VAPING IS ASSOCIATED WITH REDUCED RESPONSE TO NON-SURGICAL PERIODONTAL THERAPY: A RETROSPECTIVE CLINICAL STUDY

Running title: Vaping and periodontal therapy response

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Summary: E-cigarette users had a statistically significant less favourable response to professional-mechanical-plaque-removal than non-smokers, and no statistical difference to current smokers.

ABSTRACT

Aim: To compare periodontal treatment responses in e-cigarette users, non-smokers, former and current smokers.

Methods: A retrospective clinical study of 220 subjects with periodontitis had baseline periodontal charting, professional-mechanical-plaque-removal (PMPR) and re-evaluation by postgraduate students. Effects of smoking status on clinical outcomes were analysed by linear and negative binomial regression models adjusted for known confounders. The primary outcome was 'need for surgery' (number of sextants with ≥2non-adjacent sites of probing-pocket-depths (PPD) ≥5mm).

Results: Compared to non-smokers, e-cigarette users had a less favourable treatment response after PMPR. This included statistically significant increased 'need for surgery', number of sites with PPD≥5mm, mean PPD, number of sextants with PPD≥5mm and clinical attachment loss (CAL). There were no statistically significant differences between e-cigarette users and current smokers. Former smokers responded statistically significantly better than e-cigarette users for the primary outcome ($p<0.001$), number of sites with PPD≥5mm ($p=0.032$), mean PPD ($p=0.007$), mean CAL ($p=0.02$) and number of sextants with PPD≥5mm ($p=0.001$).

Conclusion: Overall, e-cigarette users had a statistically significant less favourable response to PMPR than non-smokers, but no statistically significant difference to current smokers. This, however, needs to be validated with further research in prospective clinical studies in different populations.

Keywords: periodontitis, electronic/e-cigarettes, clinical study

INTRODUCTION:

Many epidemiological and clinical studies have demonstrated the detrimental effects tobacco smoking can have on the periodontium, making smoking a major risk factor for periodontitis[1]. This effect is dose-dependent, with increasing risk for heavy smokers compared to light smokers[2]. The odds of having periodontitis reduces with the number of years of smoking cessation and those who had quit smoking for 11 years or more had the same odds as never smokers of having periodontitis[3].

The exact mechanism of how cigarettes can affect the periodontium is not fully understood but there are several suggested mechanisms such as an impaired immune and inflammatory response, effect on the oral bacteria and healing capacity[4]. These mechanisms can lead to increased bone loss, increased attachment loss, deeper pockets (especially in the anterior and maxillary palatal sites), fibrotic gingiva, limited gingival erythema and oedema, reduction in bleeding on probing and ultimately increased tooth loss in smokers [5]. Most studies indicated that, although current smokers can respond to PMPR with reduction in PPD indicating disease improvement, their response in terms of PPD reduction and CAL gain is significantly less than in never-smokers[1, 7 8,].

Smoking cessation has been shown to improve the overall success of the periodontal treatment outcome and so this should be advised to patients [19, 20]. One of the most recent methods suggested for smoking cessation is the use of electronic cigarettes (also termed 'e-cigarettes' or 'vaping'). E-cigarettes have been introduced to the U.K. since 2007 and their use among smokers and recent former smokers has continued to rise[9]. E-cigarettes provide nicotine for inhalation in a vapour by heating a solution containing water, propylene glycol and vegetable glycerine.

It has been indicated that after smokers switched to using e-cigarettes, gingival bleeding and gingival crevicular fluid (GCF) increased suggesting restoration of the normal inflammatory response to plaque, that is thought to be suppressed when smoking conventional cigarettes[10]. However, in vitro studies

have demonstrated that e-cigarette vapour leads to alteration of human gingival epithelial cell morphology, apoptosis and necrosis similar to when exposed to conventional cigarette smoke[11]. Data from the KNHANES showed the odds of having periodontitis were similar for individuals who used e-cigarettes and those who used conventional cigarettes but of higher odds than non-smokers[12]. A systematic review concluded that e-cigarettes may increase the risk of periodontitis as well as components of the e-cigarette vapour possibly being carcinogenic, cytotoxic and genotoxic, but more studies are needed to investigate this further[13].

However, there are currently no clinical studies evaluating the periodontal treatment outcomes in e-cigarette users. Therefore, we aimed to investigate the response to periodontal therapy in cigarette users, e-cigarettes users and former smokers in comparison to non-smokers. We hypothesized that e-cigarette users respond to PMPR in the same way as never smokers.

MATERIALS AND METHODS

This is a retrospective study over 24 months where consecutive records from Guy's Hospital of patients treated by postgraduate periodontology students at Guy's Dental Hospital were analysed. Patients fulfilling the pre-set inclusion criteria had their periodontal indices recorded from pre-treatment and post non-surgical treatment. Post-treatment indices were measured ≥6 weeks after non-surgical therapy.

As the data in this study was analysed retrospectively, operators were masked and anonymised patient records were obtained without need for individual patient consent. The study was approved as a service evaluation by the Quality Improvement and Patient Safety manager, Guys and St thomas' NHS Trust (project number: 11425, October 2020).

Inclusion Criteria were i) diagnosed with periodontitis (localised and generalised, all stages and grades), ii) adults (≥18 years old), iii) received PMPR by a periodontology postgraduate student, and iv) periodontal indices were measured and recorded before and 6-20 weeks after PMPR.

Exclusion Criteria were i)uncontrolled diabetes (defined as HbA1c >7.5% or 58 mmol/mol), ii) on medications that could contribute to drug induced overgrowth (cyclosporin, amlodipine or phenytoin), iii) pregnancy, iv) any other forms of periodontal disease (other than periodontitis), v) previous surgical treatment of periodontitis, vi) use of an adjunctive therapy (systemic or local antimicrobials, immunomodulating treatment)to PMPR, and vii) patients who report concomitant use of e-cigarettes and conventional cigarettes.

The definitions below were used[3 14]:

- Former smokers: anyone who has not smoked for more than 1 year up to a maximum of 10 years.
- Current cigarette smokers: anyone who smokes ≥1 cigarette(s) a day.
- E-cigarette users: anyone who has quit smoking and is only using e-cigarettes of any form (not using conventional cigarettes)

- Non-smokers: anyone who has never smoked any form of cigarettes or any e-cigarettes within 10 years of baseline records to re-evaluation records.

The groupings of each patient were based on patient self-reporting.

Baseline demographic and periodontal clinical data were collected from records. Data on number of PMPR visits, treatment duration (number of months from first to last PMPR visit) and periodontal clinical data were collected again after initial PMPR. Compliance was measured as either attending or not attending appointments and were categorised into either being compliant (defined >10% of appointments attended) or non-complaint (≤ 10% of appointments attended).

The primary outcome was defined as 'need for surgery' which was defined as the number of sextants with ≥2 non-adjacent sites with periodontal pockets ≥5mm after PMPR. The EFP (European Federation of Periodontology) clinical practice guidelines suggest that residual pockets can lead to further disease progression as well as tooth loss and therefore further treatment is recommended for these sites[15]. As secondary outcomes, we included number of sextants with ≥1 site with periodontal pockets ≥5mm, as well as conventional measures of periodontitis severity, namely mean PPD, mean CAL, mean recession, full mouth bleeding scores (FMBS), and full mouth plaque scores (FMPS).

All anonymised data were entered in a dedicated encrypted Excel database by the same Periodontology postgraduate student (author CS). Approximately 10% of the data was entered in duplicate, by a different colleague, to check for accuracy. This demonstrated 100% accuracy. Access was restricted to data entry personnel and study investigators. Upon completion, data were proofed for entry errors and transferred to Stata/SE software for analysis.

Sample size

A preliminary audit of patients attending the periodontology postgraduate clinic in the past 4 years, identified 20 current smokers, 20 electronic cigarette users, 60 former smokers and 120 non-smokers whose records were eligible for inclusion in the study. The power of the study was then calculated

using these numbers. In the absence of any data on e-cigarette use and outcomes, response rates for non-smoking and smoking groups (effect size) were estimated as 78% and 47% respectively based on previous studies of the effect of smoking[16].

These figures were entered into an online Chi- squared test calculator (http://hedwig.mgh.harvard.edu/sample_size/fisher/js/fisher.html), which demonstrated that the study would have a power of 80% to detect a difference between non-smoking and smoking groups with $\alpha = 0.05$.

Statistical analysis

Continuous data were presented as mean and standard deviation together with median, 25% and 75% quantiles. Categorical data were presented as numbers and percentages. To check for distributional differences across the four smoking groups, Kruskal-Wallis tests and Chi-squared tests were applied as appropriate. Violin plots were used to visualise data, containing boxplots and estimated distributions.

Linear and negative binomial regression models with robust variances were applied to evaluate effects of smoking on periodontal outcomes. Models were adjusted for age (linearly modelled), sex, compliance, number of PMPR sessions (linearly modelled), any medical conditions, time (in exact months), and baseline levels of the outcome (linearly modelled if not stated otherwise). For linear models, linear regression coefficients (B) and 95% confidence intervals (CI) were reported. For negative binomial regression models, incidence rate ratios (IRR) and 95% CIs were reported. For all continuous variables, different parameterisations were checked (including linear form and restricted cubic splines with 3, 4 or 5 knots) and compared using the Bayesian Information Criterion (BIC) to assess the model fit. Accordingly, age was always modelled linearly, while baseline levels of the periodontal variables were either modelled linearly or via restricted cubic splines with three knots. In addition, all regression models were re-run restricting patients to former smokers and e-cigarette users, adjusting also for the number of years since patients quitted smoking.

P values <0.05 were considered statistically significant. Analyses were conducted using Stata/SE 17.0[17] or R 4.0.3 (www.r-project.org).

RESULTS:

Baseline characteristics

The study sample in all four groups were treated and assessed before and after periodontal treatment by 13 operators (postgraduate periodontal students). Each operator treated a mixed range of all four groups (Supplementary Table 1).

A total of 220 subjects were included (Table 1); 120 non-smokers, 60 former smokers, 20 current smokers and 20 e-cigarette users. The ages of the population ranged from 18 to 77-year-olds. The ethnicity of the subjects could not be analysed as only 31% had ethnicity recorded. No statistical significant differences for diagnosis staging and grading across smoking groups were detected. The treatment duration in days had statistically significant differences amongst the smoking groups ($p<0.01$). It appears that the e-cigarette users had a longer treatment duration than the other groups. The most compliant groups were non-smokers and former smokers, while e-cigarette users and current smokers had similar compliance.

Periodontal status at baseline and re-evaluation

Most periodontal parameters at baseline were similar amongst all groups with any differences being not statistically significant, with the exception of number of sextants with PPD ≥5mm ($p=0.046$). At re-evaluation, the number of teeth (excluding wisdom teeth), FMBS and FMPS were not significantly different amongst the groups. However, when looking at the primary outcome ('need for surgery' or number of sextants with ≥2 non-adjacent sites of PPD ≥5mm) the groups did not respond in the same way to periodontal treatment ($p<0.01$), resulting in e-cigarette users 'needing' 5 surgeries, compared with 4 for current smokers, 3 for former smokers and 2.5 for non-smokers.

This treatment response was also reflected in the secondary outcomes of measuring treatment response. For mean PPD ($p<0.01$), mean recession ($p=0.038$), mean CAL ($p<0.01$) and number of

sextants with PPD ≥5mm (p<0.01), e-cigarette users had the least favourable response to periodontal treatment. Violin plots were also used to help visualise the data (Figures 1 and 2).

Effects of smoking status on periodontal treatment outcomes

Fully adjusted regression models were evaluated to estimate effects of smoking status on periodontal outcomes (Table 3). 'Need for surgery' at re-evaluation was again associated with smoking status, showing statistical significance in the e-cigarette user group (p<0.001), the current smoker group (p=0.002) as well as the former smoker group (p=0.035) when comparing the treatment response to non-smokers. Pocket closure (defined as sites of PPD ≤4 mm) after treatment occurred in 57% of non-smokers , 48% of former smokers, 41% of current smokers and 28% of e-cigarette users (table 2).

Among secondary outcomes, the number of teeth present (excluding wisdom teeth) in current smokers was statistically significantly higher (IRR=1.37, 95% CI: 1.001-1.86, P=0.049) compared to the non-smoker group. In addition, the number of sites with PPD ≥5mm, mean PPD, mean CAL, and number of sextants with PPD ≥5mm were statistically significantly higher at re-evaluation in the e-cigarette users group compared to the non-smoking group. In summary, these periodontal variables showed that e-cigarette users had the least favourable treatment outcome compared to non-smokers, followed by the current smokers and the former smokers.

To compare the periodontal treatment response for e-cigarette users and current smokers, regression models were repeated using e-cigarette users as the reference (Table 4 and Supplementary Table 2). There were no statistically significant differences in the periodontal treatment response between current smokers and e-cigarette users.

When looking at former smokers and e-cigarette users only, outcome levels a re-evaluation differed significantly between e-cigarette users for the primary outcome, FMBS, number of sites with PPD ≥5 mm, mean PPD, mean CAL and number of sextants with PPD ≥5mm. However, to know whether these

effects are associated with e-cigarette smoking, rather than the fact that the e-cigarette users also quit smoking in the past, analyses repeated restricting patients to former smokers and e-cigarette smokers (Supplementary Table 3). After adjustment for time of smoking cessation, the two groups still differed significantly in their treatment response for the primary outcome, the FMBS, mean PPD, and the number of sextants with PPD ≥5 mm.

Discussion

The aim of this retrospective study was to compare the periodontal treatment responses in the users of e-cigarettes, current smokers, former smokers, and non-smokers. All four groups initially presented with similar levels of disease but after PMPR (both supra- and subgingival) they had statistically significant differences in their levels of disease. Non-smokers had significantly fewer sites with PPD ≥5 mm than the other groups at re-evaluation, suggesting that they had responded to periodontal treatment with the most superior outcome. The e-cigarette users and the current smokers had the highest 'need for surgery' post-PMPR (defined as 'number of sextants with ≥2 non-adjacent sites of PPD ≥5mm').

Although we chose the outcome 'need for surgery' to be of particular clinically relevance, most previous studies in the periodontal literature have used mean PPD and CAL changes as primary outcome variables. Therefore, it is worth comparing the present results with previous studies by using these variables. When analysing the results of the study we can see that from the total population there was a baseline mean PPD of 3.33 mm. After PMPR this had reduced to a mean PPD of 2.65 mm, showing an average reduction of 0.68 mm. This demonstrated that overall, the treatment was successful, resulting in a reduction in PPD generally across the entire population. Non-smokers had a reduction of mean PPD of 0.72 mm and a CAL gain of 0.54 mm. This is fairly similar to the current evidence, showing expected PPD reduction following PMPR of approximately 1 mm and 0.5 mm CAL gain[18]. Suvan et al 2019 demonstrated in a systematic review that the number of closed pockets (defined as PPD ≤4 mm and absence of BOP) was 74% after non-surgical periodontal treatment. The data in this study shows that the number of pocket closure for non-smokers after treatment was 57%.

When comparing these study results to the current evidence on non-smokers and smokers' response we can see they are similar for PPD reduction[8] and for former smokers and non-smokers[20].

There is no current evidence in the literature comparing the periodontal treatment response in e-cigarette users and therefore the results of this study cannot be compared to the existing literature.

This study showed that when comparing the non-smoker group to the e-cigarette user group, there were statistically significant differences in treatment responses. The former smoker group, current smoker group and e-cigarette group had significantly more sextants with ≥2 non-adjacent sites of PPD ≥5 mm in comparison to non-smokers, meaning more need for further treatment. From this data it can be seen that the e-cigarette users responded with the least favourable outcome amongst the groups when comparing to non-smokers and were more likely to have sextants with ≥2 non-adjacent sites of PPD ≥5 mm in comparison to the non-smokers after PMPR. The poorer treatment response to PMPR in e-cigarette users was also significant when analysing the number of sites with PPD ≥5mm, mean PPD, mean CAL and number of sextants with PPD ≥5mm. There were no significant differences seen between e-cigarette users and the current smoker groups in this study. However, this result needs to be treated with caution as these 2 groups were relatively small and the study was not powered to specifically examine this question.

Wadia et al (2016) showed that there was an increase in percentage of sites with gingival bleeding in subjects from switching to e-cigarette users from smoking cigarettes in a short term pilot study over 2 weeks[10]. This was interpreted as suggesting a reversal of gingival response from a smoker to a non-smoker. However, although these results cannot be directly compared with this study, in the current study here there was no significant difference in FMBS between e-cigarette users and current cigarette users at baseline or re-evaluation.

One of the main limitations of the study was it being retrospective. This can be thought of being inferior in the evidence hierarchy in comparison to prospective studies. Reasons for this include the risk of selection bias. However, in order to try and reduce this bias, consecutive subjects were sampled rather than recruiting subjects based on convenience sampling.

Some limitations deserve consideration. Firstly, methodological difficulties can occur especially if unstandardised protocols are followed. For example, there was no formal sample size calculation due to there being no data available in the literature on periodontal treatment response to use in order to

estimate the sample size. Therefore, this calculation was based on several assumptions. Secondly, the definition for 'need for surgery' in this study aims to be clinically relevant, but it is arbitrary and may be questionable. It was based on the practical consideration that a single 5 mm residual pocket in one sextant does not necessarily lead to the decision of performing periodontal surgery. However, also other periodontal parameters, including at least 1 site with PPD ≥5 mm were used and reported, yielding consistent results. Thirdly, the operators of the study were 13 postgraduate periodontal students. Therefore, there may be inaccuracies of the information recorded as these students are not specialised as of yet and were not calibrated. Fifthly, it is important to note that the smoking status of each subject was based on patient self-reporting due to it being retrospective. Although this may introduce inaccuracies as there is a risk that patients may under report their smoking status, there have been studies to demonstrate reliability on self-reporting of smoking status[21]. However, we cannot be certain that the e-cigarette users were not also smoking cigarettes alongside although they had self-reported that they were not. Therefore, future studies may consider measuring smoking status of patients through other means such as using cotinine levels. However, measuring cotinine levels may not be able to identify that e-cigarette users are only using e-cigarettes or if they are smoking alongside this as nicotine is also present in e-cigarettes. Being retrospective, collection of periodontal indices and patient information could not be checked and scrutinised as it would be done in a prospective study. Sixthly, for the nature of this study, we were unable to randomly allocate smoking and e-cigarettes to the subjects. This may be difficult to control with future studies as it would be unethical to randomly allocate smoking or e-cigarettes to subjects. It would have also been beneficial to assess the type of e-cigarettes used (in terms of flavouring, nicotine content, ratio of propylene glycol and vegetable glycerine).

Although the study was pragmatic in its design with using multiple operators rather than using one examiner and one therapist, it holds external validity. Many different dentists who are training to become periodontists were the operators and this may reflect the external environment more

realistically. By designing the study allowed the recruitment of a fairly large overall sample size of 220 subjects.

Another strength of the study is its novelty as, despite extensive resources placed in smoking and outcomes of smoking on periodontal treatment, there is little substantial evidence to verify the effects of using e-cigarettes on treatment outcome. Although using e-cigarettes is relatively new, its use is increasing and therefore highlights the importance of understanding its effects on the periodontal health.

Overall, this study shows that e-cigarette users respond less favourably than non-smokers and in a similar fashion to current smokers to PMPR. This resulted in a very clinically-relevant higher 'need for surgery' or at least need for further treatment post-PMPR.

To our knowledge, this study is the first to assess periodontal treatment response of e-cigarette users. Therefore, more robust study designs assessing this would be needed to confirm the findings of this exploratory study. There is a need for prospective studies to assess this, although the difficulties with doing so would incur ethical constraints and difficulty in assessing the use of only e-cigarette dosage without relying on patient reporting. There is some value in exploring the response of e-cigarettes to periodontal treatment. This information would prove to be useful in advising periodontal patients the effects of using e-cigarettes on their treatment outcome when trying to stop smoking. Currently the advice is that e-cigarettes may provide support in smoking cessation, but the results it may have on periodontal treatment outcomes are unknown. This study may be the first in making one step forward in understanding these effects in using e-cigarettes on periodontal treatment outcomes and encourage more robust studies to confirm these findings.

Conclusion

This study suggests that e-cigarette users respond to non-surgical PMPR treatment in a less favourable manner than non-smokers and former smokers. It also suggests that e-cigarette users respond in a similar way to current smokers. Therefore, we must tread with caution when advising patients about the risks of e-cigarettes to their periodontal treatment success rate especially as an alternative to conventional smoking. The results of this study, however, need to be validated with further research.

CONFLICT OF INTEREST

There was no funding needed for the study and there are no commercial or financial relationships of any of the authors. The authors declare that there are no conflicts of interest.

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TABLES

Table 1: Baseline characteristics in total and stratified by smoking status (N=220):

	TOTAL (N=220)	NON-SMOKERS (N=120)	FORMER SMOKERS (N=60)	CURRENT SMOKERS (N=20)	E-CIGARETTE USERS (N=20)	P VALUE†
TREATMENT DURATION, MONTHS	6.6±3.4 5.9 (4.1; 8.1)	6.0±3.1 5.3 (3.7; 7.1)	7.0±3.3 6.2 (4.3; 9.5)	6.9±3.6 6.0 (5.2; 7.6)	9.2±3.7 9.0 (6.2; 11.5)	0.0006
AGE, YEARS	47.9±11.1 48 (41; 55)	48.0±12.2 48 (40.5; 57)	49.0±9.8 49 (44; 54)	44.1±10.2 43 (34.5; 53)	47.8±6.9 49 (43.5; 54)	0.39
MALE SEX	90 (40.9)	48 (40.0)	22 (36.7)	11 (55.0)	9 (45.0)	0.52
NUMBER OF CIGARETTES SMOKED	NA	NA	NA	10.2±6.4 8 (5; 17.5)	NA	NA
YEARS SMOKED, YEARS	NA	NA	NA	20.0±9.9 20 (14.5; 25.5)	NA	NA
YEARS SINCE QUITTING SMOKING, YEARS	NA	NA	4.9±3.7 3 (1.8; 9)	NA	3.4±2.6 2 (1.5; 5) *	NA
PACK YEARS	NA	NA	NA	10.7±8.5 9.2 (3.4; 17.5)	NA	NA
NUMBER OF PMPR SESSIONS	2.2±0.8 2 (2; 2)	2.1±0.8 2 (2; 2)	2.4±0.9 2 (2; 3)	2.0±0.8 2 (1.5; 2)	2.2±0.9 2 (2; 3)	0.14
ANY MEDICAL CONDITIONS, YES	75 (34.1%)	33 (27.5%)	25 (41.7%)	7 (35.0%)	10 (50.0%)	0.11
DIAGNOSIS EXTENT GENERALISED LOCALISED	 171 (77.7%) 49 (22.3%)	 93 (77.5%) 27 (22.5%)	 46 (76.7%) 14 (23.3%)	 14 (70.0%) 6 (30.0%)	 18 (90.0%) 2 (10.0%)	 0.48
DIAGNOSIS STAGE 2 3 4	 4 (1.8%) 43 (19.6%) 173 (78.6%)	 4 (3.3%) 22 (18.3%) 94 (78.3%)	 0 (0%) 15 (25.0%) 45 (75.0%)	 0 (0%) 3 (15.0%) 17 (85.0%)	 0 (0%) 3 (15.0%) 17 (85.0%)	 0.54
DIAGNOSIS GRADE B C	 9 (4.1%) 211 (95.9%)	 5 (4.2%) 115 (95.8%)	 3 (5.0%) 57 (95.0%)	 1 (5.0%) 19 (95.0%)	 0 (0%) 20 (100.0%)	 0.80
COMPLIANCE NO YES	 65 (29.6%) 155 (70.5%)	 27 (22.5%) 93 (77.5%)	 20 (33.3%) 40 (66.7%)	 9 (45.0%) 11 (55.0%)	 9 (45.0%) 11 (55.0%)	 0.049

* N=19. † Chi-squared or Kruskal-Wallis test. Abbreviations: RSD, root surface debridement. Findings with statistical significance, $p<0.05$, have been formatted in bold.

Table 2: Periodontal data at baseline and re-evaluation in total and stratified by smoking status.

	TOTAL (N=220)	NON-SMOKERS (N=120)	FORMER SMOKERS (N=60)	CURRENT SMOKERS (N=20)	E-CIGARETTE USERS (N=20)	P VALUE*
NUMBER OF SEXTANTS WITH ≥2 NON-ADJACENT SITES OF PPD ≥5 MM						
Baseline	4.4±1.4 5 (3; 6)	4.3±1.4 4 (3; 5)	4.5±1.5 5 (4; 6)	5.0±1.3 6 (4; 6)	4.7±1.6 5 (4; 6)	0.08
Re-evaluation	2.9±1.8 3 (1; 4)	2.4±1.7 2.5 (1; 4)	3.1±1.9 3 (2; 4.5)	4.0±1.7 4 (3; 6)	4.3±1.6 5 (3; 5.5)	0.0001
Change	-1.5±1.4 -1 (-2; 0)	-1.9±1.4 -2 (-3; -1)	-1.5±1.4 -1 (-2.5; 0)	-1.0±1.4 0 (-2; 0)	-0.4±0.8 0 (-1; 0)	0.0001
NUMBER OF TEETH (EXCLUDING WISDOM TEETH)						
Baseline	25.7±2.6 26 (24; 28)	26.0±2.5 27 (25; 28)	25.4±2.7 26 (24; 27.5)	25.4±2.2 25 (23.5; 28)	25.4±3.2 26 (23.5; 28)	0.16
Re-evaluation	25.5±2.7 26 (24; 28)	25.9±2.6 27 (24; 28)	25.0±2.8 25 (24; 27)	25.1±2.6 25 (23.5; 28)	25.1±3.4 26 (23.5; 28)	0.09
Change	0.2±0.7 0 (0; 0)	0.1±0.4 0 (0; 0)	0.4±1.1 0 (0; 0)	0.3±0.7 0 (0; 0)	0.3±0.6 0 (0; 0)	0.48
FULL-MOUTH PLAQUE SCORE, %						
Baseline	47.5±20.1 47.5 (31; 63)	46.3±19.1 47 (31; 60.5)	49.6±21.2 49.5 (34.5; 66)	47.8±21.6 46 (27; 66.5)	48.6±21.4 53.5 (30; 62.5)	0.86
Re-evaluation	22.5±15.3 20 (11; 29)	20.3±12.3 19 (11; 25.5)	24.8±17.3 23 (10.5; 31)	23.5±12.2 21.5 (12.5; 31)	27.9±24.0 18.5 (11; 41.5)	0.40
Change	-25±19.6 -23 (-38; -11)	-26.0±19.9 -26 (-39; -9)	-24.7±17.6 -21 (-35.5; -13)	-24.3±20.8 -28 (-40.5; -10.5)	-20.8±23.2 -16.5 (-34; -11)	0.88
FULL-MOUTH BLEEDING SCORE, %						
Baseline	41.4±24.6 38 (20.5; 59.5)	41.2±23.1 38.5 (21.5; 57.5)	43.4±27.3 37.5 (20; 66)	43.8±23.6 44 (31.5; 60)	33.7±26.1 27.5 (12.5; 49)	0.35
Re-evaluation	20.7±15.0 17 (10; 28.5)	20.1±13.8 17 (11; 25)	19.7±14.3 16.5 (8; 29)	22.6±18.4 19 (7; 31)	26.1±19.7 22.5 (10.5; 38)	0.72
Change	-20.6±22.5 -17 (-34; -6)	-21.2±21.3 -16 (-33.5; -6)	-23.6±23.8 -20 (-40.5; -7)	-21.2±20.0 -21.5 (-35.5; -4.5)	-7.6±25.3 -7 (-23.5; 9.5)	0.14
NUMBER OF SITES WITH PPD ≥5 MM						
Baseline	37.4±25.1 33 (17; 49.5)	34.6±23.2 29.5 (16; 47)	38.7±25.3 34.5 (19; 47.5)	42.5±29.8 33.5 (19.5; 61.5)	44.7±30.3 33 (24; 67)	0.37
Re-evaluation	18.8±17.0 13 (8; 24.5)	14.9±13.7 11 (7; 20)	20.0±15.2 17 (8; 30)	25.0±22.6 17 (9.5; 29)	32.2±24.2 22.5 (17.5; 40)	0.0003
Change	-18.6±18.8 -13 (-27.5; -6)	-19.8±18.4 -14 (-28; -6.5)	-18.6±16.6 -14.5 (-27; -7)	-17.5±22.6 -12.5 (-33.5; -2)	-12.5±23.2 -8.5 (-29.5; 1)	0.38
MEAN PPD, MM						
Baseline	3.33±0.87 3.21 (2.70; 3.81)	3.21±0.78 3.14 (2.65; 3.71)	3.44±0.95 3.36 (2.75; 3.90)	3.48±1.03 3.15 (2.61; 4.13)	3.53±0.95 3.23 (2.92; 4.34)	0.41
Re-evaluation	2.65±0.65 2.54 (2.20; 2.97)	2.49±0.56 2.39 (2.13; 2.77)	2.72±0.59 2.60 (2.30; 3.08)	2.86±0.89 2.75 (2.15; 3.27)	3.15±0.74 3.02 (2.66; 3.49)	0.0001
Change	-0.68±0.61 (-0.61; -1.01; -0.30)	-0.71±0.54 -0.61 (-1.05; -0.34)	-0.72±0.65 -0.66 (-0.99; -0.29)	-0.62±0.66 -0.58 (-1.11; -0.21)	-0.38±0.79 -0.42 (-0.99; 0.28)	0.38
MEAN RECESSION, MM						
Baseline	0.56±0.67 0.33 (0.09; 0.81)	0.51±0.66 0.26 (0.08; 0.66)	0.48±0.50 0.32 (0.09; 0.86)	0.69±0.69 0.43 (0.11; 1.17)	0.88±1.01 0.62 (0.12; 1.16)	0.19
Re-evaluation	0.78±0.73 0.60 (0.23; 1.19)	0.68±0.70 0.40 (0.19; 1.05)	0.81±0.66 0.64 (0.28; 1.27)	0.88±0.78 0.82 (0.19; 1.30)	1.17±0.95 1.12 (0.38; 1.55)	0.038
Change	0.22±0.46 0.13 (0; 0.45)	0.17±0.46 0.10 (-0.01; 0.32)	0.32±0.44 0.18 (0.003; 0.63)	0.19±0.48 0.15 (-0.004; 0.44)	0.28±0.44 0.19 (0.08; 0.45)	0.17

MEAN CAL, MM						
Baseline	3.88±1.15 3.75 (3.12; 4.44)	3.72±1.07 3.63 (3.01; 4.34)	3.92±1.06 3.85 (3.27; 4.44)	4.17±1.40 4.01 (3.15; 4.76)	4.42±1.43 4.07 (3.18; 5.59)	0.17
Re-evaluation	3.43±1.10 3.26 (2.58; 4.01)	3.18±0.98 3.04 (2.38; 3.74)	3.52±0.96 3.33 (2.74; 4.07)	3.74±1.30 3.47 (3.01; 4.46)	4.31±1.46 4.29 (3.33; 4.89)	0.0005
Change	-0.46±0.67 -0.40 (-0.84; -0.07)	-0.55±0.62 -0.50 (-0.89; -0.16)	-0.40±0.66 -0.31 (-0.74; -0.01)	-0.43±0.73 -0.34 (-0.90; 0.08)	-0.10±0.88 -0.12 (-0.75; 0.19)	0.094
NUMBER OF SEXTANTS WITH PPD ≥5 MM						
Baseline	5.1±1.0 5 (5; 6)	5.0±1.0 5 (4; 6)	5.3±1.0 6 (5; 6)	5.4±0.9 6 (5; 6)	5.3±1.2 6 (5; 6)	0.046
Re-evaluation	4.1±1.4 4 (3; 5)	3.8±1.4 4 (3; 5)	4.2±1.5 4 (3; 5)	4.8±1.2 5 (4; 6)	5.0±1.0 5 (4; 6)	0.0005
Change	-1.0±1.2 -1 (-2; 0)	-1.1±1.1 -1 (-2; 0)	-1.1±1.2 -1 (-2; 0)	-0.6±1.2 0 (-1.5; 0)	-0.3±0.6 0 (-1; 0)	0.003

Data are reported as means and standard deviations, along with medians, 25% and 75% quantiles. * p values were derived from Kruskal-Wallis tests. Abbreviations: PPD, pocket probing depth; CAL, clinical attachment level.

Table 3: Results from regression models with robust standard errors (reference: non-smokers)

OUTCOME	MODEL	SMOKING STATUS			
		NON-SMOKER	FORMER SMOKER	CURRENT SMOKER	E-CIGARETTE USER
			B (95% CI) P VALUE	B (95% CI) P VALUE	B (95% CI) P VALUE
NUMBER OF SEXTANTS WITH ≥2 NON-ADJACENT SITES OF PPD ≥5 MM	Linear	0.00 (ref.)	0.46 (0.03; 0.88) P=0.035	1.11 (0.42; 1.81) P=0.002	1.55 (1.05; 2.04) P<0.001
FULL-MOUTH PLAQUE SCORE, %	Linear	0.00 (ref.)	2.99 (-1.08; 7.07) P=0.15	1.31 (-4.25; 6.86) P=0.65	4.70 (-4.14; 13.54) P=0.30
FULL-MOUTH BLEEDING SCORE, %	Linear	0.00 (ref.)	-0.96 (-5.04; 3.12) P=0.64	1.09 (-5.78; 7.95) P=0.76	7.80 (-0.40; 16.00) P=0.06
NUMBER OF SITES WITH PPD ≥5 MM	Linear	0.00 (ref.)	3.77 (0.47; 7.08) P=0.026	6.82 (-0.96; 14.60) P=0.086	12.87 (4.52; 21.21) P=0.003
MEAN PROBING POCKET DEPTH, MM	Linear	0.00 (ref.)	0.12 (-0.004; 0.24) P=0.057	0.23 (-0.03; 0.49) P=0.08	0.50 (0.23; 0.77) P<0.001
MEAN RECESSION, MM	Linear	0.00 (ref.)	0.12 (-0.02; 0.26) P=0.09	0.08 (-0.13; 0.30) P=0.45	0.15 (-0.08; 0.37) P=0.20
MEAN CLINICAL ATTACHMENT LOSS, MM	Linear	0.00 (ref.)	0.17 (-0.05; 0.39) P=0.12	0.45 (0.06; 0.83) P=0.022	0.89 (0.29; 1.49) P=0.004
NUMBER OF SEXTANTS WITH PPD ≥5 MM	Linear	0.00 (ref.)	0.08 (-0.29; 0.45) P=0.67	0.64 (0.08; 1.20) P=0.025	0.81 (0.42; 1.20) P<0.001
			IRR (95% CI) P VALUE	IRR (95% CI) P VALUE	IRR (95% CI) P VALUE
NUMBER OF TEETH (EXCLUDING WISDOM TEETH)	Negative binomial *	1.00 (ref.)	1.16 (0.90; 1.49) P=0.26	1.37 (1.001; 1.86) P=0.049	0.84 (0.54; 1.32) P=0.46

Models were adjusted for age (linearly modelled), sex, compliance, number of root surface debridement sessions (linearly modelled), any medical conditions, time (in exact months), and baseline levels of the outcome (linearly modelled if not stated otherwise). For linear models, linear regression coefficients (B) and 95% confidence intervals (CI) were reported. For negative binomial regression models, incidence rate ratios (IRR) and 95% CIs were reported. * baseline levels modelled as restricted cubic splines with three knots. Abbreviations: PPD, pocket probing depth; CI, confidence interval.

Table 4: Results from regression models with robust standard errors (reference: e-cigarette users)

OUTCOME	MODEL	SMOKING STATUS			
		E-CIGARETTE USER	NON- SMOKER	FORMER SMOKER	CURRENT SMOKER
			B (95% CI) P VALUE	B (95% CI) P VALUE	B (95% CI) P VALUE
NUMBER OF SEXTANTS WITH ≥2 NON-ADJACENT SITES OF PPD ≥5 MM	Linear	0.00 (ref.)	-1.55 (-2.04; -1.05) P<0.001	-1.09 (-1.61; -0.57) P<0.001	-0.43 (-1.17; 0.30) P=0.25
FULL-MOUTH PLAQUE SCORE	Linear	0.00 (ref.)	-4.70 (-13.80; 4.40) P=0.31	-1.71 (-11.43; 8.02) P=0.73	-3.39 (-13.76; 6.97) P=0.52
FULL-MOUTH BLEEDING SCORE	Linear	0.00 (ref.)	-7.80 (-16.24; 0.64) P=0.07	-8.76 (-17.24; -0.29) P=0.043	-6.71 (-17.22; 3.79) P=0.21
NUMBER OF SITES WITH PPD ≥5 MM	Linear	0.00 (ref.)	-12.87 (-21.21; -4.52) P=0.003	-9.09 (-17.42; -0.77) P=0.032	-6.05 (-17.06; 4.96) P=0.28
MEAN PROBING POCKET DEPTH, MM	Linear	0.00 (ref.)	-0.50 (-0.77; -0.23) P<0.001	-0.38 (-0.66; -0.11) P=0.007	-0.27 (-0.63; 0.10) P=0.15
MEAN RECESSION, MM	Linear	0.00 (ref.)	-0.15 (-0.37; 0.08) P=0.20	-0.02 (-0.26; 0.21) P=0.83	-0.06 (-0.34; 0.22) P=0.66
MEAN CLINICAL ATTACHMENT LOSS, MM	Linear	0.00 (ref.)	-0.89 (-1.49; -0.29) P=0.004	-0.72 (-1.32; -0.11) P=0.02	-0.44 (-1.15; 0.26) P=0.22
NUMBER OF SEXTANTS WITH PPD ≥5 MM	Linear	0.00 (ref.)	-0.81 (-1.20; -0.42) P<0.001	-0.73 (-1.16; -0.30) P=0.001	-0.17 (-0.74; 0.40) P=0.56
			IRR (95% CI) P VALUE	IRR (95% CI) P VALUE	IRR (95% CI) P VALUE
NUMBER OF TEETH (EXCLUDING WISDOM TEETH)	Negative binomial *	1.00 (ref.)	1.19 (0.76; 1.85) P=0.46	1.37 (0.87; 2.16) P=0.17	1.62 (0.99; 2.63) P=0.051

Models were adjusted for age (linearly modelled), sex, compliance, number of root surface debridement sessions (linearly modelled), any medical conditions, time (in exact months), and baseline levels of the outcome (linearly modelled if not stated otherwise). For linear models, linear regression coefficients (B) and 95% confidence intervals (CI) were reported. For negative binomial regression models, incidence rate ratios (IRR) and 95% CIs were reported. *baseline levels modelled as restricted cubic splines with three knots. Abbreviations: PPD, pocket probing depth; CI, confidence interval.

FIGURES

Figure 1: Baseline (left) and re-evaluation (right) levels of mean pocket probing depth (A, B), mean recession (C, D) and mean clinical attachment loss (E, F) by smoking status. P values from Kruskal-Wallis tests are provided.

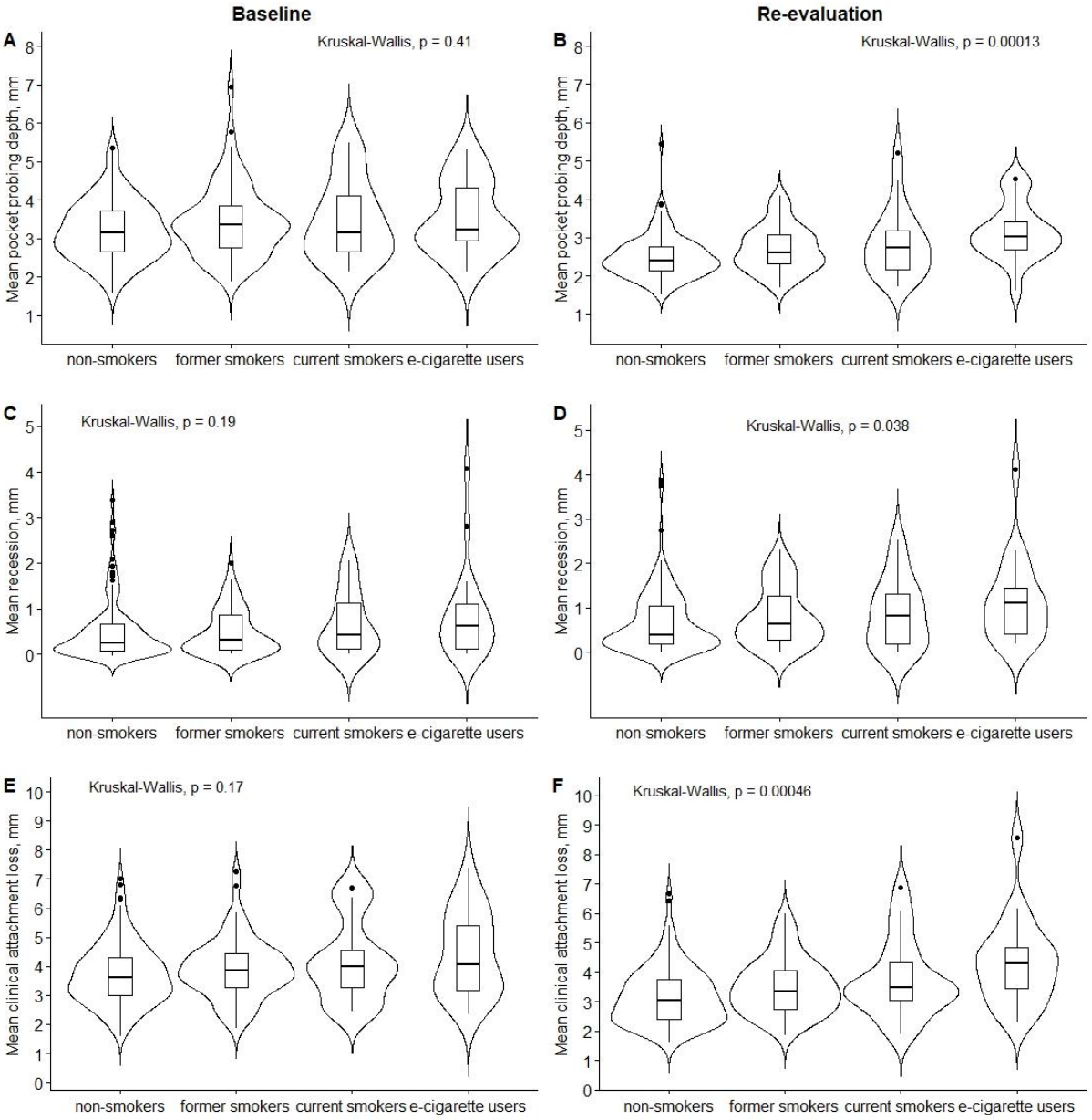

Figure 2: Baseline (left) and re-evaluation (right) levels of the number with pocket probing depths (PPD) ≥5 mm (A, B), the number of sextants with ≥2 non-adjacent (NA) sites with PPD ≥5 mm (C, D), and the number of sextants with PPD ≥5 mm (E, F) by smoking status. P values from Kruskal-Wallis tests are provided.