Simulation study of misclassification bias in association studies employing partial-mouth protocols

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ABSTRACT:

Aim. To simulate the exposure misclassification bias potential in studies of perio-systemic disease associations due to the use of PMR protocols.

Methods. Using data from 640 participants in the Dental Longitudinal Study, we evaluated distributions of clinical periodontitis parameters to simulate hypothetical outcome probabilities using bootstrap sampling. Logistic regression models were fit using the hypothetical outcome as the dependent variable. Models were run for exposure classifications based on FMR and PMR protocols over 10,000 repetitions.

Results. The impact of periodontitis exposure misclassification was dependent on periodontitis severity. Percent relative bias for simulated ORs of size 1.5, 2 and 4 ranged from 0 to 30% for the effect of severe periodontitis. The magnitude and direction of the bias was dependent on the underlying distribution of the clinical parameters used in the simulation and the size of the association being estimated. Simulated effects of moderate periodontitis were consistently biased toward the null.

Conclusion. Exposure misclassification bias occurring through the use of PMR protocols may be dependent on the sensitivity of the classification system applied. Using the CDC-AAP case definition, bias in the estimated effects of severe disease were small, on average. Whereas, effects of moderate disease were underestimated to a larger degree.

CLINICAL RELEVANCE:

Scientific Rationale for Study: There is recent and important interest in investigating periodontitis as a potential exposure or risk predictor for systemic disease conditions, such as cardiovascular disease. Documented underestimation of periodontitis prevalence by partial-mouth recording protocols has dampened enthusiasm for its use in studies of association.

Principal Findings: We report on a simulation study which demonstrates that bias in relative effect estimates due to exposure misclassification by partial-mouth recording protocols is both minimal and predictable.

Practical Implications: Partial-mouth recording protocols have the obvious advantage of reducing the burden of measurement, and may be the only feasible option to include periodontal assessments in clinical and observational studies where many other disease conditions are assessed.

INTRODUCTION

Partial-mouth recording (PMR) protocols for evaluations of periodontal disease status were first proposed more than 50 years ago. To date, PMR protocols have primarily been used to describe the periodontal disease status of populations at one point in time, often for the purposes of population surveillance. Despite the obvious advantages related to feasibility, the adoption of PMR protocols for the assessment of periodontal disease status in research has been criticized due to concerns related to underestimation of disease prevalence, but also the potential for biased estimates in studies of association (Eke et al., 2010). We have previously reported on the mechanisms of this underestimation in descriptive studies and postulated their potential relevance in studies of perio-systemic disease associations (Heaton et al., 2018) by applying the case definitions developed by the Centers for Disease Control and Prevention in collaboration with the American Academy of Periodontology (CDC-AAP) (Page and Eke, 2007).

Although the bias in estimation of disease prevalence and severity by use of PMR protocols has been well cited (Kingman et al., 2008, Beck et al., 2006, Susin et al., 2005), discussions related to the impact of PMR protocols on the validity of association studies has been limited to pure conjecture, until recently (Akinkugbe et al., 2015). The primary assumption underlying the postulated impact of PMR protocols on measures of association when periodontal disease is the outcome is that non-differential classification errors would lead to a bias toward null associations, thereby underestimating the true effect of a given exposure on the periodontitis outcome (Eke et al., 2010). While the impact of outcome misclassification by use of PMR protocol has recently been explored by Akinkugbe et al., the impact of exposure misclassification by PMR protocol has yet to be explored. It is a common expectation that non-differential misclassification of a binary exposure will, on average, bias the observed estimate of effect toward a null association. If, however, systematic errors in the classification of an exposure exist, measures of the association may be biased in either direction, depending on the

underlying distribution of exposure, the true exposure-outcome association, and the case definition i.e. classification system, applied (Brenner and Loomis, 1994). Additionally, despite expectation, the presence of a bias toward the null association in the presence of classification errors does not guarantee that those errors were non-differential. In this paper, we expect non-differential exposure misclassification to be present when the proportion of subjects who are misclassified on exposure does not depend on the outcome status of the subject (Rothman et al., 2008).

The present study utilizes simulation methods to estimate the potential for bias in measures of perio-systemic disease associations as a result of the systematic, non-differential misclassification of the periodontitis exposure through the use of PMR protocols. Simulation methods allow us to illustrate these biases by creating a scenario in which the true association can be observed and scenarios under which misclassification is present can be simulated and compared to the truth (Jurek et al., 2005). In observational studies, we are limited in our capacity to objectively evaluate whether our observed results reflect the true relative difference in the risk of the outcome and can only postulate as to potential sources of misclassification, the likelihood of its presence and the expected impact on our findings. Despite expectation, however, several situations have been identified in which there is a difference between what is expected on average (e.g. bias toward the null) and what is observed (Dosemeci et al., 1990). Meaning, non-differential misclassification of a binary exposure does not *guarantee* that results will reflect a bias toward a null association. Importantly, simulation methods determine the expectation of bias, rather than just a particular realization in a given dataset (Akinkugbe et al., 2015, Jurek et al., 2005)

We have recently demonstrated that misclassification of periodontal disease by PMR is systematic, with imperfect sensitivity and perfect specificity (Heaton et al., 2018). Specifically, the probability of a false-negative finding under PMR increases with decreasing disease severity and extent. We therefore hypothesized that the magnitude of bias observed would be less than

would be expected under conditions of random non-differential misclassification, where the probability of misclassification is equal among the exposed and unexposed. Additionally, it has been previously observed that the continuous means of clinical measures remain unbiased under PMR protocols (Beck et al., 2006, Heaton et al., 2018, Kingman et al., 2008). Therefore, we additionally hypothesized that the direction of bias would be dependent on the continuous clinical measure used to generate the hypothetical outcome.

The specific aims of this paper were to (i) evaluate the distributions of continuous clinical measures of periodontal disease (i.e. pocket probing depth [PD], clinical attachment loss [CAL], etc.) according to categorical classifications of disease (i.e. CDC-AAP definitions), (ii) simulate the effect of periodontal disease on a hypothetical outcome under varying conditions of exposure classification, and (iii) evaluate mechanisms underlying any differences between observation and expectation.

METHODS

This paper presents a simulation study in which the exposure of interest (e.g. periodontitis) was informed by the use of empirical data and the outcome of interest was simulated using the empirical data to inform parameters used in the simulation procedures. The empirical information used was drawn from the subject population described below.

Subject Population

Full-mouth examination data was obtained on 640 adult men participating in the Veterans Affairs Dental Longitudinal Study (DLS) during the years 1987-1997. The parent study for the DLS is the Veterans Affairs Normative Aging Study, an ongoing closed-panel prospective study of aging, which began in the 1960s (Bell et al., 1966). At baseline, 2,280 men aged 21 to 84 years who were free of chronic disease and lived in the greater Boston metropolitan area were enrolled. In 1968, 1,231 Normative Aging Study participants volunteered to enroll in its dental component (Kapur et al., 1972). Subjects were not Veterans Affairs patients and received both medical and dental care in the private sector. According to self-report of oral diagnoses

and receipt of specialty treatment, few DLS subjects received comprehensive or definitive treatment for periodontitis. Beginning in 1987, periodontal examinations were conducted as part of the regular study follow-up visit by a single examiner following the then National Institute of Dental Research protocol, recording measurements of CAL and PD at four sites per tooth—disto-lingual, mid-lingual, mesio-buccal, mid-buccal. Detailed information on measurement and reproducibility is presented elsewhere (Feldman et al., 1982, Glass et al., 1973). The present study utilizes a cross-sectional sample of the first full-mouth examination completed on all DLS participants (n=640). On average, participants had 20.7 teeth, with a standard deviation of 6.6 teeth. Measures of CAL and PD were obtained on 13,209 teeth and their distributions were used in the simulations. Third molars were excluded from all analyses.

Periodontal Disease Determinations and Distributions

We applied the 2007 CDC-AAP definition for no/mild, moderate and severe periodontitis (Page and Eke, 2007). This definition incorporates measures of PD and CAL obtained only from interproximal sites. We also considered modifications to this definition for disease determinations under a PMR protocol (see Table 1). Specifically, the CDC-AAP severe disease definition was modified to require that only one interproximal site with at least 6 mm CAL was present (instead of two). We also assessed an additional alternative definition, which eliminated the requirement for a site with 5+ mm PD.

Continuous measures of periodontal disease were calculated from full-mouth examination data. Mean PD and mean CAL were calculated by taking the whole-mouth average of interproximal measurements. Cumulative PD was calculated as the whole-mouth sum of interproximal pockets considered to be “pathological”, i.e., with probing depths greater than three millimeters (Dietrich et al., 2008).

Random half-mouth protocols were used for all PMR disease determinations by randomly selecting opposing oral quadrants with equal probability. Periodontal disease determinations under the PMR protocol were considered to be concordant with determinations

made under the FMR protocol if periodontal disease status was classified consistently in both full- and partial-mouth assessments, and discordant if not (see Table 1).

In order to assess true differences in periodontal disease state according to whether disease determinations by FMR and PMR protocols were concordant or discordant, distributions of continuous measures of disease were compared via distribution plots for clinical disease parameters under each classification category i.e. discordant or concordant. Specifically, mean CAL, mean PD and cumulative PD were plotted according to CDC-AAP disease determinations; 1) severe cases of periodontitis under both FMR and PMR protocols (concordant/severe), 2) severe cases of periodontitis under the FMR protocol only (discordant) and 3) non-severe cases of periodontitis under both FMR and PMR protocols (concordant/non-severe). This was repeated for moderate cases of periodontitis and again when modified definitions of periodontitis were applied. Additionally, we evaluated the average number of teeth with a specified clinical severity according to concordance of disease determinations from PMR and FMR protocols for both severe and moderate cases.

Simulation Methods

In order to assess the potential influence of exposure misclassification on the measure of association as a result of employing a PMR protocol, exposure-outcome associations were simulated using the empirical exposure information from clinical examination data among the DLS subject population and a hypothetical outcome generated for varying effect sizes and incidences of the hypothetical outcome. We assumed that 1) there is a causal association between periodontal disease severity as measured by whole-mouth means of clinical parameters and the hypothetical outcome, and 2) the risk of the outcome is a function of the continuous periodontal exposure.

Exposure. Categorical periodontal disease determinations based on the CDC-AAP definitions were assigned to DLS study subjects based on the empirical data obtained during full-mouth examinations. Within each simulated bootstrap sample, exposure categorization

based on full-mouth determinations did not vary. However, random selection of oral quadrants occurred within each simulated sample and therefore partial-mouth determinations could vary. . Binary comparisons of the periodontitis exposure were generated for each category of severity, i.e., severe vs. non-severe, moderate vs. non-moderate. Modified definitions for partial-mouth determinations were also applied and evaluated in order to test the influence of imperfect specificity and increased prevalence of exposure on the association measure.

Outcome. Hypothetical outcome probabilities were calculated for each DLS subject over 10,000 bootstrap samples using the empirical distributions of clinical parameters measured from the subject population (i.e., mean CAL, mean PD, cumulative PD) or the binary CDC-AAP disease classifications, and the values of the coefficients for the desired odds ratios (OR). We used the following formula:

$$p = e[\ln(OR) * (dx)]/(1 + e[\ln(OR) * dx])$$

where p is equal to the probability of the hypothetical outcome, OR takes on the value of the coefficient corresponding with the desired magnitude of the OR and dx is equal to the value of the continuous measure of periodontal disease severity used e.g. mean CAL, mean PD, cumulative PD or the binary disease state based on the CDC-AAP definition. The coefficients were equivalent to ORs of 1.5, 2.0 and 4.0. The coefficients were multiplied by random draws from the empirical continuous distributions of periodontal disease; therefore, ORs of the intended magnitude could not be achieved for some clinical measures.

In order to assign the occurrence of the hypothetical binary outcome to each individual, we sampled random numbers from a random uniform distribution with range 0 to 1 and compared them to the outcome probability generated for each individual. The occurrence of the outcome was assigned to an individual if the individual outcome probability was greater than the randomly sampled number. The incidence of the hypothetical outcome was held to 10% and 20% for each simulation by multiplying the outcome probability by a numerical constant.

Model. Logistic regression models were fit using the hypothetical outcome as the dependent variable and the binary periodontal disease definition as the independent variable, i.e., severe/non-severe. Models were run for exposure classifications based on FMR and PMR protocols using both the CDC-AAP definition and the modified definitions for severe periodontitis under PMR protocols. We report the median OR over 10,000 repetitions. We also report the percent relative median bias by evaluating percent change in the natural log of the OR for the PMR compared to the FMR.

Human subject research approvals were obtained from the Boston University Medical Campus and the Veterans Administration Institutional Review Boards.

RESULTS

Subject Population

Of the 640 subjects included in this analysis, 15% (n=99) were found to have mild to no disease, 66% (n=425) had moderate/non-severe disease and 18% (n=116) had severe disease according to the 2007 CDC-AAP definition. On average, men had pockets with 2.27 mm probing depth and attachment loss of 2.6 mm. At the time of examination, men were approximately 68 years of age, on average.

Periodontal Disease Determinations and Distributions

Distribution plots of the continuous clinical measures of the periodontal disease exposure according to the concordance of FMR and PMR protocol disease determinations are found in Figures 1 and 2. When the CDC-AAP definitions for severe and moderate disease were applied similarly to FMR and PMR data (see Figure 1), the disease status among those misclassified subjects (i.e., discordant) appeared to be dependent on which continuous clinical measure was under observation and whether the classification applied was for severe or moderate disease.

Severe Disease. For severe disease determinations, a clear difference in disease state between severe and non-severe concordant cases can be observed for all clinical measures

evaluated. Those subjects who were discordant and misclassified as non-severe under the PMR protocol, displayed disease states that were approximately in between that of severe and non-severe concordant cases. This did not appear to differ meaningfully according to the clinical measure under observation. Similar results are displayed in Table 2, which highlights the differences in the average number of teeth with a given clinical severity according to concordance status. For CAL of ≥6mm and PD of ≥5mm, participants with discordant severe disease determinations had numbers of teeth directly between that of concordant severe and non-severe cases.

When a modified definition of severe disease (PMR determinations requiring only one site with equivalent CAL, instead of two) was applied to the PMR protocol only (see Figure 2), thereby increasing sensitivity but decreasing specificity, those who were discordant and misclassified as severe under the PMR protocol reflected cumulative and mean PD more similar to those who were truly severe. This was also observed for those who were misclassified as non-severe. However, the opposite was true when mean CAL was evaluated.

Moderate Disease. Moderate disease determinations resulted in smaller differences in the underlying disease severity between moderate and non-moderate concordant cases. However, this did depend on which clinical measure was evaluated. Smaller differences in cumulative and mean PD were observed between moderate and non-moderate cases than for mean CAL where a clearer contrast in the underlying disease could be observed. Additionally, those who were discordant and misclassified as non-moderate under the PMR protocol displayed distributions of disease severity that were nearly the same as those of moderate cases of disease when the cumulative and mean PD were evaluated. This was not the case, however, when the mean CAL was evaluated. This can additionally be seen in Table 2 where minimal differences in the average number of teeth with PD of ≥5mm displayed compared to the differences observed for CAL ≥ 4mm.

Simulations

Results of the simulations are displayed in Tables 3 and 4.

Severe Disease. When the association between severe periodontal disease and the hypothetical outcome generated by a continuous distribution was assessed, the ORs calculated under PMR protocols overestimated the association, on average, by less than 15% when compared to the ORs calculated under the FMR protocols (Table 3). The magnitude and direction of the bias appeared somewhat dependent on which measure of the underlying disease state was used to generate the hypothetical outcomes and the size of the association being estimated. When mean CAL or PD was used to generate the outcome, a larger bias away from the null was observed for ORs larger than 1.5. Conversely, if the binary periodontal disease determinations were used to generate the outcome probability, the use of PMR protocols consistently underestimated the association and the amount of bias was greater for smaller ORs. The prevalence of the simulated outcome (e.g. 10% or 20%) did not appear to have a meaningful influence on the bias that was observed, although the degree of overestimation was somewhat greater for an outcome prevalence of 20%.

When a modified definition of severe disease (PMR determinations requiring only one site with equivalent CAL, instead of two) was applied to PMR protocol determinations only, the magnitude of bias was similar (e.g. less than 15%), but the direction of the bias differed based on which exposure distribution was used to generate the outcome (see Table 4). Mean CAL, mean PD and the use of a binary exposure distribution resulted in underestimation by PMR protocol, whereas the use of Cumulative PD resulted in overestimation.

Moderate Disease. When the simulated effects of moderate disease were under evaluation, the ORs calculated under PMR protocols were consistently biased toward the null, regardless of which clinical measure was used to generate the hypothetical outcome. Modified definitions for partial-mouth determinations resulted in an even greater bias, at times pulling the estimate below the null, potentially due to sensitivity and/or specificity of periodontitis determinations for moderate disease by the PMR protocol that were below 50%.

DISCUSSION

The primary aim of this work was to better understand the potential for exposure misclassification bias in measures of association due to the use of PMR protocols. Additionally, this work aimed to shed light on the potential presence of misclassification of true periodontal disease through categorization, in addition to misclassification by use of PMR protocols—two similar but different issues. Specifically, if systemic outcomes are a causal function of periodontal disease severity and/or extent, understanding the true periodontal disease state of misclassified subjects will allow for a better understanding of the impact of misclassification on observed estimates in association studies. Our findings confirm our earlier report that the misclassification of periodontal disease status by use of a PMR protocol is not random (Heaton et al., 2018). Additionally, we show that exposure misclassification through the use of PMR protocols produces percent relative median bias of less than 15% on average in measures of association when the effects of severe disease are under evaluation, and consistently underestimates the FMR ORs when moderate disease is evaluated the latter of which is likely due to the case definition applied.

Severe Disease. Binary comparisons of severe and non-severe subjects revealed that there were clear differences in the distributions of clinical measures of disease, indicating that the cut-off for severe disease established by the CDC-AAP is reasonable for identifying meaningful differences in disease state among men in the DLS. Additionally, subjects with severe disease that were misclassified under the PMR protocol displayed distributions of disease that were centrally located between that of the correctly classified severe and non-severe subjects for mean PD and CAL. As a result, because simulations were run with the hypothetical outcome probabilities generated as a function of the underlying continuous distributions, the hypothetical outcomes for misclassified subjects were likely equally distributed between truly severe and non-severe subjects. Therefore, no to minimal bias toward the null was observed when these measures were used. Cumulative PD on the other hand, resulted in

modest overestimates of the effect when the PMR protocol was utilized due to the misclassified subjects displaying true disease that was more reflective of non-severe subjects. In this case, severe subjects who were misclassified as non-severe had a lower risk for the outcome in truth and therefore increased the denominator of the risk of the outcome among the non-severe when they were misclassified. This is likely due to the fact that the measure of cumulative PD only incorporated pockets that were greater than three millimeters in depth.

Moderate Disease. Binary comparisons of moderate and non-moderate cases revealed that the differences in disease state between moderate and non-moderate cases were shown to be minimal for mean and cumulative PD, indicating a possibility for misclassification of the exposure by virtue of the case definition applied. If severe cases had instead been excluded from the definition of moderate cases, even greater similarities would have been observed. This lack of contrast in the distribution of mean and cumulative PD for moderate and non-moderate subjects limited our ability to simulate associations that reached a magnitude of two-fold for the effect of moderate disease on the hypothetical outcome and even more so had severe subjects been excluded. Subjects that were misclassified by the PMR protocol as non-moderate cases displayed true disease (as measured by mean and cumulative PD) that was nearly identical to that of correctly classified moderate cases thereby producing a bias toward the null since the probability for the outcome would be nearly equal for those correctly classified moderate subjects and misclassified non-moderate subjects. However, this was not observed for distributions of mean CAL where differences in severity of disease and the magnitude of the associations were similar to those comparisons of severe and non-severe disease and subjects who were misclassified as non-moderate under PMR protocols had a mean CAL that was more reflective of correctly classified non-moderate cases although minimally. Due to the lack of contrast in the underlying periodontal exposure status, the prevalence of the simulated outcome had a greater impact on the amount of bias that was present. When we increased the risk for

the outcome to 20%, differences in the periodontal exposure status were more distinguishable and the amount of bias lessened.

Given that the CDC-AAP definition for severe periodontitis requires that a subject meets a certain threshold of *both* PD and CAL, a greater difference in the distributions of each measure between severe and non-severe results and therefore, those who are misclassified as a result of PMR protocols are likely those whose periodontal exposure is truly less severe and thus, under causal assumptions, their risk of the outcome is also lower. The case definition for moderate disease, however, only requires that a subject meet one of the two clinical criteria and at a lower threshold. As a result, the majority of subjects meeting the definition for moderate disease met the definition on the basis of their CAL and few cases on the basis of their PD, leading to a lack of contrast when outcome probabilities are generated based on distributions of PD (see Figure 1).

For the simulations, 'true' disease probability was calculated based on mean PD, mean CAL or cumulative PD in a linear dose-dependent manner, as well as the binary disease definition. It should be noted that for any systemic disease outcome, the true nature of the exposure disease association is unknown, i.e., while it is unlikely a step-function as assumed when using a binary disease definition, it could be non-linear and it is unclear which of the continuous disease measures best describe the exposure.

The present study is not without limitation. We relied on a population of older, predominantly white men, participating in the Dental Longitudinal Study for estimates of the periodontal exposure. Although we do not believe our findings to be dependent on the limited population with respect to age, gender and race, one may wish to exercise caution in determining the generalizability of the simulation study. Additionally, the DLS employed the 1987 National Institute of Dental Research examination protocol, which prescribes measurement of only four sites per tooth, instead of six. As a result, true periodontal disease severity and the sensitivity of PMR determinations may be underestimated. Furthermore,

because we utilized the empirically measured periodontitis exposure in this simulation, the underlying true exposure prevalence was fixed. Simulations of exposure misclassification bias have highlighted that the magnitude and direction of the bias on the observed estimate may result from dependent associations between exposure prevalence and the sensitivity and specificity of the exposure classification (Jurek et al., 2005). As case definitions for use in association studies are further developed, future simulation work would be warranted to estimate the likely bounds on the magnitude and direction of exposure misclassification bias due to PMR protocols. Lastly, we used a logistic regression model to simulate the prevalence odds ratio. It is well recognized that the use of this model may result in overestimation when the outcome frequency is greater than 20%. Although this simulation study restricted the average outcome frequencies to 10% and 20%, we acknowledge that the possibility remains that the generated odds ratios reflect overestimates. However, we would suggest that the impact on the relative bias between the ORs generated from FMR and PMR protocols would be negligible, if present at all. One may wish to consider a model other than logistic regression if the outcome frequency is higher than 20%, or the goal of an investigation is to estimate the true causal association between an empirical exposure and outcome.

Partial-mouth recording protocols have the obvious advantage of reducing the burden of measurement, and may be the only feasible option to include periodontal assessments in larger-scale clinical and observational studies where many other disease conditions are assessed. This study is the first to explore the potential role of exposure misclassification under such conditions. It also importantly highlights the need to acknowledge the role of the exposure definition in evaluations of misclassification by PMR protocol. The findings of this work would benefit from future work, including but not limited to, external validation.

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Table 1. Description of terminology and periodontal disease definitions applied.

Terminology			
Concordant:	Disease determinations based on FMR and PMR protocols were the same		
Discordant:	Disease determinations based on FMR and PMR protocols were not the same		
2007 CDC - AAP Periodontitis Case Definitions			
	Clinical Definition		
Disease Category	Clinical Attachment Loss [CAL]		Pocket Depth [PD]
Severe periodontitis	≥2 interproximal sites with CAL ≥6 mm (not on same tooth)	and	≥1 interproximal site with PD ≥5 mm
Moderate periodontitis	≥2 interproximal sites with CAL ≥4 mm (not on same tooth)	or	≥2 interproximal site with PD ≥5 mm
Mild periodontitis/None	Neither "moderate" nor "severe" periodontitis		
PMR Severe Periodontitis Case Definitions:			
	CAL		PD
Definition 1	≥1 interproximal site with CAL ≥6mm	and	≥1 interproximal site with PD ≥5 mm
Definition 2	≥1interproximal site with CAL ≥6mm		

Table 2. Numbers of teeth with specified clinical severity according to concordance of disease determinations from PMR and FMR protocols

	SEVERE[a]			MODERATE[a]		
	Concordant Severe	Discordant	Concordant Non-Severe	Concordant Moderate	Discordant	Concordant Mild/None
CAL						
≥ 4 mm	12.46	10.66	5.54	8.75	2.73	0.43
≥ 5 mm	9.03	6.23	2.38	4.54	0.90	0.08
≥ 6 mm	5.70	2.92	0.67	1.85	0.26	0.02
≥ 7 mm	3.29	1.38	0.22	0.85	0.08	0.02
PD		**AND**			**OR**	
≥ 4 mm	6.71	3.91	2.02	3.09	2.16	1.03
≥ 5 mm	4.10	2.11	0.59	1.35	0.60	0.15
≥ 6 mm	2.03	0.83	0.14	0.51	0.14	0.01
≥ 7 mm	1.00	0.38	0.03	0.22	0.02	0.00

[a]Standard 2007 CDC-AAP case definitions were applied to both PMR and FMR protocols

Table 3. Simulated odds ratios for the effect of severe and moderate periodontitis as determined by the 2007 CDC-AAP periodontitis case definition on a hypothetical outcome

	Severe Periodontitis						Moderate Periodontitis					
Outcome Probability	**10%**			**20%**			**10%**			**20%**		
	Odds Ratios			**Odds Ratios**			**Odds Ratios**			**Odds Ratios**		
Exposure Distribution	(95% Simulation Interval)			(95% Simulation Interval)			(95% Simulation Interval)			(95% Simulation Interval)		
Mean CAL												
FMR	1.53	2.08	3.96	1.53	2.03	4	1.43	1.82	2.9	1.44	1.85	3.74
	(1.5,2.8)	(1.1,3.8)	(2.2,7.0)	(0.9,2.5)	(1.3,3.2)	(2.5,6.2)	(0.7,4.4)	(0.9,6.3)	(1.0,12)	(0.8,2.8)	(1.1,3.9)	(1.9,11.7)
PMR	1.52	2.13	4.21	1.57	2.16	4.46	1.17	1.44	2.22	1.3	1.62	3
	(0.5,3.1)	(0.9,4.1)	(2.0,7.8)	(0.8,2.8)	(1.2,3.8)	(2.5,7.8)	(0.7,2.3)	(0.8,2.9)	(1.2,5.2)	(0.9,2.1)	(1.1,2.7)	(1.9,5.5)
Percent Relative Bias	-1.54	3.24	4.45	6.07	8.77	7.85	-56.10	-39.11	-25.10	-28.05	-21.58	-16.71
Mean PD												
FMR	1.3	1.6	2.58	1.29	1.55	2.28	1.15	1.27	1.65	1.13	1.24	1.53
	(0.6,2.4)	(0.8,2.9)	(1.4,4.6)	(0.8,2.0)	(0.9,2.4)	(1.4,3.6)	(0.6,3.1)	(0.6,3.6)	0.8,5.4)	(0.7,2.1)	(0.7,2.3)	(0.9,3.0)
PMR	1.3	1.7	2.9	1.34	1.67	2.61	0.94	1.02	1.23	1.02	1.09	1.28
	(0.5,2.7)	(0.7,3.4)	(1.4,5.5)	(0.7,2.4)	(0.9,3.0)	(1.5,4.5)	(0.5,1.8)	(0.6,1.9)	(0.7,2.3)	(0.7,1.6)	(0.7,1.7)	(0.8,2.0)
Percent Relative Bias	0.00	10.38	12.70	14.93	17.01	16.40	-144.27	-91.71	-58.66	-83.80	-59.94	-41.95
Cumulative PD												
FMR	1.6	1.97	3.3	1.43	1.87	2.59	1.29	1.45	2.15	1.2	1.4	1.75
	(0.8,2.9)	(1.0,3.5)	(1.9,5.7)	(0.9,2.3)	(1.1,2.9)	(1.6,4.0)	(0.6,3.6)	(0.7,4.5)	(1.0,7.6)	(0.7,2.3)	(0.8,2.7)	(1.0,3.6)
PMR	1.79	2.3	4.13	1.57	2.2	3.21	1.11	1.21	1.64	1.1	1.25	1.47
	(0.7,3.5)	(1.0,4.4)	(2.1,7.7)	(0.8,2.8)	(1.2,3.8)	(1.8,5.6)	(0.6,2.1)	(0.7,2.4)	(0.9,3.3)	(0.4,1.8)	(0.8,2.0)	(1.0,2.4)
Percent Relative Bias	23.87	22.84	18.79	26.11	25.96	22.55	-59.02	-48.70	-35.37	-47.72	-33.68	-31.16
Binary												
FMR	1.49	2	4.02	1.49	2	4	1.13	1.23	1.61	1.11	1.2	1.5
	(0.7,2.7)	(1.0,3.5)	(2.2,7.0)	(0.9,2.4)	(1.2,3.2)	(2.5,6.3)	(0.6,2.8)	(0.6,3.3)	(0.8,4.9)	(0.7,2.1)	(0.7,2.2)	(0.9,3.0)
PMR	1.32	1.69	2.97	1.3	1.62	2.75	0.91	0.98	1.24	1.12	1.25	1.65
	(0.5,2.7)	(0.7,3.4)	(1.4,5.6)	(0.8,2.1)	(1.0,2.6)	(1.7,4.3)	(0.5,1.6)	(0.6,1.8)	(0.7,2.4)	(0.5,1.6)	(0.6,1.7)	(0.7,2.1)
Percent Relative Bias	-30.38	-24.30	-21.76	-34.21	-30.40	-27.03	-177.17	-109.76	-54.83	8.59	22.39	23.51

Table 4. Simulated odds ratios for severe and moderate periodontitis on a hypothetical outcome using modified case definitions for PMR determinations

	Severe Periodontitis						Moderate Periodontitis					
Outcome Probability	**10%**			**20%**			**10%**			**20%**		
	Odds Ratios			**Odds Ratios**			**Odds Ratios**			**Odds Ratios**		
Exposure Distribution	(95% Simulation Interval)			(95% Simulation Interval)			(95% Simulation Interval)			(95% Simulation Interval)		
Mean CAL												
FMR	1.53	2.08	3.96	1.53	2.03	4	1.43	1.82	2.9	1.44	1.85	3.74
	(1.5,2.8)	(1.1,3.8)	(2.2,7.0)	(0.9,2.5)	(1.3,3.2)	(2.5,6.2)	(0.7,4.4)	(0.9,6.3)	(1.0,12)	(0.8,2.8)	(1.1,3.9)	(1.9,11.7)
PMR*	1.34	1.74	2.97	1.39	1.76	3.08	0.96	1.16	1.68	1.17	1.47	2.66
	(0.6,2.5)	(0.9,3.1)	(1.6,5.2)	(0.8,2.3)	(1.1,2.8)	(1.9,4.8)	(0.5,2.5)	(0.6,3.4)	(0.8,5.9)	(0.7,2.3)	(0.8,3.0)	(1.5,5.8)
Percent Relative Bias	-31.18	-24.37	-20.90	-22.57	-20.16	-18.85	-111.41	-75.22	-51.27	-56.94	-37.37	-25.83
Mean PD												
FMR	1.3	1.6	2.58	1.29	1.55	2.28	1.15	1.27	1.65	1.13	1.24	1.53
	(0.6,2.4)	(0.8,2.9)	(1.4,4.6)	(0.8,2.0)	(0.9,2.4)	(1.4,3.6)	(0.6,3.1)	(0.6,3.6)	0.8,5.4)	(0.7,2.1)	(0.7,2.3)	(0.9,3.0)
PMR*	1.24	1.54	2.53	1.27	1.54	2.32	0.82	0.89	1.1	0.96	1.05	1.29
	(0.6,2.3)	(0.7,2.8)	(1.4,4.4)	(0.8,2.0)	(0.9,2.5)	(1.4,3.6)	(0.4,2.0)	(0.5,2.3)	(0.6,3.0)	(0.6,1.8)	(0.6,2.0)	(0.7,2.5)
Percent Relative Bias	-18.01	-8.13	-2.06	-6.14	-1.48	2.11	-241.99	-148.76	-80.97	-133.40	-77.32	-40.12
Cumulative PD												
FMR	1.6	1.97	3.3	1.43	1.87	2.59	1.29	1.45	2.15	1.2	1.4	1.75
	(0.8,2.9)	(1.0,3.5)	(1.9,5.7)	(0.9,2.3)	(1.1,2.9)	(1.6,4.0)	(0.6,3.6)	(0.7,4.5)	(1.0,7.6)	(0.7,2.3)	(0.8,2.7)	(1.0,3.6)
PMR*	1.64	2.07	3.65	1.48	2	2.87	1	1.08	1.51	1.05	1.22	1.49
	(0.8,2.9)	(1.0,3.7)	(2.1,6.3)	(0.9,2.3)	(1.2,3.1)	(1.8,4.5)	(0.5,2.7)	(0.5,3.1)	(0.7,4.7)	(0.6,2.1)	(0.7,2.4)	(0.8,2.5)
Percent Relative Bias	5.25	7.30	8.44	9.61	10.74	10.79	-100.00	-79.29	-46.16	-73.24	-40.90	-28.74
Binary												
FMR	1.49	2	4.02	1.49	2	4	1.13	1.23	1.61	1.11	1.2	1.5
	(0.7,2.7)	(1.0,3.5)	(2.2,7.0)	(0.9,2.4)	(1.2,3.2)	(2.5,6.3)	(0.6,2.8)	(0.6,3.3)	(0.8,4.9)	(0.7,2.1)	(0.7,2.2)	(0.9,3.0)
PMR*	1.25	1.57	2.66	1.3	1.62	2.75	0.72	0.77	0.92	1.12	1.25	1.65
	(0.6,2.3)	(0.8,2.8)	(1.5,4.7)	(0.8,2.1)	(1.0,2.6)	(1.7,4.3)	(0.4,1.6)	(0.4,1.8)	(0.5,2.2)	(0.5,1.6)	(0.6,1.7)	(0.7,2.1)
Percent Relative Bias	-44.04	-34.92	-29.68	-34.21	-30.40	-27.03	-368.79	-226.25	-117.51	8.59	22.39	23.51

* *Applied a modified case definition requiring only one site with CAL ≥6mm for severe or ≥4mm for moderate*

FIGURES

Figure 1. Distribution plots of continuous clinical measures according to concordance between FMR and PMR protocol determinations.

Figure 2. Distribution plots of continuous clinical measures according to concordance between FMR and PMR protocol determinations using modified PMR case definitions.