

Systematic Review

Effects of smoking cessation on the outcomes of non-surgical periodontal therapy: a systematic review and individual patient data meta-analysis

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Abstract

Aim: To conduct an individual patient data (IPD) meta-analysis to assess the effect of smoking cessation (SC) on clinical outcomes following the non-surgical periodontal treatment in patients with chronic periodontitis.

Methods: MEDLINE, EMBASE and CENTRAL were searched up to, and including, August 2012. Prospective cohort studies of at least 6 months' duration were included if the participants met the following criteria: (1) smokers who had expressed an interest in quitting the habit; and (2) a diagnosis of periodontitis. Search was conducted by two independent reviewers. IPD meta-analyses were undertaken using multiple linear or Poisson regression to evaluate the impact of SC on five different dependent variables.

Results: Of 2455 potentially eligible articles, two studies were included. The two studies found that SC seems to promote additional beneficial effects in reducing probing depths (PD) and improving attachment level following non-surgical periodontal treatment. The IPD approach allowed data combination but it might not have usefully added strength to the data in this review.

Conclusion: SC seems to be an important component of periodontal therapy, and smokers should be encouraged to quit as part of their overall periodontal management; however, only a limited base of evidence was available for analysis.

Key words: periodontal diseases; periodontitis; smoking; smoking cessation; systematic review

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The outcomes of high quality systematic reviews are considered a “gold standard” to be used in contemporary

Conflict of interest and source of funding statement

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clinical decision making. A number of systematic reviews have focused on the efficacy of periodontal treatments by pooling mean changes in clinical outcomes (Labriola et al. 2005, Eberhard et al. 2008, Lang et al. 2008, Esposito et al. 2009, Chambrone et al. 2010a). The most frequently used approach is to combine data from randomized controlled trials that compared a test

and a control group through pairwise meta-analyses using statistical methods to provide a general estimate of the differences in the outcomes (Whitehead 2002, Chambrone et al. 2010c, 2011b). On the other hand, for three or more treatment groups, multiple pairwise comparisons need to be conducted to evaluate the relative efficacy of those treatment procedures (Tu et al.

2012). To overcome this condition, individual patient data (IPD) meta-analysis may be used instead of conventional meta-analyses.

The IPD meta-analysis is a procedure that is used to surmount limitations of analyses that are based on aggregate data at the study level, such as the calculation of weighted mean differences and pooled odds ratio (OR) meta-analyses (Chambrone et al. 2012). With regard to mean differences, the inclusion of trials with greater baseline clinical measurements (indicating more advanced disease) seems to result in greater differences between baseline and follow-up means (i.e. outcome change), a condition that influences the calculation of mean differences (Chambrone et al. 2010a, 2012). With regard to odds ratios, IPD meta-analyses may limit potential sources of bias and heterogeneity, since this technique leads to more efficient evaluations by avoiding the impasse of combining odds ratios and risk ratios of studies that have adjusted (or not) for confounders. Furthermore, IPD meta-analysis assists in standardization of outcomes (e.g. investigation of clinical characteristics in patients with differing periodontal diagnoses). It can also integrate the patient clinical characteristics (e.g. initial probing depth (PD), clinical attachment level (CAL) and recession) into the analysis of efficacy of periodontal procedures as well as possible confounding factors (e.g. smoking), and, thus, may decrease the potential sources of bias and heterogeneity (Chambrone et al. 2012).

With respect to tobacco smoking, there is clear evidence that smoking may negatively affect the results of periodontal treatment. Tobacco smoking is a known risk factor that affects the oral environment and ecology, vascularization of the periodontium, immune and inflammatory responses and the healing potential of the periodontal connective tissues (Palmer et al. 2005, Johnson & Guthmiller 2007). Smokers are two to eight times more susceptible to periodontal disease than are non-smokers (Palmer et al. 2005, Johnson & Guthmiller 2007), as well as almost five times more susceptible to tooth loss due to periodontal reasons during long-term periodon-

tal maintenance (Chambrone et al. 2010b). Also, there is clear evidence that smoking may negatively affect the results achieved through both non-surgical and surgical periodontal therapy (Papantonopoulos 2004, Johnson & Guthmiller 2007, Chambrone et al. 2009, Wan et al. 2009, Rosa et al. 2011).

It is therefore difficult to predict accurately a patient's response to periodontal treatment if that patient is exposed to the continued effects of smoking. Previous studies have investigated the effects of quitting smoking on the clinical and radiographic outcomes of subjects who underwent periodontal treatment (Preshaw et al. 2005, Rosa et al. 2011). For instance, the studies by Preshaw et al. (2005) and Rosa et al. (2011) found that quitting smoking seems to have an additional beneficial effect in reducing probing depths over a 12-month period following non-surgical periodontal therapy.

Despite such positive findings, small sample sizes and limited patient compliance with quitting smoking are limitations of these studies. As a result, multi-centre analysis or pooled estimates using IPD would increase the sample size and, therefore, the achievement of better statistical power. To date, to our knowledge, no investigators have conducted a systematic review to compare the effect of smoking cessation and periodontal treatment in smokers. Thus, the objective of this systematic review was to conduct an IPD meta-analysis to evaluate the effect of smoking cessation on clinical outcomes following the non-surgical periodontal treatment in patients with chronic periodontitis. The following focused question was addressed: "Does quitting smoking reduce the number of residual pockets and improve the clinical outcomes of patients with periodontitis who underwent non-surgical periodontal treatment?"

Materials and methods

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO>, registration number CRD42012002760), as well as it is

in accordance to MOOSE (Stroup et al. 2000), PRISMA (Moher et al. 2009) and Check Review (Chambrone et al. 2010c) checklists. The following sections describe the specific methodological aspects of the review.

Criteria for considering studies for this review

As the research question is one of prognosis and owing to the impossibility of randomizing the risk factor of interest (i.e. smoking), the most appropriate research design to answer the focused question is a systematic review of observational studies. Therefore, only longitudinal prospective cohort studies of at least 6 months' duration were included. Studies were included if the participants met the following criteria: (1) smokers who had expressed an interest in quitting the habit and who underwent smoking cessation counselling; and (2) a diagnosis of periodontitis. Studies had to include data on the periodontal treatment procedures that were employed, smoking history, methods used to quantify the cotinine levels, and how smoking cessation was conducted.

Outcome measures

Primary outcome measures were clinical attachment level (CAL) and probing depth (PD). Secondary outcome measures were plaque score, bleeding on probing, radiographic changes of the alveolar bone level and number of teeth lost during the period of the study.

Search methods for identification of studies

Electronic searching

For the identification of studies to be included or considered for this review, detailed search strategies were developed for each database to be searched based on the search strategy presented for searching MEDLINE (via PubMed): (("periodontitis" [MeSH Term] OR "periodontal disease" [MeSH Terms] OR "periodontal pocket" [MeSH Terms] OR "periodontal attachment loss" [MeSH Terms] OR "chronic periodontitis" [MeSH Terms] OR "periodont*" [Free Term]) OR ("periodontal

treatment" [Keywords] OR "basic procedures" [Keywords] OR "scaling" [Keyword] OR "root planing" [MeSH Terms] OR "root surface debridement" [Keywords] OR "debridement" [MeSH Term] OR "root surface instrumentation" [Keywords]) AND (("smoking" [MeSH Term] OR "tobacco" [MeSH Term] OR "tobacco smoking" [Keywords]) OR ("cigarette" [Keywords] OR "cigar" [Keywords] OR "pipe" [Keywords]) OR ("cessation" [Keywords] OR "smoking cessation" [MeSH Term] OR "quitting smoking" [Keywords])).

The Cochrane Oral Health Group's Trials Register (CENTRAL), MEDLINE and EMBASE were searched without language restriction up to, and including, August 2012.

Unpublished data and hand-searching

Unpublished data were sought by searching a database listing unpublished studies (OpenGray [http://www.opengrey.eu/], formerly OpenSIGLE). Moreover, reference lists of any potential studies were examined (i.e. hand searching) in an attempt to identify any further papers that could be considered for inclusion.

Data collection, extraction and management

Initially, two review authors (LC and PMP) independently screened titles, abstracts and full texts of the search results. The review authors remained unblinded regarding the author(s), their institutional affiliations and the site of publication of reports. The full report was obtained for all studies appearing to meet the inclusion criteria or in instances where there was insufficient information from the title, keywords and abstract to make a clear decision. All studies were assessed independently for eligibility by both review authors. Disagreement between the review authors would be resolved by discussion with the inclusion of another review author (PAH). In case of missing data, authors would be contacted to provide further details. The studies meeting the inclusion criteria underwent validity assessment and data extraction.

Data on the following issues were extracted and recorded in duplicate (LC and PMP) using specially

designed data-extraction forms (Chambrone et al. 2010a, 2011a): (1) citation, publication status and year of publication; (2) location of trial; (3) characteristics of participants; (4) type of interventions; (5) outcome measures; and (6) source of funding and conflicts of interest. In addition, when IPD were not published/reported in the original paper, the raw data from each study were obtained from the original authors.

Assessment of quality in included studies

The methodological quality of the observational studies was assessed using a quality measurement tool especially developed for this study by combining topics from the Newcastle–Ottawa scale (NOS-scale) (Wells et al. 2001) adapted by Chambrone et al. (2010b, 2011a, 2013), with items designed to appraise the exposure for chronic periodontitis and other relevant domains of methodological quality. Thus, the following points were specifically assessed: (1) Selection of study groups (i.e. sample size calculation and representativeness of the patients with periodontitis [assessment whether smoking and non-smoking groups were similar with respect to disease severity, health behaviours' and demographics]), ascertainment/assessment of periodontal conditions, clear definitions of chronic periodontitis and smoking, training/calibration of assessors of outcome (periodontitis) and exposure (smoking), demonstration that outcome of interest (smoking cessation) was not provided before patients' admission (i.e. prospective data collection) and description of clear inclusion/exclusion criteria); (2) comparability (i.e. comparability of subjects on the basis of the study design or analysis and management of confounders); (3) outcome (i.e. assessment of smoking cessation outcomes, ascertainment/criteria applied to confirm smoking status and adequacy of follow-up of the patients); and (4) statistical analysis (i.e. appropriateness/validity of statistical analysis and unit of analysis reported in the statistical model).

Using the quality assessment tool, points (stars) were assigned to the various methodological quality criteria. The methodological quality

assessment tool was adapted and designed for this review and each study included could receive a maximum of 14 points. Studies with 11–14 points (approximately 80% or more of the domains satisfactorily fulfilled) were arbitrarily considered being of high quality, with 8–10 points indicating medium quality, and <8 points suggesting low methodological quality.

Data synthesis

Data were collated into evidence tables, with assessment of study characteristics, study quality and results. Because there were only two studies, one-stage fixed-effects IPD meta-analyses were undertaken using multiple linear or Poisson regression in a statistical software package (STATA, version 12.1, StataCorp, College Station, TX, USA), by assuming the effects of quitting smoking was the same for the two studies. These analyses used individual patient data reported by each included trial to evaluate PD, CAL, and BOP change, as well as the number of sites demonstrating reductions in probing depths ≥ 2 mm (i.e. clinical improvements) from baseline to final follow-up as dependent variables and the number of residual deep sites (≥ 4 mm) 12 months after treatment. The primary level of analysis was the subject. For each outcome, a single summary measure was derived for each subject by taking the mean value across all the sites for which the outcome was evaluated. The association between baseline characteristics/follow-up/compliance and the dependent variable were calculated and $p < 0.05$ were considered statistically significant.

Results

Search results and description of included studies

The flow chart of manuscripts screened through the review process is shown in Fig. 1. A total of 2455 potentially eligible articles were identified and screened for retrieval, but of them, 2453 were excluded after the title and/or abstract were reviewed. Subsequently, two publications, one conducted in the United Kingdom (Preshaw et al. 2005) and one in

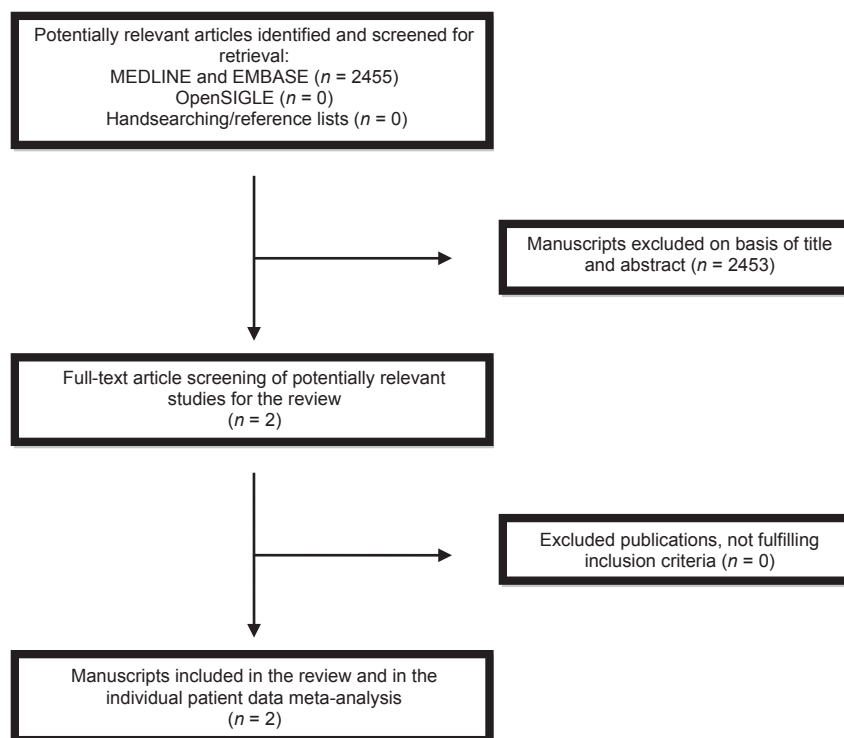


Fig. 1. Flow chart of manuscripts screened through the review process.

Brazil (Rosa et al. 2011) were considered potentially relevant for full text article screening. Following full text review, both papers met the proposed inclusion criteria and were included in the review. Their characteristics are described in Table 1.

In total, data on 78 patients with chronic periodontitis were available for analysis (54.9% of the subjects initially enrolled). Both studies had been published in full and had received support from research foundations or university programmes. The two included studies followed patients for a 12-month period, described similar inclusion/exclusion criteria and found that smoking cessation seems to promote additional beneficial effects in reducing probing depths (Preshaw et al. 2005) and improving CAL (Rosa et al. 2011) following non-surgical periodontal treatment (Table 1).

Quality assessment

The studies by Preshaw et al. (2005) and Rosa et al. (2011) both received a 11-point score (of 14), and as a result, they were considered to have high methodological quality (Appendix S1 and S2). Regarding to the meth-

odological domains assessed by the modified NOS-Scale, these are indicated below:

- Sample size: neither of the studies reported a sample size calculation;
- Representativeness of the patients with chronic periodontitis: both groups of subjects were considered to be reasonably representative of an average sample of smoking patients;
- Selection of quitters and non-quitters: these were drawn from the same community of patients with periodontitis;
- Assessment of periodontal conditions: both studies reported adequate criteria to diagnose periodontitis based on full-mouth probing measurements, that is, PD and CAL;
- Clear definitions of methods to assess smoking status: these were clearly reported in both studies;
- Training/calibration of assessors of clinical outcomes: details concerning examiners/care givers were clearly reported within studies;
- Prospective data collection and description of clear inclusion/exclusion criteria: both studies fulfilled these criteria;
- Comparability of patients on the basis of the design or analysis: for both studies, not all patients received the same smoking cessation counselling (it was tailored according to patient preference and need);
- Management of confounders: both studies reported statistical analyses performed with control for potential confounders;
- Assessment of periodontal outcomes: Only the study by Rosa et al. (2011) described that the examiner in charge of performing the clinical examinations was blind to the smoking status of the patients. In this study, before each examination, subjects underwent 'removal of all tobacco stains from their teeth and/or dental polishing, with a standardized duration of up to 30 min and they were asked to rinse with a 0.12% chlorhexidine solution to hide any tobacco smoking odour exhaled from the oral cavity'. Also, 'the examiner entered the examination room fully equipped (including a mask), in order to avoid noticing the smoking status by odour';
- Ascertainment/criteria applied to evaluate smoking status: adequate criteria based on carbon monoxide (CO) reading and/or salivary cotinine levels were described by the two studies;
- Adequacy of follow-up of patients: Preshaw et al. (2005) reported that complete data over the full duration of the study were available for 53% of patients enrolled, and Rosa et al. (2011) reported that 56% of the patients enrolled completed the study;
- Appropriateness/validity of statistical analysis; this was considered adequate for both studies;
- Unit of analysis (response rate) reported in the statistical model: both studies reported their analyses based on the number of patients who quit smoking;

Individual patient data meta-analysis

Six IPD meta-analyses were performed for PD, CAL and BOP change, for the number of sites exhibiting PD reduction ≥ 2 mm,

Table 1. Characteristics of included studies

Study	Participants and study design	Methods	Periodontitis definition	Outcomes	Conclusions
Preshaw et al. (2005)	Forty nine smoking subjects with chronic periodontitis were recruited. Thirty four subjects completed the study, but confirmed and complete smoking status data over the 12 months were available for 26 subjects (16 females) with mean age 43.2 years). The investigation was described as a 12-month, longitudinal, non-blinded, clinical trial. Of the 49 subjects recruited, 10 had confirmed continuous quit smoking at month 12 (20.4% quit rate).	A smoking history was obtained and personalized risk feedback based on the severity of chronic periodontitis status and the smoking history in pack-years was given. Smoking cessation advice was provided at the first treatment appointment as appropriate, based on the smoking history, and subsequently reinforced at each visit up to, and including month 12. Full-mouth periodontal examination (BOP, PS, PD and CAL) by one calibrated examiner. CAL was measured using an automated, pressure-controlled probe with a standardized probing force of 0.25 N. Radiographic exam to evaluate changes in bone density (bitewing radiographs). All patients received non-surgical periodontal treatment and periodontal maintenance.	Moderate-to-severe chronic periodontitis was defined as the presence of ≥ 6 posterior teeth, each with at least one inter-proximal site with probing depth ≥ 5 mm and alveolar bone destruction at least one third of the root length.	Quitters ($n = 10$) Δ CAL: -0.10 mm Δ PD: 0.96 mm Δ PS: 14.4% Δ BoP: 19.3% TL: NR Δ RB: 0.00 mm ³ Oscillators ($n=6$) Δ CAL: 0.20 mm Δ PD: 0.50 mm Δ PS: 15.20% Δ BoP: 17.90% TL: NR Δ RB: -0.08 mm ³ Non-quitters ($n = 10$) Δ CAL: 0.20 mm Δ PD: 0.61 mm Δ PS: 17.1% Δ BoP: 14.2% TL: NR Δ RB: -0.08 mm ³ At month 12, quitters had significantly greater mean PD reductions than non-quitters/oscillators and significantly more sites with PD reductions ≥ 2 mm and ≥ 3 mm.	This study concluded that "quitting smoking has an additional beneficial effect in reducing probing depths following non-surgical treatment over a 12-month period".
Rosa et al. (2011)	Ninety three smoking subjects with chronic periodontitis were recruited, but 52 patients, mean age 49.3 years, 32 females, completed the study. This investigation was described as a 12-month prospective, single-blinded study. Of the 93 subjects recruited, 17 had confirmed continuous quit status at month 12 (18.3% quit rate).	A smoking history was obtained and personalized risk feedback based on the severity of chronic periodontitis status and the smoking history in pack-years was given. Smoking cessation advice, nicotine replacement therapy and/or medication was provided at the first treatment appointment as appropriate, based on the smoking history. Advice was subsequently reinforced at each visit up to, and including month 12. Full-mouth periodontal examination (BOP, PS, PD, GR and CAL) by one blinded and calibrated examiner. CAL was measured using a manual periodontal probe. All patients received non-surgical periodontal treatment and periodontal maintenance.	Severe chronic periodontitis was defined as the presence of $\geq 30\%$ of teeth with inter-proximal CAL ≥ 5 mm	Quitters ($n = 17$) Δ CAL: 0.21 mm Δ PD: 0.29 mm Δ PS: 26.50% Δ BoP: 5.20% TL: 0.12 teeth Δ RB: NR Non-quitters ($n = 35$) Δ CAL: 0.13 mm Δ PD: 0.30 mm Δ PS: 9.53% Δ BoP: -0.3% TL: 0.51 teeth Δ RB: NR At month 12, there were no significant differences in periodontal parameters between the quitters and non-quitters.	This study concluded that "smoking cessation promoted clinical attachment gain in chronic periodontitis subjects from a smoking cessation clinic after 1 year of follow-up".

PD, Probing depth; CAL, clinical attachment level; PS, plaque score (dichotomous); BoP, bleeding on probing; TL, tooth loss; RB, radiographic bone density.

and for the number of residual probing depths ≥ 4 mm. Because there were only two studies included, which is insufficient to obtain robust estimates for random effects at the study level, fixed-effects IPD meta-analyses comparing data from smokers who quit smoking or not were used throughout.

With respect to mean PD changes from baseline to 12 months, the difference between quitters and non-quitters was not statistically significant ($p = 0.098$, Table 2). Table 2 also reveals a statistically significant effect of "Study" on PD changes over 12 months, with patients in study 2 (Rosa et al. 2011) demonstrating, on average, 0.37 mm less PD reduction than those in study 1 (Preshaw et al. 2005). However, patients in study 2 had a lower mean PD at baseline compared to those in study 1; thus, after adjusting for baseline PD, the apparent significant impact of "Study" on PD reductions was eliminated ($p = 0.36$), though this difference was again not statistically significant ($p = 0.057$). When considering CAL (Table 3) and the reduction in percentage of sites with BOP (Table 3) gain 12 months following periodontal treatment, the differences between quitters and non-quitters were not statistically significant ($p = 0.306$ and $p = 0.173$ respectively). On average, the difference in CAL gain between the two studies was very small (0.02 mm) (Table 4).

Table 5 reports the outcomes of the fixed-effects Poisson regression analysis of the impact of smoking cessation on the number of sites demonstrating PD reductions ≥ 2 mm over the course of the study. There was a highly significant beneficial impact of quitting smoking with incident rate ratio [IRR] of 1.30 (95% confidence interval (CI): 1.17–1.44; Poisson absolute value IZI = 4.93; $p < 0.001$), with quitters demonstrating 30% more number of sites with PD reductions ≥ 2 mm than non-quitters. On average, patients in study 2 (Rosa et al. 2011) demonstrated fewer sites with PD reduction ≥ 2 mm than those in study 1 (Preshaw et al. 2005), and females had fewer sites with PD reduction ≥ 2 mm than males. In addition, Table 6 shows the number of sites with residual pockets demonstrating

Table 2. Multiple linear regression analysis evaluating the effect of smoking cessation on mean probing depth reduction

	Coefficient	SE	<i>t</i>	<i>p</i> > <i>t</i>	95% CI
Without adjustment for baseline probing depth					
Quit status	0.20	0.12	1.68	0.098	−0.04 to 0.43
Gender	0.08	0.11	0.68	0.498	−0.15 to 0.30
Age	0.00	0.00	0.29	0.774	−0.01 to 0.02
Study	−0.37	0.12	−2.94	0.004	−0.62 to −0.12
Intercept	0.44	0.35	1.25	0.215	−0.26 to 1.13
With adjustment for baseline probing depth					
Quit status	0.20	0.10	1.93	0.057	−0.01 to 0.40
Gender	0.14	0.10	1.36	0.177	−0.06 to 0.33
Age	0.00	0.01	0.37	0.711	−0.01 to 0.02
Study	−0.11	0.12	−0.94	0.350	−0.35 to 0.13
Baseline PD	0.36	0.07	5.02	0.000	0.21 to 0.50
Intercept	−0.92	0.41	−2.26	0.027	−1.73 to −0.11

CI, Confidence interval; SE, standard error; PD, probing depth.

Table 3. Multiple linear regression analysis evaluating the effect of smoking cessation on mean clinical attachment level gain

	Coefficient	SE	<i>t</i>	<i>p</i> > <i>t</i>	95% CI
Quit status	−0.17	0.16	−1.03	0.306	−0.48 to 0.15
Gender	0.19	0.15	1.20	0.235	−0.12 to 0.49
Age	0.00	0.01	0.12	0.903	−0.02 to 0.02
Study	−0.02	0.17	−0.10	0.925	−0.36 to 0.33
Intercept	0.04	0.47	0.09	0.927	−0.89 to 0.98

CI, Confidence interval; SE, Standard error.

Table 4. Multiple linear regression analysis evaluating the effect of smoking cessation on % BoP reduction

	Coefficient	SE	<i>t</i>	<i>p</i> > <i>t</i>	95% CI
Quit status	0.06	0.04	1.38	0.173	−0.03 to 0.14
Gender	0.05	0.04	1.16	0.248	−0.03 to 0.13
Age	0.00	0.00	−0.36	0.722	−0.01 to 0.00
Study	−0.14	0.05	−3.03	0.003	−0.22 to −0.05
Intercept	0.15	0.12	1.24	0.219	−0.09 to 0.40

BoP, bleeding on probing; CI, confidence interval; SE, standard error.

Table 5. Fixed-effects Poisson regression analysis evaluating the effect of smoking cessation on the number of sites with probing depth reduction ≥ 2 mm

	IRR	SE	<i>z</i>	<i>p</i> > <i>z</i>	95% CI
Quit status	1.30	0.07	4.93	0.000	1.17 to 1.44
Gender	0.81	0.04	−3.97	0.000	0.74 to 0.90
Age	1.01	0.00	2.09	0.036	1.00 to 1.01
Study	0.54	0.03	−11.26	0.000	0.48 to 0.60
Intercept	0.16	0.03	−11.52	0.000	0.11 to 0.21

CI, confidence interval; IRR, incident rate ratio; SE, standard error.

PD ≥ 4 mm at 12 months. Quitters had 22% fewer sites with residual PD ≥ 4 mm than non-quitters with IRR of 0.78 (95% CI: 0.72–0.84; Poisson absolute value IZI = −6.21; $p < 0.001$). On average, patients in study 2 had 40% fewer sites with residual PD ≥ 4 mm than those in study 1.

Discussion

Summary of the main results

The influence of smoking on treatment outcomes has been considered an important factor in periodontal clinical practice and research. Few studies have assessed prospectively

Table 6. Fixed-effects Poisson regression analysis evaluating the effect of smoking cessation on the number of sites with residual probing depths ≥ 4 mm at 12 months

	IRR	SE	z	p > z	95% CI
Quit status	0.78	0.03	-6.21	0.000	0.72 to 0.84
Gender	1.00	0.04	0.11	0.911	-0.93 to 1.08
Age	1.01	0.00	3.09	0.002	1.00 to 1.01
Study	0.60	0.03	-11.98	0.000	0.56 to 0.66
Intercept	0.74	0.08	-2.79	0.005	0.60 to 0.92

CI, confidence interval; IRR, incident rate ratio; SE, standard error.

the influence of smoking cessation on periodontal treatment outcomes, and only two were identified by our systematic review. Both of these studies adopted similar inclusion criteria and used similar methodologies, and the 2011 study can be regarded as a replication of the study published in 2005. The individual outcomes from these two studies showed that quitting smoking led to an additional PD reduction (Preshaw et al. 2005) and CAL gain (Rosa et al. 2011) after non-surgical periodontal therapy over a 12-month period.

The authors of both of these studies reported the difficulty of conducting studies of this nature, in terms of ensuring compliance with the smoking cessation strategy, and both studies reported high dropout rates, with complete data only available for just over half of the patients recruited. Both studies individually lacked power to clearly identify clinically significant benefits of smoking cessation across the spectrum of clinical parameters routinely used to assess response to treatment in clinical practice. There was a (non-significant) trend towards greater mean PD reductions in those who quit smoking, with a magnitude of around 0.2 mm. Moreover, a highly statistically significant benefit of quitting smoking was identified, with quitters demonstrating 30% more sites with PD reduction ≥ 2 mm following periodontal treatment, and 22% fewer sites with residual PD ≥ 4 mm at 12 months after treatment.

Agreements and disagreements with previous studies

While only 2 studies were identified that could be included in this systematic review (i.e. prospective studies of the impact of smoking cessation on periodontal treatment outcomes in

smoking patients with periodontitis), data from different trials and reviews have clearly demonstrated that the predictability of periodontal therapy is directly linked to patients' exposure to conditions known to affect host responses, such as smoking (Labriola et al. 2005, Palmer et al. 2005, Johnson & Guthmiller 2007, Chambrone et al. 2009, Wan et al. 2009, Warnakulasuriya et al. 2010). It is also clear that successful outcomes of periodontal therapy depend on active involvement of the patient receiving the therapy, with a strong emphasis on lifestyle changes such as improving plaque control, adhering to a periodontal maintenance programme, and quitting smoking. The pathogenesis of periodontitis involves a complex interplay between the subgingival biofilm and the resultant host-derived inflammatory response, which is mediated by cells and mediators of inflammation functioning in complex networks (Kinane et al. 2011). It is not clear precisely how tobacco smoking impacts on these networks, but it is certain that risk for periodontitis is greatly increased in those individuals who smoke. As an example, patients who smoke at least 10 cigarettes per day even while complying with strict periodontal maintenance conditions may present almost five times more chance of losing their teeth due to periodontitis (Chambrone et al. 2010b). It is clear therefore, that further detailed investigation of the precise mechanisms by which smoking increases risk for periodontitis, as well as further large scale studies to evaluate the benefits of quitting smoking are required.

Quality of the evidence and potential biases in the review process

In this review, the two included studies were classified as having high

methodological quality. However, it was evident in these studies the lack of sample size calculations, the lack of a "control group" formed by non-smokers, the intra-study differences concerning the smoking cessation counselling (i.e. not all patients received exactly the same treatment), masking of examiners (only Rosa et al. 2011 fulfilled this criterion) and the numbers of dropouts. On the other hand, all other important quality criteria were satisfied. For instance, both studies applied adequate criteria to assess smoking status (e.g. by assessing the levels of CO and/or salivary cotinine) and both studies reported their outcomes based on the patient as the unit of analysis. Furthermore, the difficulties inherent in conducting these sorts of studies have to be recognized. For example, patient recruitment and retention is very challenging, as well as is achieving smoking cessation. Also, performing blind examinations in smokers is a difficult task, even employing the method reported by Rosa et al. (2011), since smokers usually present with a strong and persistent tobacco odour.

It should be considered that the application of IPD meta-analyses related to the impact of smoking cessation also deserve attention. These may lead to the following queries: 'what does an IPD approach add to the knowledge on this topic?' 'Which are the main advantages (and disadvantages) of this approach?' and 'is an IPD meta-analysis conducted with very few studies more reliable than an aggregated patient data meta-analysis with more individual studies?' Given the inherent limitations related to low number of studies and patients evaluated, and the difficulties involving patients' enrolment and compliance with smoking cessation, an IPD approach may favour the assessment of a larger sample of subjects and, thus, the achievement of more robust estimates, greater statistical power, and adjustment for characteristics of baseline defects (Sutton et al. 2000, Bennett 2003, Lyman & Kuderer 2005, Higgins & Green 2008, Chambrone et al. 2012). On the other hand, several limitations on the interpretation of such adjustment in this review should be taken into consideration. The boundaries in the

amount of data, the losses to follow-up and possible resulting selection bias, other potential biases and the difficulties of accounting for baseline differences really mean that we cannot be sure that the data retrieved can accurately support the pooled estimates. Consequently, some of the conclusions of a lack of statistical difference (e.g. mean CAL gain and BOP) might be due to type II error. Furthermore, differences between groups may be much more profound than differences in probing depths, such as health behaviours. Similarly, although IPD meta-analysis may improve efficiency, it cannot overcome the limited amount of data and methodological problems with the original studies. Consequently, the IPD meta-analysis approach used in this study may only be considered as an additional tool that could not accurately add strength to the data.

In summary, and within the limits of this systematic review, only limited information on the effects of smoking cessation on clinical outcomes following periodontal therapy is available in the current base of evidence. Overall, it is reasonable to conclude that smoking cessation is an important component of periodontal therapy, and smokers should be encouraged to quit as part of their overall periodontal management. However, controlled, prospective clinical trials are required to further investigate the impact of smoking cessation on clinical outcomes and potential prognostic factors. Such studies would ideally be of at least 12 months' duration.

References

- Bennett, D. A. (2003) Review of analytical methods for prospective cohort studies using time to event data: single studies and implications for meta-analysis. *Statistical Methods in Medical Research* **12**, 297–319.
- Chambrone, L., Chambrone, D., Lima, L. A. & Chambrone, L. A. (2010b) Predictors of tooth loss during long-term periodontal maintenance: a systematic review of observational studies. *Journal of Clinical Periodontology* **37**, 675–684.
- Chambrone, L., Chambrone, D., Pustiglioni, F. E., Chambrone, L. A. & Lima, L. A. (2009) The influence of tobacco smoking on the outcomes achieved by root-coverage procedures. A systematic review. *Journal of the American Dental Association* **140**, 294–306.
- Chambrone, L., Faggion, C. M., Pannuti, C. M. & Chambrone, L. A. (2010c) Evidence-based periodontal plastic surgery: an assessment of quality of systematic reviews in the treatment of recession-type defects. *Journal of Clinical Periodontology* **37**, 1110–1118.
- Chambrone, L., Foz, A. M., Guglielmetti, M. R., Pannuti, C. M., Artese, H. P. C., Feres, M. & Romito, G. A. (2013) Periodontitis and chronic kidney disease: a systematic review of the association of diseases and the effect of periodontal treatment on estimated glomerular filtration rate. *Journal of Clinical Periodontology* **40**, doi:10.1111/jcpe.12067.
- Chambrone, L., Guglielmetti, M. R., Pannuti, C. M. & Chambrone, L. A. (2011a) Evidence grade associating periodontitis to preterm birth and/or low birth weight: I. A systematic review of prospective cohort studies. *Journal of Clinical Periodontology* **38**, 795–808.
- Chambrone, L., Pannuti, C. M., Guglielmetti, M. R. & Chambrone, L. A. (2011b) Evidence grade associating periodontitis with preterm birth and/or low birth weight: II: a systematic review of randomized trials evaluating the effects of periodontal treatment. *Journal of Clinical Periodontology* **38**, 902–914.
- Chambrone, L., Pannuti, C. M., Tu, Y. K. & Chambrone, L. A. (2012) Evidence-based periodontal plastic surgery. II. An individual data meta-analysis for evaluating factors in achieving complete root coverage. *Journal of Periodontology* **83**, 477–490.
- Chambrone, L., Sukekava, F., Araújo, M. G., Pustiglioni, F. E., Chambrone, L. A. & Lima, L. A. (2010a) Root coverage procedures for the treatment of localized recession-type defects: A Cochrane systematic review. *Journal of Periodontology* **81**, 452–478.
- Eberhard, J., Jervøe-Storm, P. M., Needleman, I., Worthington, H. & Jepsen, S. (2008) Full-mouth treatment concepts for chronic periodontitis: a systematic review. *Journal of Clinical Periodontology* **35**, 591–604.
- Espósito, M., Grusovin, M. G., Papanikolaou, N., Coulthard, P. & Worthington, H. V. (2009) Enamel matrix derivative (Emdogain®) for periodontal tissue regeneration in intrabony defects. *The Cochrane Database of Systematic Reviews*, CD003875.
- Higgins, J. P. T. & Green, S. (2008) *Cochrane handbook for systematic reviews of interventions version 5.0.1*. The Cochrane Collaboration. Available at <http://www.cochranehandbook.org> (accessed 15 November 2008).
- Johnson, G. K. & Guthmiller, J. M. (2007) The impact of cigarette smoking on periodontal disease and treatment. *Periodontology 2000* **44**, 178–194.
- Kinane, D. F., Preshaw, P. M. & Loos, B. G. (2011) Host-response: understanding the cellular and molecular mechanisms of host-microbial interactions - Consensus of the Seventh European Workshop on Periodontology. *Journal of Clinical Periodontology* **38** (Suppl. 11), 44–48.
- Labriola, A., Needleman, I. & Moles, D. R. (2005) Systematic review of the effect of smoking on nonsurgical periodontal therapy. *Periodontology 2000* **37**, 124–137.
- Lang, N. P., Tan, W. C., Krähenmann, M. A. & Zwahlen, M. (2008) A systematic review of the effects of full-mouth debridement with and without antiseptics in patients with chronic periodontitis. *Journal of Clinical Periodontology* **35** (8 Suppl), 8–21.
- Lyman, G. H. & Kuderer, N. M. (2005) The strengths and limitations of meta-analyses based on aggregate data. *BMC Medical Research and Methodology* **5**, 14.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. & The PRISMA Group. (2009) Methods of systematic reviews and meta-analysis preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Journal of Clinical Epidemiology* **62**, 1006–1101.
- Palmer, R. M., Wilson, R. F., Hasan, A. S. & Scott, D. A. (2005) Mechanisms of action of environmental factors: tobacco smoking. *Journal of Clinical Periodontology* **32** (suppl 6), 180–195.
- Papantonopoulos, G. H. (2004) Effect of periodontal therapy in smokers and non-smokers with advanced periodontal disease: results after maintenance therapy for a minimum of 5 years. *Journal of Periodontology* **75**, 839–843.
- Preshaw, P. M., Heasman, L., Stacey, F., Steen, N., McCracken, G. I. & Heasman, P. A. (2005) The effect of quitting smoking on chronic periodontitis. *Journal of Clinical Periodontology* **32**, 869–879.
- Rosa, E. F., Corraini, P., de Carvalho, V. F., Inoue, G., Gomes, E. F., Lotufo, J. P. B., De, Micheli, G. & Pannuti, C. M. (2011) A prospective 12-month study of the effect of smoking cessation on periodontal clinical parameters. *Journal of Clinical Periodontology* **38**, 562–571.
- Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A. & Thacker, S. B. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* **283**, 2008–2012.
- Sutton, A. J., Abrams, K. R., Jones, D. R., Sheldon, T. A. & Song, F. (2000) *Methods for meta-analysis in medical research*. New York: John Wiley & Sons.
- Tu, Y. K., Needleman, I., Chambrone, L., Lu, H. K. & Faggion, C. M. Jr (2012) A Bayesian network meta-analysis on comparisons of enamel matrix derivatives, guided tissue regeneration and their combination therapies. *Journal of Clinical Periodontology* **39**, 303–314.
- Wan, C. P., Leung, W. K., Wong, M. C., Wong, R. M., Wan, P., Lo, E. C. & Corbet, E. F. (2009) Effects of smoking on healing response to non-surgical periodontal therapy: a multilevel modelling analysis. *Journal of Clinical Periodontology* **36**, 229–239.
- Warnakulasuriya, S., Dietrich, T., Bornstein, M. M., Casals Peidró, E., Preshaw, P. M., Walter, C., Wennström, J. L. & Bergström, J. (2010) Oral health risks of tobacco use and effects of cessation. *International Dental Journal* **60**, 7–30.
- Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. & Tugwell, P. (2001) *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Ottawa. University of

Ottawa. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm (Accessed on 16.12.2009).
 Whitehead, A. (2002) *Meta-Analysis of Controlled Clinical Trials*, pp. 241–257. Chichester: Wiley.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Modified NOS scale (Chambrone et al. 2010b, 2011a) adapted for this review: Preshaw et al. (2005).

Appendix S2. Modified NOS scale (Chambrone et al. 2010b, 2011a) adapted for this review: Rosa et al. (2011).

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Clinical relevance

Scientific rationale for the study: Current evidence suggests that smoking cessation may have a positive impact on non-surgical periodontal therapy; however, there are no systematic reviews that have explored this potential effect.

Principal findings: Individual studies' outcomes and the mixed effects

Poison regression analyses found a highly significant beneficial impact of quitting smoking. Quitting resulted in almost one-third more sites exhibiting probing depth reductions ≥ 2 mm than non-quitters, as well as almost one third of sites with residual pockets demonstrating PD ≥ 4 mm at 12 months. There were no significant differences between quitters and

non-quitters in terms of mean CAL gain and BOP reduction 12 months following periodontal treatment.

Practical implications: Patients should be instructed about the importance of quitting smoking to improve the clinical impact of periodontal treatment.