Baseline adjustment and change revisited: effect of smoking on change in periodontal status following periodontal therapy

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Smokers have frequently been reported to have more severe periodontitis, to respond less favorably to periodontal therapy, and to show elevated rate of recurrence compared with non-smokers. The aims of this study was to compare the results of baseline-adjusted and -unadjusted analyses when assessing the effect of smoking on change in periodontal status following therapy and to discuss the methodological issues involved. This is a secondary analysis of data from 180 periodontitis patients enrolled in a randomized controlled clinical intervention trial. Information on smoking habits was elicited from the participants before, and 12 months after, therapy. The clinical parameters analyzed were probing pocket depth and clinical attachment level, using both simple analysis of change (SAC) and analysis of covariance (ANCOVA), adjusting for age, gender, and treatment group. The current smokers presented with more severe periodontitis at baseline than did former and never smokers. Results of the SAC indicated that the current smokers benefitted more from treatment than did former or never smokers, whereas the results of the baseline-adjusted ANCOVA indicated no such differences. Both sets of results are likely to be biased with respect to valid conclusions regarding the 'causal' effect of smoking. Possible sources of bias are discussed.

Besides insufficient oral hygiene, the most prominent behavioral cause of periodontitis is smoking (1–5). Periodontitis patients who smoke tend to present with higher clinical attachment levels, deeper pockets, more furcation involvements, and less teeth than former or never smokers (6–14). The changes in periodontal status following periodontal treatment (15–20), as well as the recurrence rate (3–18), have also been reported to be negatively affected by smoking. A systematic review (21) concluded that smokers had less pocket-depth (PD) reduction after non-surgical periodontal therapy than non-smokers, whereas no differences were observed regarding clinical attachment level changes. However, troubling heterogeneity among studies was observed for a number of comparisons, which might indicate that conclusions should be drawn with caution.

Assessment of the effect of smoking on changes in periodontal status induced by therapy is difficult. The effect of smoking can only be addressed in an observational study design, and current or former smokers tend to be over-represented among periodontitis patients enrolled in periodontitis intervention studies (22–29). As current smokers also tend to present with more severe periodontitis and with higher baseline values of PD and clinical attachment level than do former or never smokers (5–14), the issue arises of whether to statistically adjust for differences in baseline values (PD and clinical attachment level) when assessing the effect of smoking on the changes in these parameters following therapy. Five (22, 30–33) of the 13 studies included in the aforementioned systematic review (21) used analysis of covariance (ANCOVA) methods, meaning that they employed baseline adjustment in linear regression analysis of the effect of smoking status on the changes in periodontal status following treatment. The remaining eight studies (34–41) employed simple analyses of change (SAC) in periodontal parameters between the smoking groups, using the *t*-test or one-way ANOVA. The unadjusted SAC approach leads to an unconditional comparison of change between groups, whereas the ANCOVA is an average conditional comparison conditioned on baseline values (42), and it remains unclear whether the two approaches arrive at similar answers. If not, caution must be exercised when carrying out meta-analyses of effect measures obtained from studies

using different analytical methods, just as the question arises of which is the more valid method.

When evaluating data from non-experimental studies, four different statistical phenomena may cause method errors. These include regression towards the mean (43–45), LORD's paradox (46, 47), the horse-racing effect (48), and floor effects. In short, regression towards the mean signifies that extreme first assessments tend to become less extreme at the second assessment as a result of assessment errors. LORD's paradox refers to the relationship between a continuous outcome and a categorical exposure being reversed when an additional continuous covariate is introduced to the analysis (46, 47). The horse-racing effect is a term describing the expected positive correlation between a true absolute value at baseline and the subsequent true rate of change. Floor effects occur when there is a lower limit to the value of the status parameter, limiting the amount of change that can be observed.

The purpose of the present study was to show that the results of baseline-adjusted and -unadjusted analyses may differ when assessing the effect of smoking on the change in periodontal status following periodontal therapy, and to discuss the methodological issues possibly involved, namely regression towards the mean (43–45), LORD's paradox (46, 47), the horse-racing effect (48), and floor effects.

Material and methods

The data used in the present analysis originate in a randomized, double-blind, four-arm placebo-controlled clinical intervention trial of the effect of a full-mouth disinfection (FDIS) approach on the treatment of periodontitis, with or without the adjunct effect of metronidazole, carried out among 184 patients with periodontitis (49). All participants signed a written informed consent form. The project protocol was approved by the Privacy Ombudsman for Norwegian Universities (#15768) and the Regional Committee for Medical Research Ethics (Oslo, Norway) (REC South East 2.2006.3573/S-06458b). US National Institutes of Health Clinical Trials Registry number – http://www.clinicaltrials.gov – is NCT01318928.

The study design and the interventions have previously been described in detail (49). Briefly, candidate participants for the study fulfilled the following criteria: referral to a periodontal specialist clinic for treatment of periodontitis; age between 35 and 75 years; no previous systematic periodontal treatment; no diagnosis of systemic diseases known to be associated with periodontitis; and not undergoing treatment with continuous medication known to affect the severity or progression of periodontitis. Following a 3-month hygiene phase the candidate participants were reviewed for eligibility based on the persistence of at least five sites with a PD of ≥ 5 mm. As the antibiotic of choice for this trial was metronidazole, patients harboring species with known low, or insensitivity to metronidazole and patients with known allergies to, or adverse effects from this antibiotic, were excluded from participation. A total of 292 candidate patients were screened in order to recruit the 184 patients. Exclusions were primarily based on failure to fulfill the clinical criteria for entry ($n = 50$) or microbiological diagnoses ($n = 41$) (49).

The participating periodontitis patients were subsequently randomized to one of four intervention groups using a computer-generated random allocation table (50). Patients allocated to groups 1 and 2 (FDIS groups) received full-mouth scaling and root planing completed within a single workday over two sessions of 65 min each (49). In groups 3 and 4 (SRP groups) the scaling and root planing was completed over two, 65-min sessions, 21 d apart. Patients in groups 1 and 3 also received metronidazole (Flagyl; Sanofi Aventis, Lysaker, Norway), 400 mg, three times daily for 10 d, starting 24 h before the two mechanical treatment sessions in group 1 and 24 h before the second scaling and root planing session (day 20) in group 3. Patients in groups 2 and 4 received placebo tablets according to the same scheme as for groups 1 and 3, respectively. Supportive treatment sessions were given 3, 6, and 12 months after the completion of active therapy (49).

A questionnaire was used to elicit information about the patients' smoking habits at baseline and at the 12-month follow-up examination. The information collected included smoking status (i.e. never-, former-, or current smoker). Never smokers were those who reported having smoked fewer than 10 cigarettes in their lives. Former smokers were those who reported quitting smoking more than 6 months before enrollment in the study. Current smokers also encompassed those who reported smoking cessation <6 months before enrollment. The questionnaire was administered at the baseline/inclusion session as well as at the 12-month follow-up visit. All eligible patients, irrespective of smoking history, received standardized verbal (3 min) and written (one page) information on how smoking affects the development and therapy of periodontitis. This session also included information about smoking-cessation aids, and smokers were offered a 2-wk use of nicotine patches (Novartis Pharma, Oslo, Norway), free of charge.

Statistical analysis

The present analysis is based on the clinical recordings of PD and clinical attachment level (in mm) made at baseline and after 12 months of follow-up. Broadly speaking, previous studies on the effect of smoking on change in periodontal status following periodontal therapy have been based on one of two different types of variables (21): mean PD based on all sites (Mean $PD_{all\ sites}$) or mean clinical attachment level based on all sites (Mean $CAL_{all\ sites}$); or mean PD based only on sites with an initial PD of ≥ 5 mm (Mean $PD_{PD \geq 5\ mm}$) or mean clinical attachment level based only on sites with an initial PD of ≥ 5 mm (Mean $CAL_{PD \geq 5\ mm}$). An alternative approach to the analysis of aggregate mean clinical attachment level or mean PD values is to carry out multilevel regression analyses, in which the site-specific observations of PD or clinical attachment level are analyzed as observations nested in subjects. We therefore also used the multilevel regression technique to analyze the site-specific change in PD or clinical attachment level following periodontal treatment, including all sites or only sites with an initial PD of ≥ 5 mm, in the analyses. Finally, we analyzed the parameters percentage of sites per person with clinical attachment level of ≥ 3 mm (% $CAL_{\geq 3\ mm}$) and percentage of sites per person with a PD of ≥ 5 mm (% $PD_{\geq 5\ mm}$).

The analyses sought to address the question of whether smoking status at baseline influences the change in periodontal status following periodontal treatment, as assessed through changes in the periodontal variables listed above. Two sets of linear regression analyses were compared for each of the periodontal parameters. In the first, the change measure (PD reduction or clinical attachment loss/gain, or reduction in % $CAL_{\geq 3\ mm}$ or in % $PD_{\geq 5mm}$) was regressed on baseline smoking status and the covariates age (continuous), gender and experimental group. In the second, the change measure was regressed on baseline smoking status and the aforementioned covariates, and was additionally adjusted for the baseline value of PD or clinical attachment level, or % $CAL_{\geq 3\ mm}$ or % $PD_{\geq 5\ mm}$, as appropriate.

Results

The descriptive characteristics of the trial participants, by baseline smoking status, are shown in Table 1. The mean number of teeth present at baseline among the 184 patients originally enrolled in the study was 23.9. Four patients did not complete the active treatment phase and left the study: one died; two were diagnosed with life-threatening diseases; and one was diagnosed with diabetes mellitus during the treatment phase. Most of the 180 patients who completed follow-up at 3 and 12 months were either current ($n = 101$) or former ($n = 57$) smokers, and only 22 participants could be classified as never smokers (Table 1). At the 1-yr follow-up examination, 10 subjects, who had been smokers at baseline, reported having stopped smoking. Seven patients had accepted the offer of free nicotine patches.

Table 2 shows the mean values of each of the subject-level periodontal parameters at baseline and at 12 months. Current smokers had statistically significantly higher baseline values for all periodontal measurements compared with former and never smokers, except for the baseline Mean $PD_{PD\geq 5\ mm}$ and the baseline Mean $CAL_{PD\geq 5\ mm}$ (Table 3), for which the

lowest values were found in current smokers (Table 2). At 12 months, current smokers had significantly higher values of Mean $PD_{all\ sites}$, Mean $CAL_{all\ sites}$, % $PD_{\geq 5\ mm}$ and % $CAL_{\geq 3\ mm}$ than did former or never smokers (Table 3). A similar, but statistically insignificant gradient at 12 months was noted for Mean $PD_{PD\geq 5\ mm}$ (Tables 2 and 3), whereas the 12-month values for Mean $CAL_{PD\geq 5\ mm}$ were highest among former smokers, although not significant. Table 4 shows the mean values of each of the site-level periodontal parameters at baseline and at 12 months. The site-level mean values were quite similar to the subject-level mean values in Table 2, but the SD values were clearly higher (Table 4).

The mean reduction in PD based on all sites was 0.79–1.01 mm and was highest among current smokers and lowest among never smokers (Table 5). The mean PD reduction in sites with an initial PD of ≥5 mm was 2.98–3.38 mm and was highest among never smokers and lowest among current smokers (Table 5). The mean clinical attachment level gain based on all sites was 0.60–0.76 mm and was highest among current smokers, whereas, when based only on sites with initially deep pockets, the mean clinical attachment level gain was 2.14–2.40 mm and was highest among never smokers (Table 5). The percentage of sites with PD ≥5 mm was reduced by an average of 18.7–28.4% and was greatest among current smokers, whilst the percentage of sites with clinical attachment level of ≥3 mm was reduced by an average of 5.1–7.5% (Table 5).

Figures 1–6 show box-plots of the observed changes for participants classified as having high or low baseline values of the periodontal status variable in question. The results show that regardless of the periodontal status variable or smoking group considered, the change in the periodontal status variable following treatment was invariably greater among those with the higher baseline values. When the baseline values were taken into account, the median changes seemed either fairly stable among the smoking groups (Figs. 1, 2, 5, 6), or tended to be larger among never smokers (Figs. 3 and 4). With the exception of the changes in Mean $PD_{PD\geq 5\ mm}$ (Fig. 4) and to some extent also Mean $CAL_{PD\geq 5\ mm}$ (Fig. 3), the largest changes were consistently found among current smokers with high baseline values. Also, the distribution of the number of subjects in the high and low baseline value groups was clearly different among the smoking groups. Therefore, most of the current smokers tended to be in the high baseline value groups, whereas most of the never smokers tended to be in the low baseline value groups (Figs. 1, 2, 5, 6). There was a tendency for this pattern to be reversed when the status measures were Mean $CAL_{PD\geq 5\ mm}$ (Fig. 3) or Mean $PD_{PD\geq 5\ mm}$ (Fig. 4).

Table 6 demonstrates that the effect of smoking status on the subject-level change in periodontal status following therapy was dependent on whether or not adjustment for differences in baseline values was made. When no baseline adjustments were used, the results indicated smaller improvements among former and

Table 1

Characteristics of the 180 trial participants who completed the 1-yr follow-up examination, according to their baseline smoking status

Characteristic	Current smokers ($n = 101$)	Former smokers ($n = 57$)	Never smokers ($n = 22$)
Age			
35–44 yr	9	9	5
45–54 yr	55	33	27
55–64 yr	27	42	41
65–74 yr	9	16	27
Male gender	41	65	55
Metronidazole group	50	51	45
FDIS group	46	49	68

All values are given in per cent.
FDIS, full-mouth disinfection.

Table 2

Periodontal parameters at baseline (BL) and at 12 months (12M), according to baseline smoking status

Periodontal parameter	Time point	Current smokers	Former smokers	Never smokers
Mean $PD_{all\ sites}$ (mm)	BL	3.30 (0.64)	3.04 (0.58)	2.94 (0.55)
	12M	2.29 (0.21)	2.19 (0.16)	2.15 (0.15)
Mean $CAL_{all\ sites}$ (mm)	BL	2.10 (1.08)	1.68 (0.94)	1.47 (0.83)
	12M	1.34 (0.76)	1.06 (0.70)	0.87 (0.52)
Mean $PD_{PD \geq 5\ mm}$ (mm)	BL	5.80 (0.48)	5.98 (0.58)	6.07 (0.57)
	12M	2.80 (0.36)	2.75 (0.35)	2.73 (0.47)
Mean $CAL_{PD \geq 5\ mm}$ (mm)	BL	5.88 (1.17)	6.20 (1.13)	6.10 (0.77)
	12M	3.74 (1.03)	4.05 (0.96)	3.66 (0.74)
% $CAL_{\geq 3\ mm}$	BL	36.2 (15.7)	27.7 (15.2)	25.2 (13.4)
	12M	28.6 (15.7)	22.5 (14.9)	18.8 (11.7)
% $PD_{\geq 5\ mm}$	BL	30.2 (14.9)	23.1 (12.8)	19.7 (10.1)
	12M	1.8 (3.2)	1.1 (1.8)	1.1 (1.3)

Data are given as person-level mean values (SD).

% $CAL_{\geq 3\ mm}$, percentage of sites per person with clinical attachment level ≥3 mm; % $PD_{\geq 5\ mm}$, percentage of sites per person with a PD of ≥5 mm; Mean $CAL_{all\ sites}$, mean clinical attachment level based on all sites; Mean $CAL_{PD \geq 5\ mm}$, mean clinical attachment level based only on sites with an initial PD of ≥5 mm; Mean $PD_{all\ sites}$, mean PD based on all sites; Mean $PD_{PD \geq 5\ mm}$, mean PD based only on sites with an initial PD of ≥5 mm.

Table 3

Regression coefficients for baseline smoking status estimated by linear regression analysis of the values of the subject-level periodontal parameters at baseline (BL) and at 12 months (12M) of follow-up

Cross-sectional regressions	Time point	Former smokers (ref = Current smokers)		Never smokers (ref = Current smokers)	
		β	95% CI	β	95% CI
Mean $PD_{all\ sites}$	BL	−0.36	−0.56 to −0.15	−0.43	−0.71 to −0.14
	12M	−0.11	−0.17 to −0.05	−0.14	−0.23 to −0.05
Mean $CAL_{all\ sites}$	BL	−0.59	−0.92 to −0.26	−0.77	−1.24 to −0.30
	12M	−0.38	−0.62 to −0.14	−0.55	−0.89 to −0.21
Mean $PD_{PD \geq 5\ mm}$	BL	0.11	−0.06 to 0.29	0.24	−0.01 to 0.49
	12M	−0.09	−0.21 to 0.04	−0.11	−0.29 to 0.06
Mean $CAL_{PD \geq 5\ mm}$	BL	0.14	−0.23 to 0.51	0.02	−0.50 to 0.55
	12M	−0.03	−0.35 to 0.29	−0.18	−0.64 to 0.27
% $CAL_{\geq 3\ mm}$	BL	−10.4	−15.6 to −5.3	−12.5	−19.8 to −5.2
	12M	−8.1	−13.2 to −3.1	−11.8	−18.9 to −4.6
% $PD_{\geq 5\ mm}$	BL	−8.9	−13.5 to −4.3	−11.9	−18.4 to −5.4
	12M	−0.5	−1.4 to 0.4	−0.4	−1.7 to 0.8

Regression models are adjusted for age, gender and experimental group.

% $CAL_{\geq 3\ mm}$, percentage of sites per person with clinical attachment level ≥3 mm;% $PD_{\geq 5\ mm}$, percentage of sites per person with a PD of ≥5 mm; Mean $CAL_{all\ sites}$, mean clinical attachment level based on all sites; Mean $CAL_{PD \geq 5\ mm}$, mean clinical attachment level based only on sites with an initial PD of ≥5 mm; Mean $PD_{all\ sites}$, mean PD based on all sites; Mean $PD_{PD \geq 5\ mm}$, mean PD based only on sites with an initial PD of ≥5 mm; ref, reference.

never smokers than among current smokers for all periodontal parameters, except for those based on sites with an initial PD of ≥5 mm, for which never and former smokers had greater PD reductions than did current smokers (Table 6). When baseline adjustments were employed, there was no indication of an effect of smoking status on the improvements following periodontal therapy. These results were essentially confirmed in the multilevel linear regression analyses of the effect of baseline smoking status on the site-specific changes in the periodontal parameters PD and clinical attachment level, regardless of whether this was based on all sites or based only on sites with an initial PD of ≥5 mm (Table 7).

Discussion

The findings presented here corroborate the common observation that current smokers generally present with worse periodontal conditions than do former smokers, who, in turn, have higher scores than never smokers (6–14).

The present findings have also demonstrated that the analysis of change in observational studies is fraught with problems, as the conclusions drawn depended on the analytical method used. The results of the ANCOVA approach (SAC with adjustment for differences in baseline values) indicated no effect of smoking for any of the periodontal parameters considered, whereas the

Table 4

Periodontal parameters pocket depth (PD) and clinical attachment level (CAL) at baseline (BL) and at 12 months (12M) according to baseline smoking status

Periodontal parameter	Time period	Current smokers	Former smokers	Never smokers
PD (all sites) (mm)	BL	3.30 (1.88)	3.02 (1.84)	2.91 (1.79)
	12M	2.28 (0.60)	2.18 (0.49)	2.14 (0.48)
PD (sites with PD ≥5 mm) (mm)	BL	5.86 (1.25)	6.08 (1.48)	6.18 (1.56)
	12M	2.86 (0.81)	2.75 (0.78)	2.69 (0.89)
CAL (all sites) (mm)	BL	2.02 (2.94)	1.63 (2.88)	1.42 (2.69)
	12M	1.28 (1.97)	1.01 (1.88)	0.83 (1.68)
CAL (sites with PD ≥ 5 mm) (mm)	BL	5.91 (2.00)	6.30 (2.09)	6.22 (2.10)
	12M	3.74 (1.62)	3.97 (1.59)	3.76 (1.66)

Data are given as site-level mean values (SD).
CAL, clinical attachment level; PD, pocket depth.

Table 5

Changes from baseline to 12 months (BL-12M) in the observed values of the subject-level periodontal parameters according to baseline smoking status

Periodontal outcome variable	Time period	Current smokers	Former smokers	Never smokers
Mean $PD_{all\ sites}$	BL-12M	1.01 (0.50)	0.85 (0.47)	0.79 (0.49)
Mean $CAL_{all\ sites}$	BL-12M	0.76 (0.45)	0.62 (0.36)	0.60 (0.36)
Mean $PD_{PD\geq5\ mm}$	BL-12M	2.98 (0.54)	3.26 (0.60)	3.38 (0.78)
Mean $CAL_{PD\geq5\ mm}$	BL-12M	2.14 (0.63)	2.36 (0.74)	2.40 (0.56)
% $CAL_{\geq3\ mm}$	BL-12M	7.50 (6.30)	5.10 (4.50)	6.40 (4.60)
% $PD_{\geq5\ mm}$	BL-12M	28.40 (13.70)	22.0 (12.0)	18.70 (9.60)

Values are given as mean change (SD).
CAL, clinical attachment level PD, pocket depth.
% $CAL_{\geq3\ mm}$, percentage of sites per person with clinical attachment level ≥3 mm;% $PD_{\geq5\ mm}$, percentage of sites per person with a PD of ≥5 mm; Mean $CAL_{all\ sites}$, mean clinical attachment level based on all sites; Mean $CAL_{PD\geq5\ mm}$, mean clinical attachment level based only on sites with an initial PD of ≥5 mm; Mean $PD_{all\ sites}$, mean PD based on all sites; Mean $PD_{PD\geq5\ mm}$, mean PD based only on sites with an initial PD of ≥5 mm.
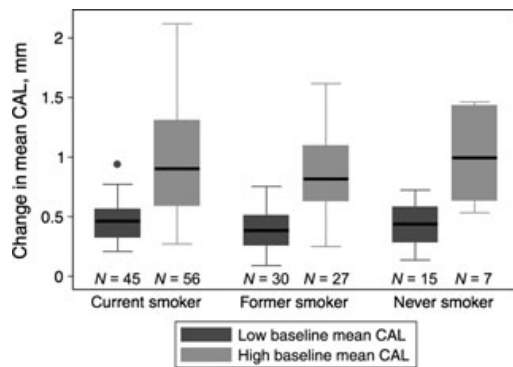

Fig. 1. Box plot of the change over 1 yr of mean clinical attachment level, according to the baseline level of mean clinical attachment level and smoking status. The baseline mean clinical attachment level was dichotomized into high (baseline values the same as or higher than the overall median mean clinical attachment level) and low (baseline values lower than the overall median mean clinical attachment level). The boxes indicate the interquartile range (IQR); the black line inside each box indicates the median; the whiskers show the range of the adjacent values (defined as the upper and lower borders of IQR ± 1.5IQR*), and the dot indicates observations outside the range of adjacent values. CAL, clinical attachment level.
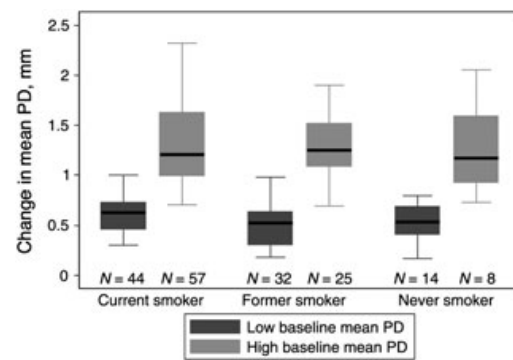

Fig. 2. Box plot of the change over 1 yr of the mean PD, according to the baseline mean PD and smoking status. The baseline mean PD was dichotomized into high (baseline values the same as or higher than the overall median mean PD) and low (baseline values lower than the overall median mean PD) baseline values. PD, pocket depth.

unadjusted SAC approach (the analysis of change without adjustment for baseline differences) indicated that current smokers benefit more from treatment (show
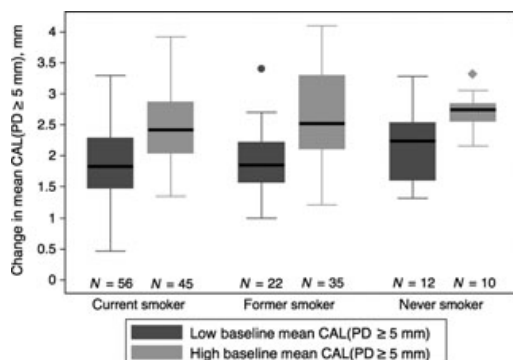
Fig. 3. Box plot of the change over 1 yr of the mean clinical attachment level based only on sites with an initial PD of ≥ 5 mm (Mean $CAL_{PD \geq 5 \, mm}$), according to the baseline level of Mean $CAL_{PD \geq 5 \, mm}$ and smoking status. The baseline level of Mean $CAL_{PD \geq 5 \, mm}$ was dichotomized into high (baseline values the same as or higher than the overall median Mean $CAL_{PD \geq 5 \, mm}$) and low (baseline values lower than the overall median Mean $CAL_{PD \geq 5 \, mm}$). CAL, clinical attachment level; PD, pocket depth.
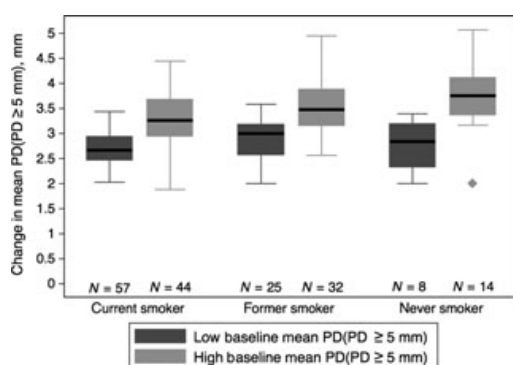

Fig. 5. Box plot of the change over 1 yr of the percentage of sites per person with clinical attachment level ≥ 3 mm (% $CAL_{\geq 3 \, mm}$), according to the baseline level of % $CAL_{\geq 3 \, mm}$ and smoking status. The baseline level of % $CAL_{\geq 3 \, mm}$ was dichotomized into high (baseline values the same as or higher than the overall median % $CAL_{\geq 3 \, mm}$) and low (baseline values lower than the overall median % $CAL_{\geq 3 \, mm}$).

Fig. 4. Box plot of the change over 1 yr of the mean PD based only on sites with an initial PD of ≥ 5 mm (Mean $PD_{PD \geq 5 \, mm}$), according to the baseline level of Mean $PD_{PD \geq 5 \, mm}$ and smoking status. The baseline level of Mean $PD_{PD \geq 5 \, mm}$ was dichotomized into high (baseline values the same as or higher than the overall median Mean $PD_{PD \geq 5 \, mm}$) and low (baseline values lower than the overall median Mean $PD_{PD \geq 5 \, mm}$).

Fig. 6. Box plot of the change over 1 yr of the percentage of sites per person with a PD of ≥ 5 mm (% $PD_{\geq 5 \, mm}$) according to the baseline level of % $PD_{\geq 5 \, mm}$ and smoking status. The baseline level of % $PD_{\geq 5 \, mm}$ has been dichotomized into high (baseline values the same as or higher than the overall median % $PD_{\geq 5 \, mm}$) and low (baseline values lower than the overall median % $PD_{\geq 5 \, mm}$).

greater improvements) than do former and never smokers when the periodontal status measures were based on all sites present. When based only on sites with initial PDs of ≥ 5 mm, the unadjusted SAC approach indicated the reverse effect of smoking, such that never or former smokers showed greater PD reductions than did current smokers, and a similar tendency was noted for clinical attachment level gains.

Regardless of which, if any, of these findings are valid or unbiased, they differ from the outcomes of a systematic review involving meta-analyses of the effect of smoking on the change in periodontal status as a result of nonsurgical therapy (21). The systematic review distinguished between two sets of studies: the 'all-sites studies', in which the changes in periodontal status were assessed based on all sites present; and the
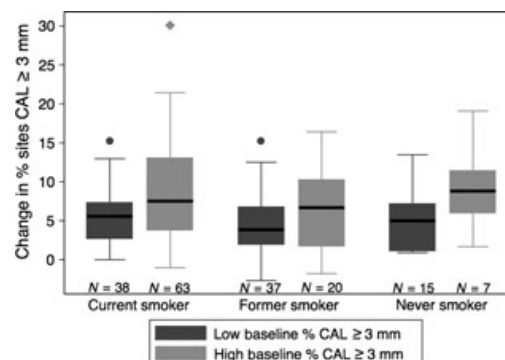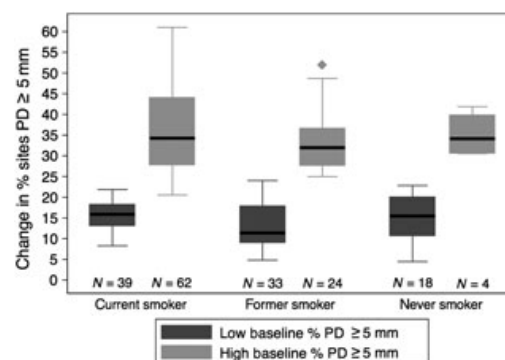
'threshold studies', in which only initially deep sites were considered in the estimation of change in periodontal status. Most of the 'all-sites studies' included found larger PD reductions in non-smokers than in smokers (22, 30–33, 35, 36, 39–41), which contrasts with the findings of the present study, regardless of whether the changes were analyzed by SAC or ANCOVA. However, it should be noted that the results of two of the 'all sites studies' (33, 37) indicated more favorable probing PD reductions among smokers than among non-smokers, which agrees with the outcomes of the SAC analyses of the present study. The results of the 'threshold studies' were in concordance with the findings from our analyses of the periodontal status change in sites with a PD of ≥ 5 mm as they indicated more favorable PD and clinical attachment level changes following therapy for never or former smokers than for current smokers, although the ANCOVA analyses attenu-

Table 6

Regression coefficients for baseline smoking status estimated by linear regression of the change in each of the periodontal parameters between baseline and 12 months (BL-12M)

Change regressions	Former smokers (ref = current smokers)		Never smokers (ref = current smokers)	
	β	95% CI	β	95% CI
No baseline adjustment				
Mean PD$_{all\ sites}$	−0.25	−0.41 to −0.09	−0.29	−0.52 to −0.06
Mean CAL$_{all\ sites}$	−0.21	−0.35 to −0.08	−0.22	−0.41 to −0.03
Mean PD$_{PD≥5\ mm}$	0.20	0.01 to 0.40	0.36	0.08 to 0.64
Mean CAL$_{PD≥5\ mm}$	0.17	−0.06 to 0.39	0.21	−0.11 to 0.52
% CAL$_{≥3\ mm}$	−2.30	−4.20 to −0.40	−0.70	−3.40 to 2.00
% PD$_{≥5\ mm}$	−8.40	−12.60 to −4.20	−11.50	−17.50 to −5.60
With baseline adjustment				
Mean PD$_{all\ sites}$	0.03	−0.02 to 0.07	0.04	−0.02 to 0.10
Mean CAL$_{all\ sites}$	−0.02	−0.11 to 0.06	0.03	−0.09 to 0.15
Mean PD$_{PD≥5\ mm}$	0.10	−0.02 to 0.23	0.14	−0.03 to 0.32
Mean CAL$_{PD≥5\ mm}$	0.13	−0.07 to 0.32	0.20	−0.08 to 0.47
% CAL$_{≥3\ mm}$	−1.40	−3.30 to 0.60	0.40	−2.30 to 3.10
% PD$_{≥5\ mm}$	−0.40	−1.20 to 0.40	−0.80	−1.90 to 0.30

Regression models are adjusted for age, gender and experimental group (without baseline adjustment) and additionally for baseline values (with baseline adjustment).
% CAL$_{≥3\ mm}$, percentage of sites per person with clinical attachment level ≥3 mm;% PD$_{≥5\ mm}$, percentage of sites per person with a PD of ≥5 mm; Mean CAL$_{all\ sites}$, mean clinical attachment level based on all sites; Mean CAL$_{PD≥5\ mm}$, mean clinical attachment level based only on sites with an initial PD of ≥5 mm; Mean PD$_{all\ sites}$, mean PD based on all sites; Mean PD$_{PD≥5\ mm}$, mean PD based only on sites with an initial PD of ≥5 mm.; ref, reference.

Table 7

Regression coefficients for the effect of baseline smoking status on the change in each periodontal parameter between baseline and 12 months, respectively

Periodontal parameter	Baseline adjustment	Former smokers (ref = current smokers)		Never smokers (ref = current smokers)	
		β	95% CI	β	95% CI
PD reduction (all sites)	No	−0.22	−0.36 to −0.07	−0.28	−0.48 to −0.07
PD reduction (all sites)	Yes	0.04	0.00 to 0.08	0.05	−0.00 to 0.11
PD reduction (sites with PD≥5 mm)	No	0.23	0.07 to 0.40	0.38	0.14 to 0.62
PD reduction (sites with PD≥5 mm)	Yes	0.12	−0.00 to 0.24	0.17	−0.00 to 0.34
CAL gain (all sites)	No	−0.16	−0.27 to −0.05	−0.19	−0.33 to −0.04
CAL gain (all sites)	Yes	0.04	−0.03 to 0.11	0.09	−0.01 to 0.19
CAL gain (sites with PD≥5 mm)	No	0.17	−0.05 to 0.38	0.24	−0.07 to 0.54
CAL gain (sites with PD≥5 mm)	Yes	0.07	−0.14 to 0.29	0.19	−0.11 to 0.50

Estimated by multilevel linear regression analysis. Models are adjusted for age, gender and experimental group (without baseline adjustment) and additionally for baseline values (with baseline adjustment).
CAL, clinical attachment level; PD, pocket depth; ref, reference.

ated these contrasts. The systematic review found no statistically significant differences when considering whether or not the studies were adjusted for baseline values (21), which is in contrast to the findings of the present study in which baseline adjustment altered the conclusions on the effect of smoking status on PD reductions and clinical attachment level gains when based on all sites, and diminished the effect on PD reductions and clinical attachment level gains when based only on initially deep sites.

Our observation that the conclusions reached regarding the effect of smoking on the changes in periodontal status following therapy may differ depending on the analytical method used, signifies that at least one (possibly both) of the analytical approaches is biased. The observation of conflicting outcomes of baseline-adjusted

and baseline-unadjusted analyses in observational studies of groups with different baseline means, known as LORD's paradox (46), is not novel, and several researchers have discussed the problems involved (42, 51–59). Some have argued that the outcomes of the two analytical approaches differ because they answer different questions (42). Proponents of this view posit that SAC tests the unconditional statement that change is the same across the groups being compared; that is, across smoking groups in the present study. Moreover, they suggest that ANCOVA tests the conditional statement that if groups with identical baseline values are selected, the baseline-adjusted analysis will show the differences between groups in the amount of improvement as a result of treatment. As shown in the figures, it might be impossible to find former or never smokers with base-

line values as high as those seen in a number of the current smokers. One may therefore question the meaning of assuming identical baseline values across smoking groups when the clinical reality is that they are (on average) different (56), as shown in Table 2. In this context, it is important to stress that both SAC and AN-COVA are statistically valid procedures and that the problems in their interpretation originate in the study design and in the necessity to make different and inherently untestable assumptions, discussed below.

The inclination to use baseline-adjusted methods (such as ANCOVA) when analyzing changes in observational nonrandomized studies may partly originate from the fact that ANCOVA is generally recommended as the method of choice for the analysis of randomized controlled clinical trials (RCTs) (54, 56–58). In the adequately randomized RCT, the exposure (the intervention whose effect is estimated) is not confounded with the baseline measurements because the interventions are subsequent to the randomization and to the recording of the baseline measurements. Therefore, baseline values are, in principle, balanced across intervention groups. This means that regression to the mean, which may be expected as a result of measurement error or physiological variation in the baseline measurements, will result in regression towards a common mean (59), and ANCOVA and SAC will therefore give rise to the same results. The superiority of ANCOVA over SAC in the analysis of RCTs lies in the ability to reduce within-group heterogeneity (54), which results in more study power (57, 59, 60) and thus the advantage is related not to bias but to efficiency.

In the present study we attempted to compare study groups that generally had different disease levels observed at baseline. However, a person with high baseline values either has a truly high baseline value or a large positive measurement error (or both), just as a person has a low baseline value either has a truly low baseline value or a large negative measurement error (or both). Thereby, the scene is set for the regression-to-the-mean phenomenon to exert its effect when estimating changes. When subjects are selected on the basis of a variable that is subject to such error variation, the regression-to-the-mean phenomenon will lead those with initially high values to appear as having changed to have lower values, whereas those observed with initially low values will appear to have changed toward higher values (61). Conditioning (as performed in ANCOVA) on baseline disease levels may therefore result in biased estimates of change. Moreover, ANCOVA assumes that covariates are measured without error (62), and when ANCOVA is used to adjust for the differences in the baseline disease levels, the measurement error in this covariate may contribute to LORD's paradox, that is, enhance the contrast between the outcomes of ANCOVA and SAC analyses.

The continued debates over the use of ANCOVA or SAC methods (51–56, 58, 59) testify to the intuitive appeal associated with the idea that analytical adjustment for baseline values will compensate for any baseline imbalances between the groups being compared

and thereby allow us to disclose the 'causal' effect of the exposure, *in-casu* smoking, on the change in periodontal status following therapy. Unfortunately, this is not what ANCOVA achieves. ANCOVA cannot be used to adjust for pre-existing differences between naturally occurring groups and therefore will provide biased results when so used (55, 59, 63). This is partly because the regression-to-the-mean effect is no longer regression toward a common mean (as was the case in the RCT scenario) but toward the respective group means (58), which differ for reasons that are not entirely clear. We do not know to what extent the observed study group differences reflect the differences in smoking groups in the population, but it is probably fair to assume that periodontal patients who are referred to a specialist clinic have persisting deep pockets after a 3-month pre-study hygiene phase and harbor a metronidazole-sensitive subgingival flora, as was the case in the present study, may represent a special subset of the periodontitis-affected population. This may have led to a differential selection of current, former, and never smokers into the study.

Estimation of 'causal' effects would be akin to comparing the post-treatment scores actually observed with the scores that the participants would have had, had they not been given treatment (42, 63). However, the latter scores could obviously not be obtained, and both ANCOVA and SAC employ inherently untestable assumptions regarding their relationship with the observed baseline scores. 'Causal' inferences, regarding the effect of smoking on the change following periodontal therapy, on the basis of ANCOVA methods are based on the assumption that the follow-up values of the periodontal parameters in the case of no periodontal treatment are a linear function of the baseline values (63). Similarly, 'causal' inferences on the basis of SAC methods are based on the assumption that the baseline values represent the participants' follow-up measurements had they not undergone periodontal treatment (63). In our view, it is not plausible to assume that there would have been no change in the periodontal parameters over a 1-yr period had the participants not been treated. The assumption underpinning ANCOVA, that the unknown change following no treatment is a linear function of the baseline values, would have appeared more plausible, as a result of what has been called the horse-racing effect (48). Paraphrasing PETO (48) we might consider current smokers to be the fastest horses in a horse race involving medium–fast former smokers and slower never smokers. Our baseline observations of periodontal status represent the position of the horses when they have already been racing for some time before the measurements are made. Not only should we expect the faster horses – the smokers – to be leading the race – have the deepest pockets – at 'baseline', we should also expect to see that they continue running (that is change status) at a higher speed than seen for the slower former or never-smokers. Thereby, we would expect the amount of change to correlate with baseline status. However, as pointed out by PETO (48), this expected correlation has no causal interpretation.

As indicated above, the horse-racing effect originates in the fact that the so-called baseline measurements in non-randomized follow-up studies, such as the present, are not true baseline measurements. The baseline measurements in the non-randomized study have not been taken before exposure to smoking and before the commencement of any attempts to influence the change in periodontal status. In a non-randomized observational study the word 'baseline' just marks the beginning of an observation period that is subsequent to the commencement of exposure, and this results in the baseline values becoming confounded with the exposure due to selection phenomena. In the context of the present study it is clear that the effect of smoking on periodontal tissues in current and former smokers had been present for a long time before the baseline recordings were obtained, and this might explain the baseline gradient in periodontitis severity across the three groups of current, former, and never smokers. Our observation, that the majority of patients included were either current or former smokers, provides additional evidence for the confounding effect of smoking-group exposure and baseline disease levels. In the present study these selection phenomena might have been further enhanced by the inclusion requirement for at least five persisting pockets of ≥5 mm following a 3-month prestudy hygiene phase. If non-smokers respond better to nonsurgical periodontal therapy than do smokers (21), it is possible that the relatively few never smokers treated in the present study represent a particularly therapy-resistant fraction of never smokers, which would explain why never smokers were observed – in the all sites analysed – to gain less from treatment compared with current smokers. Although current smokers had more persistent pockets of ≥5 mm at baseline than did never smokers (30% of sites vs. 20% of sites; Table 2) these persistent pockets were, on average, deeper among non-smokers than among smokers (Table 2). This may explain the seemingly paradoxical observation that never smokers appeared to gain more from treatment, when considering only the initially deep sites (PD ≥5 mm) in the SAC analyses. In the present study, this restriction reversed both the baseline and the change contrasts among current smokers, former smokers, and never smokers. Once again, this underlines the difficulties incurred when attempting to interpret the results of analysis of change in the presence of baseline differences.

Floor effects may represent an additional problem in the analyses of change following periodontal therapy in a nonrandomized observational study such as the present. Floor effects occur when there is a lower limit to the value of the outcome variable. The number of sites with a PD of ≥5 mm and the number of sites with clinical attachment level of ≥3 mm all have a lower limit of 0, which means that in particular the outcome % $PD_{≥5\ mm}$ is likely to show floor effects in a treatment study. As the clinical PD in health is rarely below 2 mm, even the mean PD outcomes may show signs of floor effects. The effect of such floors is to make it impossible for subjects with a low baseline value to be observed to improve much, whereas subjects with a high baseline value have a much greater potential for observed changes.

To conclude, the findings of the present non-randomized observational study demonstrate differences between baseline-adjusted and -unadjusted analyses of the effect of smoking on the change in periodontal status following therapy. Both analyses are likely to have given biased results owing a combination of biasing factors: the horse-racing effect, which explains the correlation between pre-existing differences at the designated baseline and subsequent change; the uncontrollable regression to the mean effect that results from pre-existing baseline differences; the possibility of differential recruitment of subjects and sites into the smoking groups, which may have led to selection biases; and the floor effects in the post-treatment periodontal parameters that made it impossible for some subjects to improve beyond a limited level. The conclusion that the current, former, and never smokers included in the present study differed with respect to their periodontal status at baseline is valid, just as it is valid to conclude that current smokers were observed to show greater improvements across all sites and smaller improvement in initially deep sites over the 1-yr period than were former or never smokers. What cannot be concluded on the basis of studies such as the present is whether these differences can be 'causally' attributed to smoking. Therefore, the findings of the present study highlight the fact that randomized clinical trial data cannot be used for valid inference regarding the effect of exposures other than those to which the participants were randomized. In randomized clinical trials the mere recruitment of participants invokes selection phenomena because participants must fulfill predefined inclusion criteria and pass certain diagnostic thresholds, and this sets the scene for the introduction of baseline differences and biases, the magnitude and direction of which cannot be estimated or controlled for using statistical techniques.

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