
0.99 (0.65, 1.51) 73.92 .96
Overall (I-squared = 95.7%, p = 0.000)
1.68 (1.17, 2.42) 100.00
.1
1
10
Odds ratio

(B)


Pocket Probing Depth
authors
year
n
Odds Ratios (95% CI)
%
Weight
p
value
Hesham et al.
2018
250
29.14 (14.13, 60.12)
20.79
<0.001
Baldomero et al.
2019
56
1.15 (0.40, 3.29)
9.82
.79
Liu et al.
2012
392
0.99 (0.67, 1.48)
69.40
.97
Overall (I-squared = 97.0%, p = 0.000)
2.03 (1.46, 2.82)
100.00
.1
1
10
Odds ratio

(C)

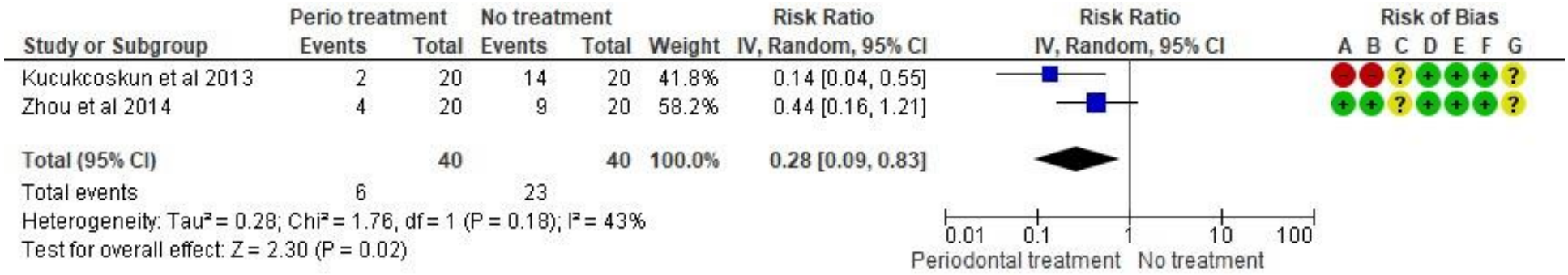

Perio treatment
No treatment
Risk Ratio
Risk Ratio
Risk of Bias
Study or Subgroup
Events
Total
Events
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
A B C D E F G
Kucukcoskun et al 2013 2 20 14 20 41.8% 0.14 [0.04, 0.55]
Zhou et al 2014 4 20 9 20 58.2% 0.44 [0.16, 1.21]
Total (95% CI) 40 40 100.0% 0.28 [0.09, 0.83]
Total events 6 23
Heterogeneity: Tau² = 0.28; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 2.30 (P = 0.02)
0.01
0.1
1
10
100
Periodontal treatment
No treatment

Figure 3

Acknowledgement

The authors would like to thank Richard Fallis and Patrick Elliot, Librarians at Queen's University Belfast for assistance with search methods. This research did not receive any specific grant from funding agencies in the public, commercial, or notfor-profit sectors and the authors declare no conflict of interests related to this systematic review.

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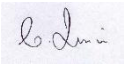
Prof Chris Irwin 

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Dr Dermot Linden 

Prof Gerald J Linden

CONSORT statement

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	01-02
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	03-05
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	05
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	05
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	06
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	05
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	05-06
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	06-07

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	07-08
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	08
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	07
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	08

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	07
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig1 9-10
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

PRISMA 2009 Checklist

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Supplementary table1

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Supplementary table2

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Supplementary table3

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