Periodontal Health and Chronic Obstructive Pulmonary Disease (COPD) Exacerbations: A Systematic Review

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Research Article

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Abstract

Background

A growing body of evidence suggests a role for oral bacteria in lung infections. This systematic review aimed to analyse the association between poor periodontal health and the frequency of chronic obstructive pulmonary disease (COPD) exacerbations.

Methods

PubMed, Embase, Web of Science, CINAHL and Medline were searched for studies published until May 2020, with no language restriction. Studies reporting periodontal condition, or periodontal treatment outcomes, with data on the frequency of exacerbations of COPD, were identified. The primary outcome was the frequency of exacerbations and secondary outcomes included quality of life and hospitalisation. Studies were assessed for eligibility and quality by two assessors independently.

Results

Searches identified 532 records and 8 met the inclusion criteria. The data from intervention studies showed reduction in the frequency of exacerbations following periodontal treatment. Data from observational studies suggest association of worse plaque scores with exacerbation but not pocket depth or clinical attachment loss. Better periodontal health was also associated with reduced frequency of COPD exacerbations, hospitalisations and improved quality of life in COPD patients. Due to the high heterogeneity no meta-analysis was performed. The quality of some of the included studies was low and there was evidence of high risk of bias.

Conclusion

The data supports possible association between poor periodontal health, the frequency of exacerbations and quality of life in COPD patients. The evidence is limited by high risk of bias suggesting need for well-designed and adequately powered randomised control trials.

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Background

Periodontitis is a chronic inflammatory disease, caused by anaerobic bacteria and characterised by destruction of tooth-supporting structures [1]. Emerging evidence suggests oral bacteria and local inflammatory response in periodontal tissues contribute to systemic inflammation and increase the risk for development of chronic inflammatory conditions including diabetes, cardiovascular and respiratory disease [2][3][4].

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable respiratory 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 [5]. 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 [6]. It is well recognised that smoking is the primary risk factor for COPD[6], but emerging evidence suggests that periodontitis may contribute to the risk of COPD [7]. COPD and periodontitis share several risk factors such as age, smoking, stress and ethnicity [8]. 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 [9]. Patients with confirmed COPD have lower tooth brushing frequency and poorer periodontal health than comparable control groups [10][11]. 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 [12].

Progressive lung function decline may be accelerated by acute exacerbations of COPD (AE-COPD)[6]. 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 [13]. The majority of AE-COPD respond to antibiotic treatment, providing further evidence that infection is an important factor [14]. Increased microbial diversity in COPD patients has been demonstrated with the identification of oral bacteria in their lung microbiome and tissue [15][16]. In COPD patients, it is possible that reduced laryngotracheal mechanosensitivity and decreased airway clearance due to impaired mucociliary function [17][18], 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 [19][20]. 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 [21][7]. Poor oral hygiene may contribute to the colonisation of dental plaque by respiratory pathogens [22]. 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 [23].

Frequent AE-COPD is 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 [24][25]. 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 [26] there is currently no clear evidence on the strength of any association between periodontal disease and COPD exacerbations to inform clinical practice.

Methods

The aim of this systematic review 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.

The 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.

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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, and 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 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, and 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 [27] 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 [28]. 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-evidence-march-2009/).

Data extraction and analysis

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, quality of life assessment and hospitalisation. The final data included for analysis were agreed by three authors (NK, LW, IEK) and any differences of opinion were resolved by further discussion. Due to the heterogeneity of study designs no meta-analysis was performed. Narrative synthesis of included studies outlining the primary outcome (frequency of COPD exacerbations) and secondary outcomes (QOL and hospitalisations) was included.

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) [29] and (Baldemero *et al.* 2019) [30] were assessed to be of good quality while that of (AbdelHalim *et al.* 2018) [31] was graded as poor (Supplementary Table 3). AbdelHalim et al, 2018 [29], found that frequent exacerbation is associated with plaque scores more than 2mm ($p<0.029$), moderate to severe clinical attachment loss (CAL) and probing pocket depth (PPD) ($p<0.001$). Baldomero et al [28] also concluded that the unadjusted odds ratios of severe exacerbations relative to mild exacerbations trended higher in those with worse plaque index scores and worse CAL and PPD, however, statistical significance was not reached. Liu et al [27] also

found that a greater number of patients with frequent exacerbation had plaque index scores >2, (OR = 1.97, 95% CI: 1.11–3.49), but found that there was no significant difference in clinical attachment loss and pocket depth between the frequent and infrequent exacerbator groups. Results of primary outcome are summarised in Table 3.

Periodontal treatment and frequency of COPD exacerbations

Two intervention studies that investigated the effect of periodontal treatment on the frequency of exacerbations in patients with COPD were identified. Zhou et al [31] and Kucukcoskun et al [30] found that periodontal therapy in COPD patients improve lung function and decrease the frequency of COPD exacerbations. Kucukcoskun et al [30] concluded that there was a significant reduction in exacerbation frequency during the follow-up period (P=0.01). Median exacerbations declined from 3 to 2 in the test group, and increased from 2 to 3 in the control group. Zhou et al [31] concluded that the frequency of COPD exacerbation was significantly lower in periodontal therapy group when compared with the control group at 2-year follow-up ($p < 0.05$). Moreover, (FEV1/FVC) and FEV1 were significantly higher in the therapy groups when compared with the control group during the follow-up period ($p < 0.05$).

Risk of bias assessment showed evidence of high risk of selection bias in (Kucukcoskun *et al*. 2013)[32] study. There was an unclear risk of bias for participant blinding in both studies (Kucukcoskun *et al*. 2013 [32], Zhou *et al*. 2014[33] and also insufficient information to assess whether other risks of bias existed (e.g. bias towards specific study design).

Periodontal health and quality of life in COPD patients

Zhou *et al.* 2011[34] and Baldomero *et al.* 2019 [30]) showed an association between better periodontal health and the quality of life of COPD patients. Baldomero *et al.* 2019 [30] found 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 the quality of life related to respiratory health status. Zhou et al. (2011) [34] found that poor periodontal health was significantly associated with poorer quality of life, assessed by SGRQ, in COPD patients. However, Agado *et al.* 2012 [35] found that periodontal debridement for chronic periodontitis did not affect the quality of life and illness in patients with COPD. Details of these studies are summarised in Table 4.

Periodontal health and risk of hospitalisation in COPD patients

Four studies included an assessment of hospitalisation frequency as a result of COPD exacerbations (Table 4). Two studies concluded better baseline oral health or providing periodontal treatment reduced hospital admissions, AbdelHalim *et al.* 2018, [31], Barros *et al.* 2013[36]. Baldomero *et al.* 2019 [30] 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 [32] 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.

Discussion

Acute exacerbations are the key risk factor for the progression of COPD [37] and severe exacerbations that result in hospital admission are associated with high mortality levels [38][39]. 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 [12][3][2]. COPD and periodontitis are believed to have similar pathophysiology, as both diseases are characterised by chronic inflammation and shared risk factors [40]. Given the previously demonstrated role for oral bacteria in lung infections and pneumonia [22][7], 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.

For the primary outcome it appears that higher plaque scores were associated with an increased frequency of COPD exacerbations for the majority of included studies, except for Baldomero et al [28] study. Moreover, the included clinical trials, (Zhou et al 2014 [31] and Kucukcoskun et al 2013 [30]) concluded that periodontal therapy in COPD patients may improve lung function and decrease the frequency of COPD exacerbations. Improving oral health by treating periodontal disease, which in turn improved plaque scores, also showed a similar trend. Data from the only two intervention studies available Kucukcoskun *et al*. 2013 [32] and Zhou *et al*. 2014 [33] supported an association between improvements in periodontal health resulting from treatment and a reduction in exacerbations during at least one year of follow-up.

These results are however not unexpected as evidence for a link between oral bacteria and pneumonia is strong [22][4]. The dental plaque biofilm may be a source of microorganisms associated with lung infections [21] 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 [19].

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 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 evidence also suggest providing periodontal treatment and 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. Also, 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.

List Of Abbreviations

COPD: Chronic Obstructive Pulmonary Disease

CAL: clinical attachment loss

PPD: probing pocket depth

PI: plaque index

SGRQ: St George's respiratory questionnaire

OHIP-5: Oral Health Impact Profile-5

Declarations

Ethics approval and consent to participate: NA

Consent for publication: NA

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Tables

Table 1: Characteristics of included studies.

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

Abbreviations: GOLD-Global Initiative for Obstructive Lung Disease; 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; NS-not stated; ISTCRG -International Science and

Technology Cooperation Research Grant, Beijing Municipal Science and Technology Commission, ISUIM (Idaho State University Intra Mural).

Table 2: Population characteristics

Author (Year)	Number (Gender)	Age (Years)	Periodontal status	Respiratory outcomes	QoL Measures
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)	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; hospitalisation frequency	N/A
Kucukcokun *et al.* (2013)	40 (35 M/ 5 F)	Intervention: 61.8 ±7.57 Control: 57.85 ±12.09	Periodontal examination (PI, GI, PPD, BOP and CAL)	COPD exacerbations; 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)	Intervention: 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 measurements	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/	65	Periodontal examination (PPD, CAL)	Spirometry measurements; COPD-related events frequency;	N/A

705F)		hospitalisation frequency

PI-plaque index; BI-bleeding index; BOP-bleeding on probing; GI-gingival index; PPD-probing pocket depth; CAL-clinical attachment level); N/A: Not available; QoL (quality of life); SGRQ-St George's Respiratory Questionnaire; OHIP-5-Oral health impact profile -5

Table 3. Summary primary outcome: COPD exacerbation frequency

Study	Outcome measured	Results	Level of Evidence*
Baldomero *et al.* **(2019)**	Self-reported COPD exacerbations	COPD exacerbations requiring hospitalisation or ED visits were associated with worse dental exam parameters. Poorer OHIP-5 scores were strongly associated with poorer SGRQ scores.	3b
AbdelHalim *et al.* **(2018)**	Self-reported COPD exacerbations and spirometry	All periodontal health parameters were significantly associated with frequency of COPD exacerbations and hospitalisations	4
Kucukcoskun *et al.* **(2013)**	Self-reported COPD exacerbations, confirmed by physician	Periodontal parameters correlate significantly with most of the spirometry data.	2b
Liu *et al.* **(2012)**	Self-reported COPD exacerbations/change in clinical symptoms and medication/spirometry	Fewer remaining teeth and high PI scores are significantly associated with COPD exacerbations.	4
Zhou *et al.* **(2014)**	Self-reported COPD exacerbations/ change in clinical symptoms and medication/ spirometry	The frequency of COPD exacerbations were significantly lower in treatment compared to the control group at 2-year follow-up.	2b

* Oxford Centre for Evidence-Based Medicine; 2009.

Table 4. Summary of secondary outcomes: Hospitalisations and Quality of Life.

Study	Outcome Measured	Results	Level of Evidence*
Brooke et al, 2012	QoL measured by SGRQ-A and self- assessment of overall current health in COPD patients receiving periodontal treatment and control group with no treatment Hospitalisation confirmed by physician.	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.	2b
Kucukcoskun et al, 2013	Frequency of COPD-related events and hospitalisation from hospital records	There were 7 hospitalisations in the test group and 12 in the control group over 12 months follow-up.	2b
Barros et al 2013	Quality of life assessed by SGRQ scores	Edentulism and poor oral hygiene increased the risk of hospitalisation or death as a result of COPD. Participants with severe periodontal disease had the highest rate of COPD events.	2b
Zhou et al 2011	St. George's Respiratory Questionnaire (SGRQ) and OHIP-5), hospitalisations	After adjusting for age, gender, body mass index, and smoking status, missing teeth remained significantly associated with symptom score and activity score, while plaque index was significantly associated with symptom score.	3b
Baldomero et al 2019	Self-reported number of hospitalisations	Worse 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 hospitalisations in those with worse periodontal health indices.	3b
		Periodontal health parameters were significantly associated with the number of hospitalisations.	4

AbdelHalim et al, 2018

* Oxford Centre for Evidence-Based Medicine; 2009.

Figures

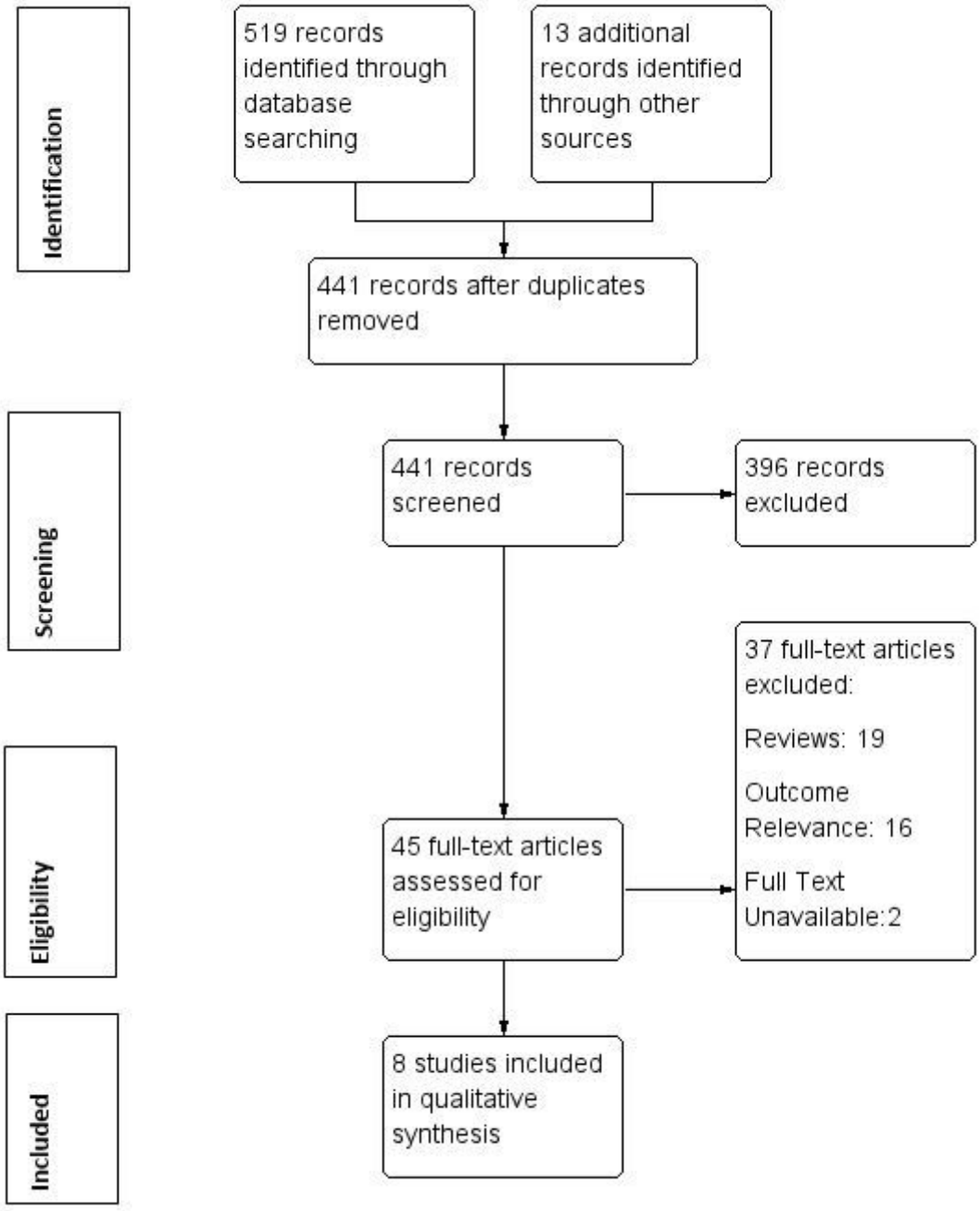

Figure 1

PRISMA Flow Diagram

Supplementary Files

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- Suppdata.pdf