ACTA ODONTOLOGICA SCANDINAVICA
2021, VOL. 79, NO. 5, 344–353
https://doi.org/10.1080/00016357.2020.1859132

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REVIEW ARTICLE

Association between periodontal disease and inflammatory bowel disease: a systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this systematic review was to investigate the association between periodontal disease (PD) and inflammatory bowel disease (IBD), and its two major forms Crohn's disease (CD) and ulcerative colitis (UC).

Materials and methods: We searched articles in PubMed/MEDLINE, Web of Science, and LILACS published until March 2020. Observational studies evaluating the coexistence of PD in IBD and reported values of clinical periodontal parameters, or radiographic bone loss; and IBD diagnosis established by clinical, radiological, endoscopic and histological criteria were deemed eligible.

Results: A total of 9 studies were included (33,216 individuals). Only one study reported longitudinal data on IBDs onset in patients with PD. Several case-control studies reported coexistence. Meta-analysis showed that the presence of PD was associated with IBD (2.78 [95%CI 1.36–5.69]). PD was strongly associated both with CD (3.41 [95%CI 1.36–8.56]) and UC (3.98 [95%CI 2.02–7.87]).

Conclusion: This review presents clear evidence for an association between PD and IBDs. Future studies should avoid non-longitudinal designs and focus on addressing direction. PD screening may be included in the multidisciplinary management of IBD patients. The mere theoretical possibility that PD may predispose to IBDs may be of key significance due to the rising incidence of diseases.

ARTICLE HISTORY
Received 12 September 2020
Revised 21 November 2020
Accepted 27 November 2020

KEYWORDS
Periodontal disease; inflammatory bowel disease; meta-analysis; periodontitis; review; risk factor

Introduction

Inflammatory bowel diseases (IBDs) are chronic and relapsing inflammatory diseases, which cause continuous inflammation of the intestinal mucosa [1]. According to the 2019 update of the Global Burden of Disease (GBD) study, more than 4.8 million people are estimated to be living with IBD worldwide, representing a considerable public health concern [2]. The major forms of idiopathic IBDs are ulcerative colitis (UC) and Crohn's disease (CD). Clinical experience and research have led to the generally accepted notion that they are distinct, if not discrete, chronic diseases. In brief, CD can involve any part of the gastrointestinal tract from the mouth to the anus, whereas UC primarily affects the colon and the rectum [3]. Up to 36% of patients with IBD have at least one extraintestinal manifestation, involving oral cavity among other anatomical locations. These extraintestinal manifestations may precede gastrointestinal symptomatology in some patients [4]. Aetiology and pathogenesis of these pathologies remain not fully understood, although the main accepted hypothesis is that environmental, genetic, microbial, cellular, and molecular factors are responsible for an initiation and perpetuation of gastrointestinal inflammation [5].

Periodontal disease (PD) is a chronic non-communicable inflammatory disease characterised by periodontium progressive destruction [6]. Severe PD globally affects 1,087 million individuals globally according to a recent systematic review carried out within the framework of GBD study last update [7]. The current model of PD pathogenesis is based upon a circular relationship between the periodontal biofilm and the inflammatory immune response [7].

Some observational studies have shown an increased risk of IBD among people with a history of PD. The systemic inflammation that is associated with PD may therefore trigger the presence of IBDs or even enhance its activity. Microbiome, immune-mediated inflammatory processes and common risk factors play important roles in both pathologies. Nonetheless, the complete mechanism of this increased risk is not fully understood, and also if the interaction between these diseases may be uni or bidirectional is yet to be demonstrated [8].

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Supplemental data for this article can be accessed here.

This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Although two meta-analyses relating to the association between PD and IBDs have been carried out [9,10], one of the main bias was that exposure and outcome were not defined a priori and only studies with a case-control design were included [9,10]. Case-control study designs are valuable for generating hypotheses but cannot confirm causality. This cause-effect relationship can be only by clarified by cohort studies. In addition, the present systematic revision in comparison with the latest from She et al. [10] included 3 additional studies and multiplied by 30 the number of individuals included (1047 vs. 33,216) making in our humble opinion, our results more consistent.

Prompted by discussed literature, we therefore sought to explore the evidence to date investigating the association between PD and IBDs through a systematic review and meta-analysis.

Materials and methods

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11] statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist [12].

Focussed question

The population, exposure, comparison, and outcome (PECO) format was used to develop the following focussed question: subjects (P = patients); PD (E = exposure); patients without PD (C = comparison); IBD (O = outcome). Thus, we set the following research questions: Do subjects with PD have a higher risk of suffering from IBD than individuals without PD?

Search strategy

An electronic search without date or language restriction was carried out in PubMed/MEDLINE, Web of Science, and LILACS until March 2020. Furthermore, a specific electronic search was performed on the following journals' websites: European Journal of Gastroenterology & Hepatology, Gastroenterology, Gut, Inflammatory Bowel Diseases, Journal of Crohn's and Colitis, Journal of Periodontology, Journal of Clinical Periodontology, and Journal of Periodontal Research. Searches in references of the included studies (i.e. cross referencing) were also conducted.

MeSH terms, keywords, and other free terms related to 'periodontal disease [All Fields]'; 'periodontitis [MeSH Terms]'; and 'alveolar bone loss [MeSH Terms]'; '[MeSH Terms]'; 'inflammatory bowel disease [MeSH Terms]'; 'ulcerative colitis [MeSH Terms]'; 'Crohn disease [MeSH Terms]'; were used with Boolean operators (OR, AND) to combine searches. The search strategy included appropriate changes in the keywords and followed the syntax rules of each database.

Eligibility criteria

The following inclusion criteria were applied: cohort (retrospective and prospective), case-control or cross-sectional design; evaluate the presence of PD in IBD subjects; report values of clinical periodontal parameters [i.e. clinical attachment level (CAL) or probing pocket depth (PPD)], or radiographic bone loss; an IBD diagnosis established by clinical, radiological, endoscopic and histological strict criteria. This systemic review excluded case series, case reports, reviews, animal studies, non-clinical studies and studies with insecure/unclear diagnosis for both pathologies under investigation.

Screening process and data extraction

The search and screening process was carried out by two independent reviewers (AILP and MPS) in two phases: (1) starting with analysis of titles and abstracts, and (2) full papers were selected for careful reading and analysed according to eligibility criteria for future data extraction. Disagreements between reviewing authors were resolved through careful discussion, and a third co-author with expertise in gastroenterology (PV). After adequate agreement was achieved (κ score = 0.78), all selected data were extracted from the included studies by two independent reviewing authors in a pilot tested form.

Quality assessment

The Newcastle-Ottawa Scale (NOS) [13], and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) score [14]. They were used to assess the risk of bias and quality of evidence respectively were assessed independently by two authors (AILP and MPS).

NOS scale was originally developed in order to evaluate the risk of bias in cohort, and case-control studies. NOS evaluates three dimensions (selection, comparability of cohorts, and outcome) with a total of 9 items. In the analysis, the studies with NOS scores (asterisks) of 1–3, 4–6 and 7–9 were defined as low, medium and high quality, respectively. A validated assessment tool for cross-sectional studies was not located. In this vein, the quality of cross-sectional studies was assessed using questions from the NOS for case-control study designs that were considered applicable to the cross-sectional study designs, according to a previous NOS variation proposed by our group [15].

The GRADE system includes six main domains: risk of bias, inconsistency, indirectness, imprecision, publication bias, and magnitude of effect size. Overall these domains classify studies in four thresholds according to the quality of evidence: very low, low, moderate, or high. Discrepancies in the score were resolved through discussion by the authors. The inference of the quality of evidence is probably best described and well accepted by GRADE [14]. Thus, subgroup analysis was based on this system.

Statistical analysis

Odds ratios (ORs) were treated as risk ratios approximations (RRs) in the current study. If the selected studies provided only hazard ratios (HRs), we transformed them to RR in

accordance with Cochrane Handbook (available at: www.handbook.cochrane.org). When the selected studies did not contain such statistical information, we directly calculated crude ORs using the number of cases and controls reported there with a standard procedure. In order to facilitate the interpretation of results, we planned a sensitivity analysis by means of the stratification of these statistics.

We used DerSimonian and Laird Q test to check for heterogeneity. I^2 statistic that indicates the percentage of variance in a meta-analysis was also used to test for heterogeneity using 25, 50, and 75%, respectively indicative of low, moderate, and high heterogeneity [16]. A p value lower than 0.05 of the DerSimonian and Laird Q test or and I^2 percentage larger than 50% were considered as the thresholds for significant heterogeneity.

Both fixed effects and random effects pooled estimates were computed. Fixed or random effects models were used based on the presence or absence of heterogeneity according to DerSimonian and Laird Q, and I^2 tests. Publication bias was evaluated through Funnel plots, and Egger's test for 'small-study effects'. All analyses and figures constructions were performed using the meta package of free R software (v.3.6.2) (available at: https://www.r-project.org) and PUB_BIAS: A SAS ® (a macro developed by G Rendina-Gobioff and JD Kromrey) using commands and variations written by the user for both digital utilities [17].

Results

Literature search

The combined total of references obtained from aforementioned databases was 478 citations, one article was retrieved on the basis of hand searching, and removal of duplicates resulted in 192 unique citations to be screened. Among these manuscripts 9 met all the eligibility criteria (2 cross-sectional, 6 case-control studies, 1 cohort study) [18–26]. A flow diagram is displayed as Figure 1.

One case control study was identified as part of a conjugation of publications carried out at the same unit, and due

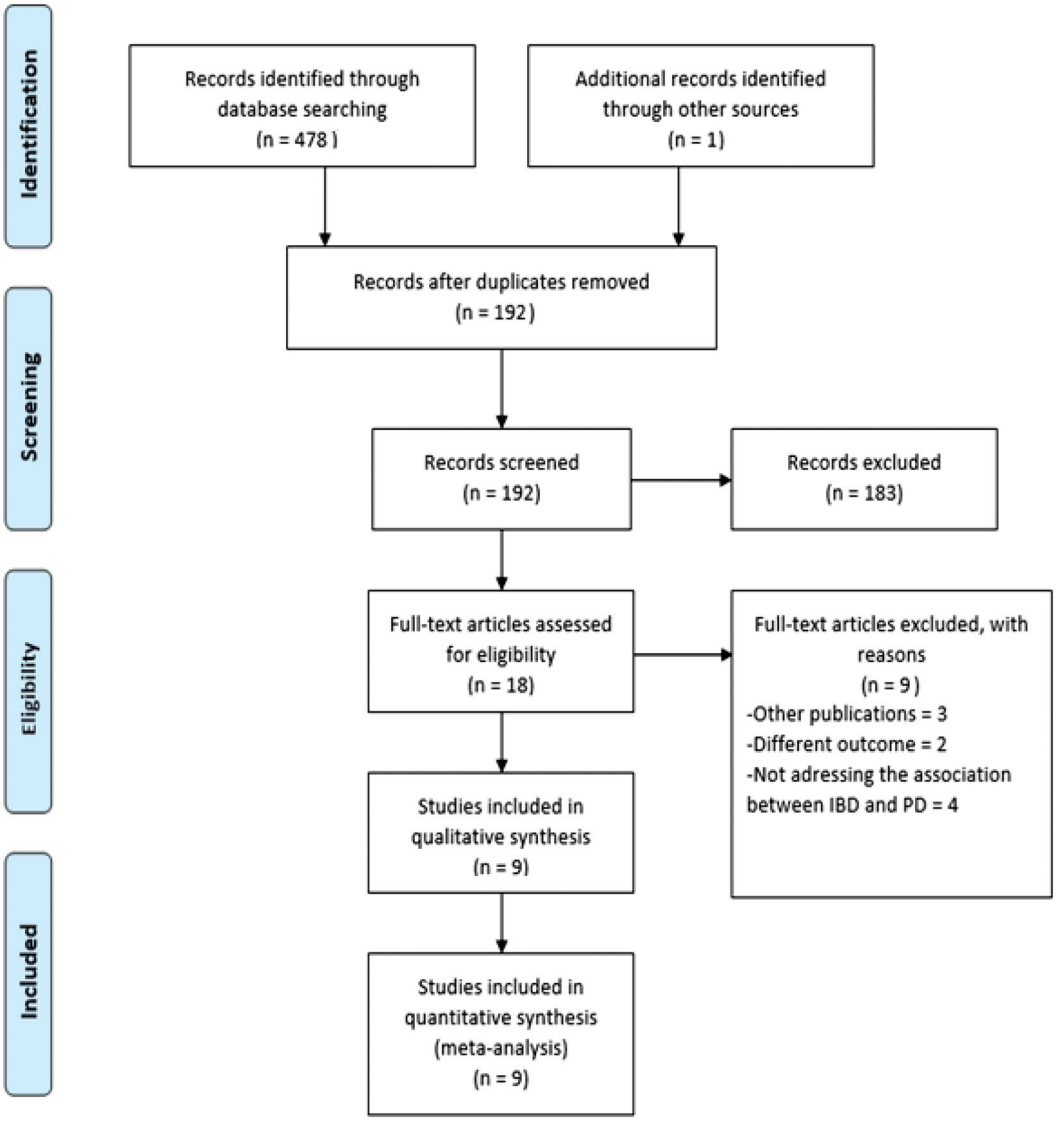

Figure 1. Flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for selection process, eligibility, and reasons for exclusion and inclusion of the final studies. For more information, visit www.prism-statement.org.

to the plausible possibility of having overlapping patients identified after comprehensively reading the methodology of all citations [21]. Only the aforementioned study was included due to its best description of methods, and higher number of cases and controls. This methodology was applied in order to reduce the potential exacerbated risk of random error due to overlapping [27].

Characteristics of included studies, assessments of the quality and level of evidence

Table 1 summarises the characteristics of the nine studies selected, which reported on a total of 6,439 IBD patients and 26,777 healthy controls. The studies are listed according to their level of evidence beginning with cohort studies, and ending with cross-sectional studies. The 9 citations included in the present systematic review were conducted in 7 different countries across Europe [19,20,22–25], South America [21] and Asia [18,26]. These studies were published between 2004 [19] and 2019 [18]. According to GRADE checklist (Table 2), four studies have shown a low quality [18,20–23], while five studies were of high quality [19,24–26]. In relation to NOS assessment form, risk of bias for included cohort and case-control plus cross-sectional studies is displayed as Supplementary material. Three studies had a low risk of bias [19,22,23] reaching 7–8 points, whereas six studies had a medium risk of bias [20,21,24–26].

The definition of PD was mainly based on PPD or CAL thresholds for number of affected sites or on full mouth mean [19–26]. Nonetheless, these thresholds varied largely due to the lack of international consensus on the definitions for exposure at the time-point when studies were conducted [28]. Some authors opted for consensus criteria or authoritative authors-based definitions [29–33], others for definitions based on previous manuscripts from other research groups [34]. Whereas others simply took arbitrary decisions in order to establish PD diagnosis [19,20,23].

The IBD diagnosis of included studies was mostly based on classical criteria defined by Lennard-Jones [35] which include clinical, endoscopic, radiologic and histological criteria [18,20–23,26]. In one study performed in paediatric population [24], IBD diagnosis was based on the Porto criteria defined in the European IBD Working Group [36], and in two studies there was not conclusive information about diagnosis criteria [19,25].

Data synthesis and meta-analysis

Our analysis showed almost a 3-fold increased risk of having IBDs when PD was diagnosed (RR: 2.78 (95% CI: 1.36–5.69) (Figure 2(A)). Pooled effect estimates for all 9 studies included in this meta-analysis and subgroup analyses are shown in Table 3. Heterogeneity was extremely large as shown by the value of the statistic I^2 When, we stratified by design, case-control studies obtained a higher pooled RR 3.73 (95% CI: 2.61–5.32) with negligible heterogeneity. In addition, PD was associated with CD (RR: 3.41 [95% CI: 1.36–8.56]) (Figure 2(B)), and UC (RR: 3.98 [95% CI: 2.02–7.87]) (Figure 2(C)), both estimates presented a considerable heterogeneity. UC studies showed a pooled RR estimate of 6.48 (95% CI: 3.67–11.43), whilst CD studies 5.15 (95% CI: 2.02–13.09). Subgroup analysis provided further insight into the sources of heterogeneity; UC studies were homogeneous (Q test $p = 0.17$), whereas CD studies and low-quality studies harboured high heterogeneity values (Q test $p = 0.001$). When the study that reported only HR was excluded from the analysis, the result showed that exposure to PD can increase the risk for developing IBD 3.73 times (95% CI: 2.61–5.32), and heterogeneity was also present (Table 3). In a pooled analysis for the exposure and primary outcome higher quality studies showed a lower magnitude of association (RR: 2.67 [95% CI: 1.14–6.22]), whilst lower quality studies showed a moderately higher association (RR: 2.80 [95% CI: 0.77–10.13]) (Table 3). Sensitivity analysis is displayed also at Table 3 showing that the Leave-one-out technique excluding Lin et al. study [18] resulted in a higher effect (RR: 3.42 [95% CI: 2.33–5.03]).

The funnel plot was asymmetrical displaying a marked skewness to the right (Figure 3); less precise (smaller) studies reported higher risk metrics than did larger studies as in the case of studies without proper confounding adjustment. Egger's test for 'small-study effects' displayed also a significance ($P_{Egger} = 0.008$) [19,24].

Discussion

The aim of this study was to explore the evidence to date investigating the association and causality between PD and IBDs through a systematic review and meta-analysis.

Summary of evidences

Our systematic review and meta-analysis of 9 studies including 33,216 patients revealed a positive association between IBDs and prevalence of PD. The risk of IBDs was higher in subjects with PD (RR = 2.78 (95% CI: 1.36–5.69). An important finding of our study was that this association is likely overestimated in the literature, because no previous systematic approach included cohort studies to establish a cause-and-effect relationship. Our pooled analysis may be more reliable due to the accumulation of studies with high quality scores, and that at the same time new studies adds a substantial weight (30.63%) to the present meta-analysis according to random effects (i.e. DerSimonian and Laird method) with respect to the previous ones [9,10].

There is a relevant gap between association and causation in the relationship investigated in the present systematic review. IBD and PD are autoimmune-based chronic diseases, with a disproportionate mucosal inflammatory response to a dysregulated local microbiota in a genetic predisposition context, leading to tissue destruction. Specifically, neutrophil abnormalities driving its chemotaxis observed in patients with IBD were also observed in patients with PD eliciting host response mechanisms of paramount importance in both pathologies [8]. It is worth mentioning that despite advances in the study of gut microbiota, the intestinal dysbiosis role in

Table 1. Characteristics of the included studies.

Author (year)	Study population	Country	Periodontal diagnosis and related secondary outcomes	Inflammatory bowel disease diagnostic criteria	Follow-up (years)	Cofounders adjusted	Inflammatory bowel diseases	Crohn's disease	Ulcerative colitis
Cohort studies							HRs (95% CIs)		
Lin et al. (2018) [18]	135190 subjects (over 20 years)	Taiwan	ICD-9-CM: 523.3, 523.4, and 523.5	Lennard-Jones criteria	13	Age, Gender, income, geography, urbanisation, and comorbidity	1.01 (0.94–1.08)	0.99 (0.92–1.06)	1.56 (1.13–2.15)
Case-control studies							ORs (95% CIs)		
Zervou et al. (2004) [19]	30 IBD (15 CD, and 15 UC) patients, and 47 control	Greece	Periodontitis definition not clearly stated.	Not clearly stated		Age, IBD severity, and smoking	8.33 (0.39–177.92)	16.60 (1.51–33.40)	12.80 (1.20–26.50)
Grossner-Schreiber et al (2006) [20]	62 IBD (46 CD, and 16 UC) patients, and 59 control	Germany	PPD, and CAL Arbitrary definition	Lennard-Jones criteria		NA	2.29 (0.94–5.79)	NA	NA
Brito et al. (2008) [21]	179 IBD (99 CD and 80 UC) patients, and 79 controls	Brazil	PPD, and CAL Lopez, Smith , Gutierrez (2002) [34]	Lennard-Jones criteria		NA	2.83 (1.49–5.36)	2.16 (1.07–4.37)	4.32 (1.80–10.39)
Habashneh et al. (2012) [22]	160 IBD patients (59 CD and 101 UC), and 100 controls	Jordania	PPD, and CAL Oliver, Brown, and Löe (1998) [30].	Lennard-Jones criteria		Age, and number of missing teeth	5.93 (3.05–11.55)	4.92 (1.80–13.20)	7.00 (2.80–17.50)
Vavricka et al. (2013) [23]	113 IBD (69 CD, and 44 UC) patients, and 112 controls	Switzerland	PPD, and CAL Arbitrary definition	Lennard-Jones criteria		Extraintestinal manifestation, tooth brushing, and smoking	3.94 (1.91–8.05)	3.91 (1.78–8.57)	3.94 (1.64–9.46)
Koutsochristou et al. (2015) [24]	55 IBD (36 CD, and 19 UC) patients, and 55 controls	Greece	CPITN and PPD Ainamo J, Barmes D et al. (1982) [31]	Porto criteria		NA	12.09 (0.65–224.16)	NA	NA
Cross-sectional studies							ORs (95% CIs)		
Schmidt et al. (2018) [25]	59 IBD(30 CD, 29 UC) patients, and 59 controls	Germany	PPD, and CAL Page and Eke (2007) [32]"	Not clearly stated		NA	1.52 (0.54–4.29)	1.76 (0.45–6.99)	1.33 (0.38–4.65)
Zhang et al. (2019) [26]	389 IBD (265 CD, 124 UC) patients, and 265 controls	China	PPD, and CAL Eke, Page et al. (2012) [33].	Lennard-Jones criteria		Age, gender, education level, smoking, and tooth–brushing	NA	4.46 (2.50–7.95)	4.66 (2.49–8.71)

CAL: clinical attachment loss; CD: Crohn's disease; CI: confidential interval; CPITN: community periodontal index of treatment needs; HR: hazard ratio; IBD: inflammatory bowel disease; ICD-9-CM: International Classification of Diseases, ninth revision, clinical modification; NA: not available; OR: odd ratio; UC: ulcerative colitis.

Table 2. Study quality as assessed by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) checklist.

			Quality assessment					
Author (year)	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Magnitude of effect size	Grade
Lin et al. (2018) [18]	Retrospective cohort study	Not serious	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Zervou et al. (2004) [19]	Case-control study	Serious	Not serious	Not serious	Not serious	Serious	Not serious	⊕⊖⊖⊖ Very low
Grossner-Schreiber et al (2006) [20]	Case-control study	Not serious	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊖ Moderate
Brito et al. (2008) [21]	Case-control study	Not serious	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊖ Moderate
Habashneh et al. (2012) [22]	Case-control study	Not serious	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ High
Vavricka et al. (2013) [23]	Case-control study	Not serious	Not serious	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊖ Moderate
Koutsochristou et al (2015) [24]	Case-control study	Not serious	Not serious	Not serious	Not serious	Serious	Not serious	⊕⊖⊖⊖ Very low
Schmidt et al. (2018) [25]	Cross-sectional study	Not serious	Not serious	Serious	Not serious	Not serious	Not serious	⊕⊖⊖⊖ Very low
Zhang et al. (2019) [26]	Cross-sectional study	Not serious	Not serious	Serious	Not serious	Not serious	Not serious	⊕⊖⊖⊖ Very low

IBDs onset remains unknown. Two main theories are the more feasible according the current body of literature: (i) the presence of an unidentified persistent pathogen able build pathogen-associated molecular patterns, and (ii) and the disruption of beneficial species of intestinal flora by harmful non-identified agents inducing danger-associated molecular patterns. Some PD-related microbiota may contribute to this hypothesis such as *F. nucleatum*, *C. concisus,* and *C. rectus* [8]. In addition, animal studies have elucidated that colitis leads to alveolar bone loss, specifically these studies have used as models HLA-b27, 129/SvEv, and C57BL/6J transgenic rats which are characterised for spontaneously inducing a chronic colitis phenotype [37,38].

Limitations and strengths

Varying extent of PD prevalence was reflected in UC and CD patients. The average age of onset of IBDs subtypes varies. In the vast majority of populations, patients with CD and UC are usually diagnosed in their 20 and 30 s; however, the diagnosis can be made at any age. Although, peak in incidence of those patients diagnosed with UC is in general, 5–10 years later than in CD affected patients [39]. Even though peak in incidence in PD may vary in different populations, longitudinal observational studies using empirical evidence-driven definitions for this outcome have identified age as feasible risk factor [40]. We hypothesise about the influence of disease modifying drugs used for IBD management in PD prevalence due to its mayor use in CD. Taking together, these factors could justify the higher pooled RR for UC versus CD.

The relatively consistency of the results across study designs and settings provide substantial epidemiological evidence about the link between PD and IBDs. The publication of a well-designed large cohort study [18] has considerably attenuated these outcomes association bearing in mind the previous systematic approaches addressing this topic and according to our sensitivity analysis [41]. In fact, the aforementioned longitudinal study only found history of PD as a risk factor for UC after adjusting confounding factors (HR = 1.56 [95% CI 1.13–2.15]) [18]. In this sense, the magnitude of the effect showed in the present systematic review is less in comparison with previous results published in the literature. However, causal explanations of the relation should be carefully evaluated. Meta-analyses are often built on an assumption that directions of effect are consistent across studies as in this case we planned, but to contrast comprehensively against the plausible two hypothesis of direction was not possible due the presence of a single cohort study [42].

Initially, a main reason for the discrepancy between this meta-analysis and the previous literature may be the potential threat of publication bias and 'small study effects'. Considerable evidence from many clinical domains indicates that observational studies with 'negative' or 'not positive' results, especially small ones, may have difficulty getting published or may be published with considerable delays compared with studies that find significant associations [43]. Resulting in the accumulation of observational studies with significant associations [19], and sometimes with poor quality studies, or lacking cofounding adjustment [24] enhancing this effect. Although, it is worth mentioning that the different ratio metrics combined in the present report is acceptable according to COSMOS-E guidelines [44] – due to the outcome under study (i.e. IBD) is rare (<4%) in the case of the unique etiologic study included [18].

Secondly, residual confounding may have introduced bias as in any meta-analysis of observational studies. A factor affecting the pooled results may be periodontitis diagnostic criteria used in the included studies. Nonetheless, the introduced definitions of PD were secure and restricted to PPD or CAL thresholds as suggested by both the American Academy of Periodontology and the European Federation of Periodontology. This approach prevented selection bias during the synthesis of results due to the exclusion of insecure PD definitions as self-reported ones or simply the presence

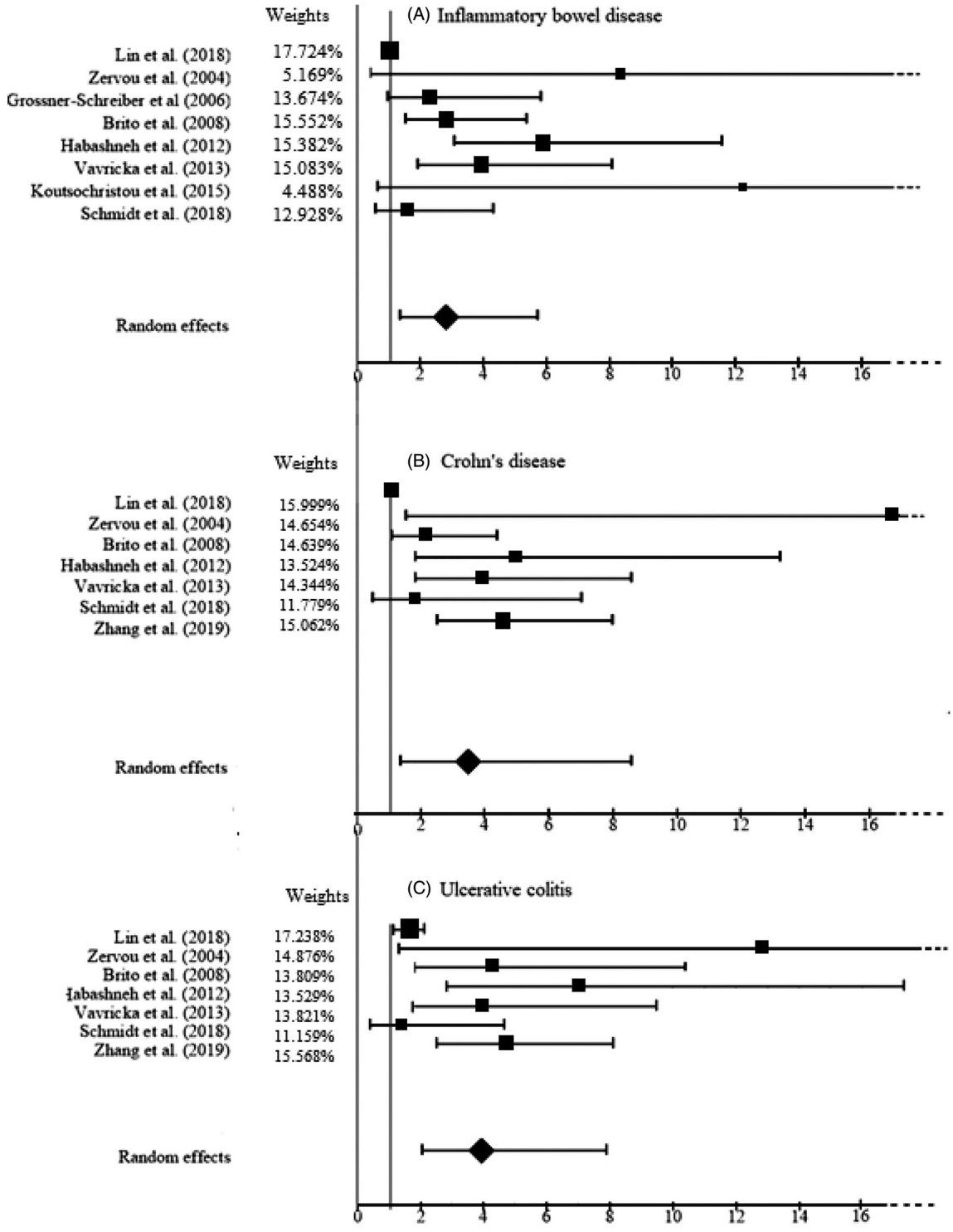

Figure 2. Forest plot of study-specific and pooled relative risks (RRs) and confidential intervals (CIs) of periodontal disease and inflammatory bowel disease according to random effects models: (A) inflammatory bowel diseases; (B) Crohn's disease; (C) ulcerative colitis. Squares represent study-specific RRs (the square sizes are proportional to the weight of each study in the overall estimate); horizontal lines represent 95% CIs; diamonds represent pooled RRs.

of tooth loss [28]. On the other hand, there is not a large amount of shared risk factors among PD and IBDs. The majority of studies analysed in the present systematic review have included potential PD risk factors (i.e. age, gender, or smoking) and were adjusted according to a multivariate analysis, as wat not the chase of IBD-related risk factors. Interestingly, smoking is a clear risk factor for PD [6], and CD, whereas it seems to play a protective role for UC [5]. Furthermore, other confounders that were not measured in the studies included in this meta-analysis could reinforce our results. For example, explainable susceptibility genetic risk factors in IBDs discovered so far, account for 20–25% of the heritability. Three major coding region polymorphisms within NOD2/CARD15 have been highly associated with IBDs.

Table 3. Pooled relative risks and 95 % confidence intervals (CI) of periodontitis and inflammatory bowel diseases.

	Number of studies	Pooled RR (95% CI) fixed effects	Pooled RR (95% CI) random effects	I^2 (%)	DerSimonian-Laird Q test p value
IBD					
All studies	8	1.06 (0.99–1.13)	2.78 (1.36–5.69)	87.89	.00001
Case-control studies	5	3.73 (2.61–5.32)	3.73 (2.61–5.32)	0	.42
High quality	5	1.06 (0.99–1.13)	2.67 (1.14–6.22)	92.35	.00001
Low quality	3	2.20 (0.87–5.58)	2.80 (0.77–10.13)	27.50	.28
Crohn's disease					
All studies	7	1.06 (0.99–1.14)	3.41 (1.36–8.56)	94.60	.00001
Case–control studies	4	5.27 (3.58–7.75)	5.15 (2.02–13.09)	82.39	.001
Ulcerative colitis					
All studies	7	1.04 (0.80–1.27)	3.98 (2.02–7.87)	72.88	.00001
Case–control studies	4	6.72 (4.41–10.22)	6.48 (3.67–11.43)	0	.17

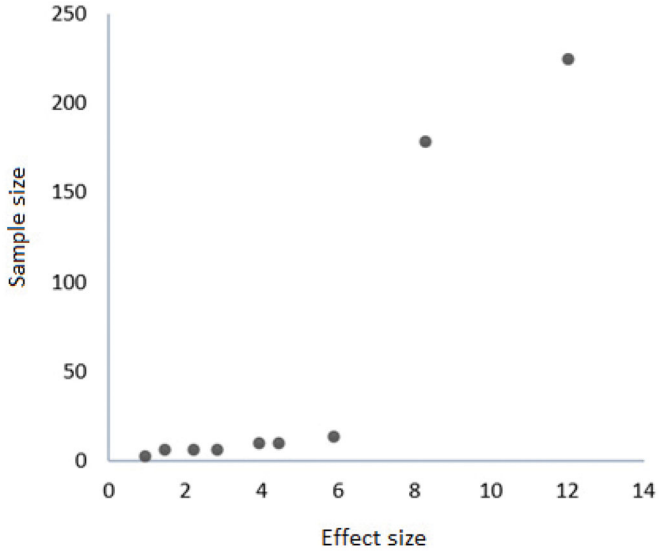

Figure 3. Funnel plot of natural log (Ln) relative risk (RR) versus standard error of Ln RR of periodontitis and inflammatory bowel disease.

Consequently, we have delved into studies in which this genetic risk kinked IBDs and PD on the other hand [45]. We retrieved four studies all of which concluded that NOD2/CARD15 gene polymorphisms does not seem to influence the pathophysiology of PD [46–49]. In this vein, from a genetic standpoint the possible bias introduced, if any, is towards the null value prompted by aforementioned literature. Furthermore, this association could be fuelled of amplified by the use of potential use of antimicrobials for the management of PD-affected patients which have been both linked to a higher incidence of IBDs, and worse control [50,51]. In author's opinion the existence of other unknown factors so strongly related to both exposure and outcome is plausible but at the same time uncertain according to available evidences. Third, in subgroup analyses, we were able to identify a main factor that accounted for study substantial heterogeneity which was the inclusion of the cohort study [18]. This situation is extremely frequent and in meta-analysis, even more a rule rather than the exception. As recommended by experts when moderate or high heterogeneity is present, we computed random-effects models on the basis of Higgins [16] criteria, due to their ability to be more conservative and give wider confidence intervals than fixed effect models [52].

Implications for clinical practice

Gastroenterologist and oral health care professionals should join hands to monitor the periodontal condition of their patients periodically in order to implement the proper multidisciplinary approaches to address this concomitance or even the plausible possibility of reducing the incidence of the outcome under study.

Recommendations for further research

There are interesting points that should be studied in future studies to address gaps in current evidence. In relation to the exposure, there is an emergent need to perform studies according to the new classification scheme for periodontal diseases on the basis of the workshop by the American Academy of Periodontology, and the European Federation of Periodontology. Secondly in terms of the outcome, further studies should to take into account the activity of the disease by validated indices, extent, and phenotype (e.g. patterns such as fistulising versus pure inflammatory ones) in order to more comprehensively elucidate this association or plausible causality.

Conclusion

Periodontal screening may be included in the multidisciplinary management of inflammatory bowel disease patients due its higher prevalence in comparison with non-affected individuals. Moreover, the mere theoretical possibility that periodontal disease may predispose to inflammatory bowel diseases may be of key significance due to the rising incidence of both outcome and exposure globally. Future studies should avoid non-longitudinal designs and focus on determining causality rather than association to provide robust evidence. If a clear cause-effect relationship is established in the future, that would emphasise the need of carefully designed interventional studies to determine precisely the importance of such multidisciplinary management.

Acknowledgements

All authors had access to the data and a role in writing the manuscript. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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