Prevalence of Periodontitis and Annual Alveolar Bone Loss in a Patient Population at Harvard School of Dental Medicine: a Longitudinal Data Analysis

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"Prevalence of Periodontitis and Annual Alveolar Bone Loss in a Patient Population at Harvard School of Dental Medicine: a Longitudinal Data Analysis"

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Chapter 1:

Background and Significance:

Periodontal diseases are inflammatory diseases of the oral cavity that can be confined only to the gingiva as in gingivitis or exceed beyond that to result in soft and hard tissue loss which would affect the attachment of the teeth to the alveolar bone as in periodontitis.[1] An inflammatory process that has been discussed for decades of its nature, risk factors, and whether it has specific or non-specific etiological factors including the underlying microbiology.[2–5]

It is commonly found as a chronic state of disease that is characterized by slow bursts of progression of varying durations.[6–9] However, other studies are still investigating the fashion of periodontal diseases progression. Emerging evidence suggesting that both theories of progression, linear and burst theories, are manifestations of the same phenomena and occur simultaneously in the same patients.[10,11]

Research continues to define all the factors participating in the initiation and progression of periodontal diseases. Cekici et al published a report in 2015 discussing this particular inflammatory process and the mechanisms behind

its occurrence.[12]

The authors concluded, "*Periodontal diseases are inflammatory diseases in which microbial etiologic factors induce a series of host responses that mediate inflammatory events. In susceptible individuals, dysregulation of inflammatory and immune pathways leads to chronic inflammation, tissue destruction and disease. Physiologic inflammation is a well-orchestrated network of cells, mediators and tissues. It is very important to consider the inflammatory / immune response as a whole, rather than many different modules working separately. As disease appears to be the result of loss of regulation and a failure to return to homeostasis, it is important to achieve a more complete understanding of the molecular and cellular events in this complex system*".

Overall, periodontal diseases have common etiological factors and many risk factors predisposing disease initiation and progression. Periodontal diseases of different types exhibit distinctive etiological and risk factors.[13–15] Many risk factors have been reported in the literature to be associated with periodontal diseases.[16] Several studies found that although periodontitis occurs in most age groups, it is more prevalent in older age groups and seniors.[17–19] Nevertheless, it is still unclear if this increase is due to the

cumulative effect of time or to an increased risk of the diseases itself.[20–23] Ethnicity and racial group also plays a role in the individuals' susceptibility to periodontitis with African Americans as being more susceptible than other racial groups and ethnicities.[16]

Some investigators have suggested that Mexican-Americans have the highest susceptibility to periodontal attachment loss.[24] Many studies have found that men have greater risk than women for advancing periodontal diseases.[17,18] Several studies have also reported that individuals with lower socioeconomic status to be at greater risk of periodontitis.[17,18,25] Studies are still being conducted to determine whether these differences in the susceptibility and distribution to periodontal diseases should be attributed to predisposing genetic factors or other socio-behavioral practices.[26–30]

Other risk factors were reported to be associated with periodontitis including oral hygiene status[21,31], smoking[32–35], and systemic diseases such as diabetes mellitus and cardiovascular diseases.[32,36,37] Evidence suggests that periodontitis and diabetes mellitus have two-way relationship with diabetes increasing the risk for periodontitis, and periodontal inflammation affecting the glycemic control in a negative way.[38] Debates continue on the nature of

the relationship between systemic and periodontal diseases. Lewis et al 2017 published a review discussing the relationship between a number of systemic diseases and periodontitis and concluded that confounding still remains to draw solid inference.[39]

The National Institute of Dental and Craniofacial Research refer to periodontal diseases as the most common cause of tooth loss in adults.[40] Studies have also suggested that periodontal disease is the most common reason for tooth loss. Mandibular incisors are most frequently lost due to periodontal diseases followed by maxillary incisors and molars.[41–45]

In 2013, Marcenes et al published a paper estimating the global burden of oral conditions from 1990 to 2010.[46] In this paper, the disability adjusted life-years (DALYs) were measured, which is the sum of life years lost due to premature death and years lived with disabilities (Figure 1.0).[47] Based on this study, the global burden of oral conditions in 2010 affected nearly 4 billion people. Untreated dental caries of permanent dentition was ranked the first most prevalent condition affecting around 35% of all humans.

Severe periodontitis was ranked the sixth most prevalent condition affecting about 744 million individuals globally. Over this twenty-year period,

DALYs due to severe periodontitis has the highest increase of all oral conditions by 57%. Moreover, severe periodontitis is considered as the primary cause of DALYs in the age group of 35 to 59 year-old and accounted for more than five million DALYs globally implying an average of 108 healthy life years per 100,000 people lost just due to a preventable disease such as severe periodontitis.

Utilization of radiographs as a tool to assess alveolar bone loss/level:

The use of radiographs to assess alveolar bone loss appears frequently in the literature. The rational for using bitewing (BW) radiographs is to minimize angular distortion. Only in BW films does the x-ray beam penetrate perpendicularly through the teeth to the x-ray film or sensor while at the same time being parallel to the occlusal plane. An ideal bitewing radiograph should provide a clear view of the mandibular and maxillary alveolar bone and teeth with minimal overlap of anatomical structures.[48] Radiographic beam angulation has been reported to affect the radiographic measurements by an amount of ±1.6 mm comparing clinical and radiographic alveolar bone crest.[49,50]

The use of non-standardized BW radiographs was reported in the literature to have the ability to detect less than 1 mm alveolar bone change indicating its usefulness for monitoring periodontal diseases progression.[48,51] Studies that have used repeated radiograph measurements of the same sites have found a mean difference of 0.09 mm between the measurements suggesting a 9% discrepancy for repeated radiographs. [52]

Hausmann et al previously conducted intra and inter examiner reliabilities to calibrate two examiners in measuring the distance between the cementoenamel junction and the alveolar crestal bone in digital radiographs, choosing twenty periodontal sites and well-defined reference points. The two examiners produced measurements with a mean difference between readings of 0.34 mm. For repeated measurements, the two examiners would be able to detect a true change of 0.71–0.83 mm in alveolar bone level.[53]

Specific Aims:

The objectives of this study were:

1. Determine the prevalence of periodontitis using bitewings radiographs among the patients enrolled in the clinics at HSDM and addressing risk factors associated with the disease (i.e. sex, age, BMI, etc.).

2. Predict annual alveolar bone loss in a subpopulation of patients with CVD adjusting for associated systemic diseases and risk factors.

3. Predict annual alveolar bone loss in a subpopulation of elderly patients who were taking oral bisphosphonate adjusting for systemic diseases and associated risk factors.

Materials and Methods:

The information technology (IT) team of Harvard University School of Dental Medicine (HSDM) performed a database search of up to 6265 patient records. The database search observed completed comprehensive oral examinations and radiographs (either full mouth series or bitewing radiographs) for each individual patient in any year and a recent visit within the year 2015. No records were collected or reviewed after December 31, 2015. Data gathered from AxiUm®, an electronic health records system at HSDM, including age, gender, body mass index (BMI), chronic medical

conditions (diabetes, hypertension, cardiovascular diseases, etc.), tobacco use, race/ethnicity, as well as each patient's radiographs. The electronic health records did not contain information directly related to socioeconomic status (SES). To estimate SES we collected ZIP codes of all patients. Median income for each zip code was determined using U.S. Census Bureau statistics.[54] The patient pool was selected based on their age at their last appointment at HSDM. One examiner reviewed all 6265 patients and selected 2320 suitable patients for the study.

Exclusion criteria used were: Any patients that were not within the specified age range. Any patient with no BW radiographs. Any radiographs in which the cement-enamel junction (CEJ) and alveolar bone crest were not visible. Any patients who did not have at least two approximating teeth or where the interproximal space was too narrow to observe the bone crest. Presence of dental restorations that obliterate the CEJ, rendering the distance between CEJ and alveolar crest questionable. Any case in which a tooth was found adjacent to an edentulous site with alveolar bone levels greater than 2mm from the CEJ was not considered pathognomonic due to possible surgical trauma. Any records indicating sites receiving osseous surgery or bone grafts were excluded. Third molar teeth were not included due to their tendency of

not being captured by BW radiographs. Non-functional teeth were excluded for the possibility of super eruption.

Alveolar bone loss/level was measured on the mesial and distal sites of first and second mandibular and maxillary premolars and molars using the calibrated measuring tool of Emago® (Oral Diagnostic Systems, Amsterdam, Netherlands) software– the radiographic imaging software at HSDM.

Outcome:

Radiographic indication of interproximal bone loss occurs when the distance between the CEJ and the alveolar bone crest is greater than or equal to 2 mm, as determined on a bitewing radiograph.[55–58] The outcome of our interest was carried out in two major fashions. First, for linear regression, the outcome was analyzed as continuous, while for logistic regression; the outcome was categorized as binary by transforming each site measure into 0 category if the measure did not satisfy the case definition of the disease and 1 if the case definition was satisfied.

Both models of outcome, continuous for linear regression and binary for logistic regressions, were analyzed. The former was used as the primary analysis and the later as secondary analysis and is presented under sensitivity

analysis in the appendix. We also categorized amount of bone loss based on case definition by AAP[58] into mild, moderate, and severe periodontitis to estimate the prevalence of each case definition for descriptive and baseline characteristics. More details for each specific aim analyses are provided under each aim's methodology section.

Predictors:

Age: five categories of age were generated. Age groups of this study were defined as less than thirty-year-old, 30-34 year-old, 35-49 year-old, 50-64 year-old, and 65 or more years old. Reference group for age differed for each specific aim and detailed description of each is provided under each aim's methods section.

Sex: binary variable of sex was coded 1 if the subject was male and 0 if subject was female. Analysis of estimates comparing two sexes used females as reference group.

Race: we generated five categories of race variable based on the reported race of subjects. Categories included White, African American, Asian, Other, and Unknown. Race is self reported and we did not have information

about races that were reported as Other. However, Hispanic race was few (N=21); hence it was coded under Other race category. White race was chosen as reference group for this variable.

BMI: based on the criteria of the Center of Disease Control and Prevention (CDC), BMI was categorized into 4 groups (5 groups in our study including not reported BMI)[59]. Patients were categorized as Underweight if their BMI was lower than 18.5 kg/m^2, Normal Weight if BMI was equal or higher than 18.5 kg/m^2 and lower than 25 kg/m^2, Overweight if BMI was equal or higher than 25 kg/m^2 and lower than 30 kg/m^2, and Obese if BMI was equal or higher than 30 kg/m^2.

Limitations, however, exist for BMI, as a sole indicator for obesity; BMI measurements may be misleading because it is a measure for excess weight not excess body fat. [60] Hence, interpretation of BMI associated estimates to the outcome should be interpreted cautiously. Lastly, Normal Weight group was used as the reference group.

Systemic Diseases:

Medical history of three main systemic diseases was collected from the electronic health records. Systemic diseases included cardiovascular disease

(CVD), hypertension, and diabetes. CVD and diabetes were coded 1 if the patient had the disease and 0 if they had not. The CVD variable was used as the primary predictor for specific aim 2.

For hypertension, we used the new categories by the American College of Cardiology and the American Heart Association[61] to develop four diagnostic categories. Using systolic (SBP) and diastolic (DBP) blood pressure measured for patients, blood pressure was considered *normal* (reference group=1) if the patient had SBP less than 120 mmHg and DBP less than 80 mmHg, *elevated* (=2) if they had SBP equal to or more than 120 mmHg and less than or equal to 129 mmHg & DBP less than 80 mmHg, *stage 1 hypertension* (=3) if the patient had SBP equal to or more than 130 mmHg and less than or equal to 139 mmHg **or** DBP equal to or more than 80 mmHg and less than or equal to 89 mmHg, and *stage 2 hypertension* (=4) if they had SBP equal to or more than 140 mmHg **or** DBP equal to or more than 90 mmHg. Hypertensive crisis, the last new category, was not used in the study. Reference group for all three diseases, CVD, diabetes, and hypertension, was the group of patients that did not have the diseases.

Smoking status:

We generated three categories to describe smoking status. Patients that did not smoke were categorized as never smoker, and patients who reported that they were smoking were categorized as current smoker. Patients who reported that they were smokers and had quit smoking were categorized as former smoker. Never smoker group was used as reference group. It is important to note that we did not have information regarding how many years a patient smoked or how many cigarettes.

Median house income:

Based on the ZIP code for each patient, estimates of house income were collected using U.S. Census Bureau, 2012-2016 American Community Survey 5-Year Estimates.[54] The variable was categorized into either higher than median house income (=1) or lower than median house income (reference=0). Map of ZIP codes was generated using Mapline®; an online map generating software providing users with easy interactive tools to build density maps online based on data imported to the software. This map also helped us to collect house income estimates based on area specific data.

Other variables were included in analysis to adjust for any potential confounding that might exist due to pre existing periodontal diseases or procedures that would affect the outcome of interest. These variables are not primary predictors and their inclusion or removal from analysis depended on how significantly they are associated with the outcome. Treatments and procedures included were gingival flap, bone replacement graft, tissue regeneration, osseous surgery, and scaling and root planing. Table 2.0 presents description of each variable selected.

Oral Bisphosphonate (BIS) intake:

Searching medical history records, we identified patients that reported taking oral BIS to be analyzed for annual bone loss compared to patients that did not take oral BIS. This variable is the primary predictor for specific aim 3.

Sample size:

To determine the adequate sample size, a power calculation was conducted. Assuming an odds ratio of 2.315, and that the prevalence of periodontitis is 36.6% among 35 to 49 years old individuals[24], a sample size of n=450 is adequate to obtain a Type I error rate of 5% and a power greater than 80%. Based on sample size calculation, each age group required a minimum of 90

patients, however, we conducted a random sample of 1300 out of the 2320 patients that were suitable for analysis and exceeded the minimum number of patients in each age category to have larger number of patients in other categories as well since we were also studying risk factors other than age and desired higher number of subjects in other categorical variables included.

During the measurement process for all 1300 patients, 171 patients were excluded either due to their electronic files were closed, or their BW radiographs were not calibrated with the measuring tool. The final number of patients that were included in the analysis was 1131 patients.

Data Analysis:

Descriptive statistics (means and standard deviations for continuous variables, counts and percentages for categorical variables) were calculated. The percentage of subjects with periodontal bone loss was computed for each age bracket.

Statistical significance of the association between age and other predictors and periodontal bone loss was assessed via multiple linear regression. A multiple logistic regression model has also been conducted as secondary

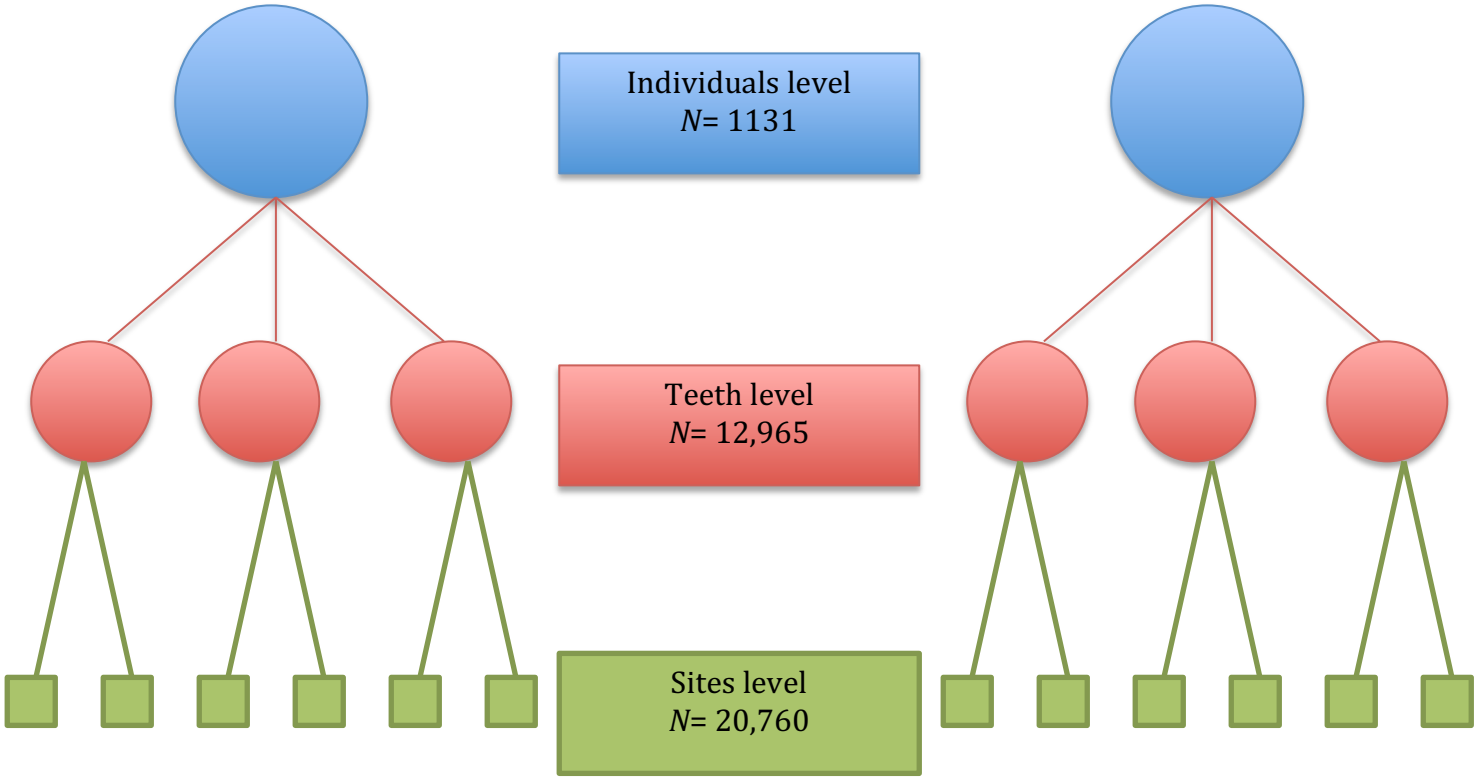
analysis to estimate the odds of developing the disease across different predictors adjusting for other variables.

The amount of annual bone loss was assessed through multi-level liner regression using mixed-effect model to estimate fixed-effect shared by the whole population and random-effect to account for variability between individuals and teeth examined. Multi-level analysis is further explained the next page. P-values less than 0.05 were considered statistically significant. All analyses were conducted using STATA V.14.2 statistical software package.

Multi level mixed effect model:

Sites measured are nested within teeth that are nested within individuals. Fixed-effect model estimates the grand mean of the population (intercept), and random-effect model estimates the standard deviation (variability) of each observation from its nested mean. Estimates of mixed-effect model explained as the following:

Fixed-effect Model	Intercept (grand mean) for whole sample
Random-effect Model	Allows variability between individuals, teeth, and sites
SD Individuals	SD of each individual's mean from the overall grand mean
SD Teeth	SD of each tooth's mean from its individual's mean
SD Sites	SD of each observation (site) from its tooth's mean



Chapter 2:

Calibration and Reliability Study:

Reliability and validity of the measuring tools of any research are factors that are fundamentally important to be achieved to accurately describe observations and results as well as to precisely compare prevalence of diseases and changing trends nationally. Hence, inter and intra examiner reliabilities have been conducted.

Radiographic Discrepancy:

We wanted to measure the expected magnification discrepancy of the x-ray machines that were used to take the radiographs of our sample of interest. A random sample of 22 BW radiographs were selected and measured for the widths of the implants then compared to the true measurements provided by the clinician in the patients' medical records. The mean of radiographic measures was 4.5 (±0.47) while the mean of real measurements provided by the manufacture was 4.36 (±0.49).

We expected an amount of almost 15% magnification error that would affect our measurements. This magnification error was taken into account for generating variables based on periodontal disease case definition. Based on the AAP Task Force Report 2015, the earliest sign of mild periodontitis on

radiographs is to observe bone loss (measured from CEJ to crestal bone) that is equal to or greater than 2 mm and less than or equal to 3 mm without any recommendations about magnification error correction.[58]

We adjusted for this error by incorporating 15% for every 1 mm in case definition variables generated. For instance, if a real measurement from CEJ to crestal bone is 1.8 mm, which is not an indication of mild periodontitis, the radiograph measurement for that site is expected to be 1.8 x 15% = 2.07 mm which might lead to overestimation of the diseases if we used 2 mm as the cutoff. Hence, we generated case definitions of periodontitis based on this expected radiography magnification error and for the example mentioned, a cutoff of 2.3 mm (corrected for radiographic magnification error) would not result in overestimation of the disease.

We also generated periodontitis case definition based on the recommendation by AAP Task Force Report 2015 and compared the two cut-offs for sensitivity and false positive rate (Figure 2.0). The two cut-offs did not significantly differ and more details and test statistic are provided in the appendix.

Intra- and Inter-Examiners Calibration:

According to Fleiss in his book The Design and Analysis of Clinical Experiments [62], conducting a calibration study can be carried out by choosing 20 subjects randomly from the whole sample. However, the two examiners of the study assessed BW radiographs for 80 patients by measuring the alveolar bone level from the most coronal point of the crestal bone to the most apical point of the CEJ both on the mesial and distal surfaces of posterior teeth with the measuring ruler being parallel to the root of each surface of each site. The measurements were repeated one week later with the initial reading being blinded. To achieve a high consistency, each examiner repeated the measurements until we achieved a high degree of agreement between the readings of the same set.

Further, inter-examiner reliability test was conducted to eliminate the possibility of chance agreement. Two-way random-effects[63] intra class correlation coefficient (ICC) test was performed to check both intra- and inter-examiner reliabilities using STATA V.14.2 statistical software. ICC agreement is interpreted as poor if it scores less than 0.40, fair between 0.40 to 0.59, good between 0.60 to 0.74, and excellent if it scores between 0.75 and 1.00.[64]

Examiner 1 (MH), had 0.92 agreement (95% CI 0.87 – 0.95) for repeated individual measurements and 0.96 (95% CI 0.93 – 0.97) for averages agreement for intra-examiner reliability comparing the first and second times measurements of alveolar bone level for the mesial site of tooth number 3 for the same subset.

Examiner 2 (HH), had an agreement of 0.92 (95% CI 0.86 – 0.95) for individual measurements and 0.96 (95% CI 0.92 – 0.97) for averages agreement for the same variable. We also had excellent agreement for inter-examiner reliability between the two examiners. For example, consistency of agreement for inter-examiner reliability comparing the alveolar bone level measurement on the mesial site of tooth number 3 is 0.86 (95% CI 0.78 – 0.92) for individual measurements and 0.93 (95% CI 0.87 – 0.95) for average agreement for the same subset.

We have reached even higher agreement, for instance, ICC score comparing the two examiners alveolar bone level measurement on the distal site of tooth number 13 is 0.96 (95% CI 0.92 – 0.97) for individual measurements and 0.98 (95% CI 0.95 – 0.98) for averages agreement for the same subset. Table 1.0 presents results and randomly selected teeth for calibration testing.

Chapter 3:

Aim 1:

Prevalence of periodontitis using bitewings radiographs among the patients enrolled in the clinics at HSDM and risk factors associated with the disease

Introduction:

Several studies have reported the prevalence of periodontitis in the United States. Dye et al published a paper in 2007 manifesting the trends of oral health in United States.[17] The study was based on data analyses of the National Health and Nutrition Examination Survey (NHANES). Comparison was made between NHANES III (1988-1994) and NHANES 1999-2004.

The overall prevalence of moderate/severe periodontitis was estimated to be 5% of all individuals from the age of 20 to 64 years old in NHANES 1999-2004 compared to 10% of the same age group in NHANES III. While it was almost 28% for seniors 65 years of age or older in NHANES III compared to 17% in NHANES 1999-2004 for the same age group.

However, prevalence of attachment loss greater than or equal to 3 millimeters, which can capture less severe periodontitis, affected nearly 42% and 37% of all individuals from the age of 20 to 64 years old in NHANES III and NHANES 1999-2004 respectively. For seniors 65 years of age or older, however, it was almost two folds higher for both periods.

In 2015, Eke et al published a paper using NHANES data from 2009-2012 finding that 46% of adults 30 years of age or older have periodontitis representing almost 65 million people with nine percent having sever periodontitis.[18] A second paper from this group was published in 2016 measuring the prevalence of periodontitis for seniors 65 years of age or older.[19] The overall prevalence of periodontitis was 66% for all seniors 65 years of age or older with males to be more significantly affected by severe periodontitis (16%) compared to females (6%). Periodontitis was mainly addressed in the literature, as mentioned earlier, to be more prevalent and most associated with older age groups[17–19], males [17,18], African American [16] and Mexican American [24] race groups, lower socioeconomic status [17,18,25], poor oral hygiene [21,31], smoking [32–35], and systemic diseases such as diabetes mellitus and cardiovascular diseases[32,36,37].

Specific Aim:

The objective of this study was to measure the prevalence of periodontitis using BW radiographs among the patients enrolled in the clinics at HSDM

and address risk factors associated with the disease to compare them to predisposing factors reported in the literature and whether similarities exist.

Methods:

Method section under each specific aim focuses on specific changes related to that aim of interest. Methodology of all aims is overall similar and was discussed earlier in chapter 1. A total number of 1131 patients were eligible for radiography analysis. Alveolar bone level on mesial and distal sites of posterior teeth was measured for all 1131 patients on BW radiographs that were taken from January 1, 2014 to December 31, 2015.

Statistical Analyses:

Mixed-effect linear regression model was chosen to estimate the amount of bone loss/level across different age groups and other predictors. The distribution of the primary outcome showed skewedness to the right (Figure 1.1) with multiple outliers that were detected by graphing a box plot (Figure 2.1). After restricting on outliers, the distribution approximated normality (Figure 3.1 and 4.1).

We tested for linearity by conducting simple linear regression model using age as primary predictor. We noticed that the distribution around the regression line before restricting outliers showed fan shaped which could violate linearity (Figure 5.1). After restricting on outliers, the distribution around the regression line exhibited a more symmetrical pattern (Figure 6.1). Figure 7.1 illustrates the normal distribution found in residuals.

Residuals of the regression model were plotted against fitted values to check for homoscedasticity. Figure 8.1 shows a violation of homoscedasticity by fanning out, and after restricting on outliers, the plotted residuals versus fitted values showed no fanning and no pattern was observed across the fitted values (Figure 9.1). Moreover, we can notice the lack of data points in the upper right and lower left corners and that is explained by the restricted range of possible values (outliers restriction) and is not indicative of heteroscedasticity.

The model with no restriction for outliers was used for sensitivity analysis and is presented in the appendix. Moreover, we have also conducted non-parametric analyses using Wilcoxon Mann-Whitney-rank-sum test and Kruskal-Wallis rank test and the results were similar compared to its

parametric counterparts. This type of analysis, comparing non-parametric to parametric tests was also used as part of the sensitivity analysis for this study. Sensitivity analysis with different tests is shown in the appendix.

We have also conducted kurtosis statistics to assess the model reproducibility of outliers and had a test statistic equals to 3.3 and a p-value = 0.0681. An ideal value of kurtosis is 3, however the value we had was 3.3, it is still platykurtic which means that the distribution produced fewer and less extreme outliers than a normal distribution does.

Using mixed-effect model, we are measuring the fixed-effect of the primary predictors, that is assumed to be shared by all individuals in the sample, as well as the random-effects between individuals, teeth, and sites that respond differently to our primary predictors. We also used logistic regression model as secondary analysis to estimate the odds ratio of developing mild/severe periodontitis across different predictors. The criteria of developing this binary outcome for logistic regression are discussed below under primary outcomes.

Primary predictors:

Independent variables of this study included age, sex, race, median house income, body mass index, and smoking status. We also included periodontics procedures and treatments codes (Table 2.0) and kept only the code of scaling and root planing as it was the only significant and most frequent code received by patients. Other variables were included in the model such as the history of diabetes, CVD, and hypertension to adjust for any confounding by them.

Age was categorized into 5 different groups. Age groups were less than 30-year-old (reference group), 30-34, 35-49, 50-64, and 65+ years old. The cut off points of the groups were chosen as supported by the literature by multiple studies[17,24,65] to enhance comparisons of our study to others. Sex, race, and smoking variables were included in the model based on the characteristics describes in Chapter 1.

Median House Income had a bimodal distribution (Figure 10.1). Categorizing it to 4 different groups based on its interquartile ranges resulted in very few to none observations in 2 out of the 4 categories. Hence, the predictor was transformed into a binary one by scoring 1 if house income

was higher than the median of the population, or zero if house income was lower than the median of the population.

BMI was obtained as a continuous variable but was transformed into a categorical variable to enhance results by adjusting for outliers and also to give a more accurate estimate of different cut points of Body Mass Index that is used by legitimate organizations such as the Center of Diseases Control and Prevention.[59]

Procedure code D434 is used by the clinicians at the school to indicate performing a procedure of scaling and root planning for 4 teeth or more for their patients. We included it in the model to adjust for patients who had higher risk or active disease of periodontal tissues. Other codes provided in Table 2.0 were checked for frequencies and after including them in the analysis model, we found that D4341 is the only one that had a significant influence on the outcome of interest and was included in the final model of analysis.

Primary outcomes:

Our primary outcome is the level of alveolar bone on mesial and distal sites of posterior teeth as a continuous variable. We also used this variable to develop binary variables based on case definition of periodontitis by the AAP for each case definition of mild, moderate, and severe periodontitis and were used to estimate proportions and prevalence of these conditions among all study subjects.

A binary outcome was assigned as 0 for the group that had no sign of bone loss or mild periodontitis, and as 1 for the group that had moderate or severe periodontitis for logistic regression model. This logistic regression model was used as a secondary analysis and it is provided in the appendix.

Results:

Descriptive statistics (Univariate Analysis):

In descriptive statistics, the term bone level will be used as a description of the readings.

A total of 1131 individuals were included in the analysis with a mean alveolar bone level of 1.30 mm (±0.006). Mean bone level ranged between 0.77 mm (±0.006) to 2.04 mm (±0.019) across the different age groups. 55%

of the sample was composed of females with a mean bone level of 1.26 mm (±0.008) compared to 45% males with a mean bone level of 1.34 (±0.009).

White race composed 36.5% of the sample, followed by Other (22.1%), Unknown (20.5%), African American (9.0%), and Asian (7.5%). 55% of the sample had higher house income than the median of the sample with a bone level that equals to 1.28 mm (±0.007) compared to 1.32 mm (±0.009) for individuals with lower than median house income. Areas of highest and lowest median house income are presented in Figure 11.1 and Figure 12.1 respectively. 60% of the sample consisted of never smokers, with only 7% who were currently smoking, and 12.5% who were former smokers. Table 1.1 presents descriptive statistics for the whole sample. Table 2.1 lists areas from where 60% of the patients who are visiting clinics at HSDM are coming from.

Severity of the disease and proportions of case definitions:

Overall mild periodontitis prevalence for the sample was 55.5% (±1.4%). Moderate periodontitis prevalence was 20.7% (±1.2%), while 2.8% (±0.5%) of the whole sample had severe periodontitis. All three case definitions were highest among 65+ year-old, males, former smokers, having CVD, and stage

2 hypertension subjects. More detailed prevalence of each case definition across different groups is presented in Table 1.1. Furthermore, Figure 13.1 illustrates prevalence of mild, moderate, and severe periodontitis across different age groups and gender and Figure 14.1 presents mean alveolar bone level in millimeters over age groups and gender as well.

Linear regression:

The term bone loss will be used in bivariate and multi-variable analysis to describe the amount of change of bone level across different predictors.

Unadjusted estimates (Bivariate Analysis):

Bivariate analysis was carried out to assess the unadjusted estimates of bone levels with the primary predictors. Individuals for age group 65+ exhibited highest bone loss of 1.27 mm (95% CI: 1.23, 1.31. P-value <0.001) compared to the reference group of individuals aged less than thirty-year-old. Males had 0.08 mm (95% CI: 0.05, 0.10. P-value <0.001) higher bone loss compared to females. For different race groups, Asian race had the highest amount of bone loss compared to White race (reference) of 0.13 more mm (95% CI: 0.09, 0.18. P-value <0.001) followed by African American race of an estimate of bone loss equals to 0.06 mm (95% CI: 0.01, 0.10. P-value =0.006).

Individuals who had higher than median house income had had -0.04 mm (95% CI: -0.06, -0.02. P-value =0.001) compared to individuals who had lower than median house income. Using normal weight category as a reference, obese category of BMI had 0.21 mm (95% CI: 0.17, 0.25. P-value <0.001) more bone loss. Comparing current smokers to never smokers, current smokers had 0.21 mm (95% CI: 0.17, 0.26. P-value <0.001) higher bone loss. However, former smokers had the highest amount of bone loss equals to 0.52 mm (95% CI: 0.48, 0.56. P-value <0.001). Table 3.1 presents detailed estimates of bivariate analysis.

Model Selection for multi-variable analysis:

To choose our multi-variable analysis model, Likelihood ratio test (LRT) was used to nest reduced model of predictors in full model to describe whether reduced model adequately describes the data. Reduced model contained all predictors with no interaction terms to check for any influence on the outcome by effect measure modification between predictors. Full model included all variables we wanted to assess, as well as terms of interaction to check for effect measure modifications.

We found a significant interaction between BMI and median house income that affected our outcome of interest. The null hypothesis of LRT is that reduced model adequately describes the data. The test statistic was 10.64 with 4 degrees of freedom and a p-value = 0.0310. At 0.05 level of significance, we concluded that the reduced model does not adequately describe the data and the interaction term is needed.

Adjusted estimates (Multi-variable Analysis):

Almost all variables included in the multi-variable model kept their significant association with the outcome except for African American race, diabetes, CVD, and hypertension. Mean increase in bone loss compared to age group of less than 30-year-old, was 0.20 mm (95% CI: 0.10, 0.30. P-value <0.001) for 30-34-year-old, 0.43 mm (95% CI: 0.36, 0.50. P-value <0.001) for 35-49-year-old, 0.87 mm (95% CI: 0.79, 0.95. P-value <0.001) for 50-64-year-old, and 1.09 mm (95% CI: 0.99, 1.18. P-value <0.001) for 65+ year-old, adjusting for sex, race, house income, BMI, smoking, reported CVD, Diabetes, and Hypertension. Almost all other estimates changed after adjusting for other covariates.

The overall significance for groups stayed the same as older age groups had increased amount of bone loss compared to younger age groups. Males had higher amount of bone loss than females (Mean difference = 0.096 mm [95% CI: 0.04, 0.14. P-value <0.001]), Asian race had higher bone loss compared to White race (Mean difference = 0.23 mm [95% CI: 0.13, 0.33. P-value <0.001]), and higher house income was also associated with reduced amount of bone loss compared to lower house income (Mean difference = -0.06 mm [95% CI: -0.11, -0.007. P-value <0.026]). For BMI on the other hand, the association had been reduced to be not significant for all categories except for obese group as it showed a significant decline in bone loss compared to normal weight group equals to -0.13 mm (95% CI: (-0.22)-(-0.04). P-value = 0.003).

We introduced interaction terms to assess any effect measure modification between BMI and other covariates. We did not find any significant interactions except for median house income and BMI and it showed a decreased amount of bone loss for obese group who also had higher than median house income (Mean difference = -0.25 mm [95% CI: -0.38, -0.12. P-value <0.001]). Finally, smoking status exhibited similar association as the bivariate analysis except for current smokers having higher amount of bone loss as it exceeded with few fractions former smokers which also had higher

amount of bone loss compared to never smokers. Provided in Table 4.1 more details of each adjusted mean change in bone level (bone loss) for all variables included in the analysis.

For the random effect part, we found that estimates (mean change) vary between individuals and teeth by 0.164 mm (95% CI: 0.15, 0.18) and 0.066 mm (95% CI: 0.060, 0.072), respectively. Random-effect coefficients are also provided in Table 4.1.

Discussion:

Many studies have been conducted to estimate prevalence of periodontal diseases in United Sates.[17,18,31] Our results are in agreement with similar prevalence of periodontal diseases among different groups that exhibit specific features and risk factors to periodontal diseases. A study conducted by Eke et al in 2012 to evaluate the prevalence of periodontitis in adults in 2009-2010 showed that older age groups have a higher risk and proportion of periodontal diseases compared to younger age groups.[24] Our results indicate that males have a higher risk of developing periodontal diseases for their significantly higher alveolar bone loss compared to females and this

result coincides with similar results reported in literature indicating males having higher risk of developing the disease.[17,24]

Many studies have reported that smoking is a primary predictor of periodontal diseases.[14,35,65] In our study, current and former smokers had increased risk of bone loss compared to never smokers (Table 4.1). Although we did not have any information about the duration of smoking, how many cigarettes, or what type of tobacco, the overall conclusion is that patients in our study who were ever smokers had higher amount of bone loss compared to never smokers.

Defining demographics for our population is a main characteristic of primary data analysis. We used subjects ZIP codes to generate a map to illustrate the pool from which we had our subjects drawn from (Map 1.1-7.1).

Subjects with higher than median house income were associated with 0.06 mm lower rate of bone loss compared to subjects with lower than median house income (95% CI: -0.11, -0.007). P-value=0.026). Observations of higher risk to periodontal diseases to poverty and low house income were reported in multiple studies in the literature.[17,33] Our results showed

significant reduction in bone loss also for individuals who were categorized as obese using BMI.

Notwithstanding the limitations of BMI, we further analyzed this observation to check for any misclassification. Since median house income was the only variable that was associated with decreased risk of bone loss, we created different interaction terms between median house income variable and different predictors. We found that subjects who were obese with higher than median house income had 0.25 mm lower rate of bone loss (95% CI: -0.38, -0.12. P-value<0.001) compared to individuals who had normal weight and low house income.

This observation suggests that subjects with addressed risk factors would have better health and less adverse outcomes if they had had more income to afford better access to the health care system.

Different case definitions of recording periodontal diseases result in different estimates that would complicate comparison between studies. Many studies have discussed the methodologies used for reporting periodontal diseases. It has been suggested that the prevalence of periodontitis is influenced by the recording protocols, and the case definitions of periodontal diseases.[66] Various indices and protocols of measuring periodontal diseases (probing depth, gingival recession, attachment loss, and severity of inflammation) were used in previous studies, which resulted in different readings of the prevalence of the diseases.[31,67–74] Hence, complexities may arise comparing results between studies.

Our study exhibits limitations. Focusing on posterior teeth using BW radiographs only, due to the angulation discrepancy that might arise in periapical radiographs for anterior teeth compared to BW radiographs, is considered as partial mouth periodontal examination (PMPE). PMPE showed tendencies to underestimate prevalence of periodontal diseases when compared to full mouth examination protocol (FMPE).[66,75] Furthermore, BW radiographs have a limitation in detecting craters, furcation involvements, and different angular defects[76,77] which would result in underestimating the prevalence of the diseases.

Conclusion:

Although limitations exist in our study, results of this study indicate that different predictive factors have different risks of the progression of periodontal diseases. Primary factors that were associated with higher rate of bone loss were older age, male, Asian racial group, and smoking. Moreover, access to healthcare, dental or medical in general, can be an important factor in determining the severity and prevalence of diseases. Our results show that individuals with high house income had lower prevalence of periodontal diseases and lower amount of bone loss compared to individuals with low house income.

This manifestation of protective effect by high house income on the amount of bone loss can be powerful to the degree that high house income can influence the outcome even for individuals who had higher risk of developing the disease.

Chapter 4:

Aim 2:

Predict annual alveolar bone loss in a subpopulation of patients with CVD adjusting for associated systemic diseases and risk factors

Introduction:

Many studies have been conducted to address the relationship between periodontal diseases and cardiovascular diseases. In 2008, Humphrey et al published a systematic review and meta-analysis based on seven cohort studies that revealed significant association between periodontitis and the incidence of coronary heart disease.[37] Authors of the study concluded that the summary relative risk estimates for different categories of periodontal diseases (including gingivitis, periodontitis, bone loss, and tooth loss), to develop coronary heart disease, ranged from 1.24 to 1.34 (95% CI: 1.01-1.63).

Moreover, DeStefano et al, found that patients with more progressive periodontitis had 25% higher risk of developing coronary heart disease compared to patients that had less progression of periodontitis.[78] Several studies have been conducted as well not to just assess the association or relationship between the two diseases, but also to investigate and understand the underlying inflammatory responses shared by periodontal diseases and cardiovascular diseases.

A cohort study on men was conducted using joined data from the Normative Aging Study and the Dental Longitudinal Study between 1968 and 1971.[79] The study hypothesized that periodontitis and coronary heart disease share same predisposing factors that might put individuals at higher risk of developing both of the diseases.

This manifestation of periodontal diseases was not only confined in patients with cardiovascular diseases, but further with other systemic diseases. In 2006, a study published by Al-Emadi et al found that individuals with moderate and severe periodontitis have higher prevalence of diabetes and hypertension.[80] These observations suggest that patients with systemic diseases such as diabetes and CVD pose a higher risk of developing periodontitis.

In 1986, Albandar et al published a 2-year longitudinal study that was conducted on 180 subjects that did not receive any periodontal procedures or treatments. Mean alveolar bone level was measured using radiographs over the two-year period and found that the total amount of bone loss detected for the whole population was 0.11 mm.[9]

Moreover, studies on the natural progression of periodontal diseases in general populations, either clinical or radiographic, have estimated a mean annual clinical and radiographic bone loss equals to 0.05 mm.[81,82] Another study, by Onabolu et al, estimated a radiographic mean alveolar bone loss of 0.2 mm – 0.3 mm per year after following 858 proximal sites over 6 years.[83]

Methods:

The sample of aim 2 was drawn from the main sample of 1131 patients used in aim 1. We identified all subjects that reported having CVD from 2008 – 2015 (N=132). We examined the electronic health records of each patient to identify suitable radiographs for analysis. Exclusion criteria were similar to the ones mentioned in Chapter 1.

For longitudinal data analysis, we required that eligible subjects for inclusion to have at least two exposures of CMS or repeated BW radiographs with at least one-year interval. We identified 58 patients that satisfied these criteria. This group is the exposure group; patients who reported having CVD. 100 subjects of control group were also randomly sampled from the main sample with the condition that everyone included to be free of CVD. After examining each patient's electronic health records, a

total of 87 patients were identified and their BW radiographs were suitable for examination and analysis.

Radiographs of a total of 145 patients (58 reported having CVD, 87 without CVD) were analyzed over a two-year period. The number of patients with suitable radiographs had decreased to a total of 70 patients with radiographs that are suitable for analysis after four years (21 with CVD, 49 without CVD).

27 out of the 87 subjects in the control group had reported having diabetes, hypertension, or both. Table 1.2 presents frequency of systemic diseases over the CVD and no CVD groups. No other diseases were reported in the control group. We conducted two analyses, one with all 87-control subjects and one restricted to 60 individuals who were free of all diseases. The two analyses did not differ in terms of significance since we were controlling for diabetes and hypertension. The whole sample of 145 subjects was used as the main analysis while the restricted one (N=118) is shown in the appendix for minor changes in the estimates.

Statistical Analyses:

Analyses for specific aim 2 were carried out in similar fashion of specific aim 1. Mixed-effect linear regression model with multi-level design has been conducted to estimate the difference of change in mean bone level in mm. Moreover, we included the time term to the model to assess the amount of change across the years of follow up.

Primary predictor:

The main difference in this specific aim is that our primary predictor was whether the subjects had cardiovascular diseases (CVD) or not. Other variables were included in the model to adjust for any type of confounding expected. These variables included age, sex, race, BMI, median house income, smoking status, diabetes, and hypertension. The criteria identifying each variable were similar to the criteria described in chapter 1. However, specific aim 2 included fewer subjects per age group, therefore, subjects 34 years of age and younger were joined together and this category was used as reference group.

Large number of patients did not have their SBP and DBP measured or reported. Hence, hypertension was treated as CVD and diabetes based on the reported condition by the patient at their visit by coding it 1 if the patient had hypertension and 0 if they had not. Also due to small numbers in each

category, we created binary smoking variable for analysis by coding everyone who have ever smoked as ever smoker (=1) and those who had never smoked as never smoker (=0). Treatment codes for patients who received scaling and root planning were included in the model to adjust for preexisting periodontitis.

Primary outcome:

The primary outcome is the difference of mean alveolar bone level in millimeters between the group that were having CVD and the group that were free of any CVD, comparing mean bone levels at follow up visits to baseline mean of both groups. AAP case definitions of periodontitis severity were also used to create mild, moderate, and severe periodontitis variables to estimate the prevalence of each one for descriptive statistics and analysis.

Results:

Descriptive statistics of baseline characteristics (Univariate Analysis):

In descriptive statistics, the term bone level will be used as a description of the readings.

A total of 145 subjects were included for analysis. Mean total alveolar bone level was 1.49 mm (±0.015). Mean age of the sample was almost 71-year-old (Ranged from 18-94) with 63% of the subjects being females (Table 2.2).

65+ year-old patients had the highest reading of alveolar bone level compared to any other age groups. Almost half of the sample was White with bone level of 1.61 mm (±0.021). 50% of the subjects have never smoked and only seven individuals who were reported as current smokers. Table 3.2 presents all groups included with their measured mean bone levels.

Severity of the disease and proportions of case definitions:

Overall mild periodontitis prevalence for the sample was 71.7% (±3.7%) while moderate periodontitis prevalence was almost 27% (±3.6%). Severe periodontitis was the least prevalent by an estimate of 2.7% (±1.3) for the whole sample (Table 3.2). Mild and moderate periodontitis were higher among the free of CVD group compared to the group with CVD; however, severe periodontitis was higher in the CVD group (Table 2.2). Moderate and severe periodontitis were higher among individuals with lower than median house income (Figure 1.2).

Unadjusted estimates overtime (Bivariate Analysis):

The term bone loss will be used to describe the amount of change of bone level between the two groups in this bivariate and the following multi-variable analyses.

Our results indicated that over two-year period, the group without CVD had 0.044 mm more bone loss compared to baseline (95% CI: 0.014, 0.075. P-value = 0.004) that increased to 0.120 mm (95% CI: 0.081, 0.159. P-value < 0.001) after 4 years compared to baseline. On the other hand, the group with CVD had experienced higher bone loss on both occasions of follow up compared to the group without CVD.

After two years, CVD group had 0.122 mm more bone loss (difference) compared to the group without CVD (95% CI: 0.072, 0.172. P-value < 0.001) and 0.130 mm (95% CI: 0.061, 0.200. P-value < 0.001) difference in bone loss after four years compared to the group without CVD. Table 4.2 presents the estimates at baseline and over time.

Adjusted estimates overtime (Multi-variable Analysis):

Estimated difference in means did not change drastically after controlling for other variables. After the two-year interval, the group without CVD had 0.044 mm more bone loss compared to baseline (95% CI: 0.014, 0.075. P-value = 0.004) that increased to 0.121 mm (95% CI: 0.021, 0.160. P-value < 0.001) after 4 years compared to baseline, controlling for age, sex, race, house income, BMI, smoking status, diabetes, hypertension.

On the other hand, the group with CVD had experienced higher bone loss on both occasions of follow up compared to the group without CVD. The group of patients with CVD had 0.121 mm more bone loss compared to the group without CVD (95% CI: 0.071, 0.172. P-value < 0.001) after two years and 0.130 mm (95% CI: 0.060, 0.199. P-value < 0.001) more bone loss after four years compared to the group without CVD, adjusting for all other variables included in the model.

Table 5.2 presents the estimates at baseline and over time, in addition to the adjusted estimates of all other variables. The variables that were significantly associated with our primary outcome (bone loss) were age, house income, smoking, and hypertension. House income also showed a significant interaction with hypertension with protective effect on bone loss.

Figure 2.2 presents the change of bone loss comparing CVD group to no CVD group over the four-year period of time. 60% of CVD group received periodontal treatments while 38% of no CVD received periodontal treatments (Table 6.2).

Random-effect estimates:

For the random effect part, we found that estimates (mean change) vary between individuals and teeth by 0.13 mm (95% CI: 0.10, 0.17) and 0.12 mm (95% CI: 0.10, 0.13), respectively. Random-effect coefficients are also provided in Table 5.2.

Discussion:

Our results support that individuals with CVD have a higher risk of bone loss and periodontal diseases in general. Multiple studies found similar results and associations were observed between both diseases.[78,79,84]

Furthermore, C-reactive protein (CRP), a protein that its level increases in acute inflammation, was also reported in literature to be associated with periodontitis and cardiovascular diseases that can put patients at higher risk of developing the disease or to worsen the condition.[85–87] In 2003, moreover,

Saito et al found that alveolar bone loss of posterior teeth was significantly associated with increased levels of CRP.[88]

Another observation was reported in 2005 by Buhlin et al after conducting a study to evaluate oral heath of 143 age-matched women indicating that women with coronary heart disease had more pathological periodontal pockets and vertical bone defects compared to control group of women who did not have history of coronary heart diseases and concluded that women with coronary heart disease had worse oral health in general compared to the control group[89]

Regardless of the significant increase in bone loss in the CVD group compared to no CVD group over time, our results also showed that at baseline the two groups did not have statistically significant difference comparing their mean alveolar bone levels. This can be a result of normal variation since the control group was randomly selected. However, CVD group showed higher prevalence of severe periodontitis at baseline (Table 1.2) compared to no CVD group, which may also add more risk of bone loss to the CVD group over time.

Although several studies in the literature reported an association between hypertension and periodontal diseases[80,90,91], we found that hypertensive patients, who were living in areas where median house income was high, having lower bone loss compared to individuals who were living in areas where median house income was low (Table 5.2).

This is also supporting to the observation we had in aim 1, that is individuals with high house income experienced lower difference in mean bone loss, which may indicate that access to healthcare system plays an important role by reducing the adverse effect of the outcome even among individuals who have predisposing conditions that put them at higher risk of the disease.

Nevertheless, limitations exist in this study. First, data were collected using partial mouth periodontal examination and therefore would result in underestimating the true rate of bone loss. Second, after following all patients over two years interval, 48% of the total sample was lost due to lack of radiographs. However, the difference between CVD group to no CVD group after two years (=0.121. CI: 0.021-0.160. P-value<0.001) was not extremely far from the difference between CVD group to no CVD group after four years (=0.131. CI: 0.060-0.199. P-value<0.001).

Incompleteness of data can be categorized into three main types. Missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).[92] MCAR is a benign incompleteness that does not have specific cause of incompleteness and the outcomes of missing data can be considered as a random sample of all outcomes and can be ignored totally.

However, MCAR holds strong assumptions that are often very difficult to maintain in the real world. MAR, on the other hand, depends on observable variables other than unobserved ones (i.e. there is a known cause for incompleteness that depends on observable information). MAR is also ignorable incompleteness (after taking the cause of MAR into account). The third type of incompleteness is MNAR; missing data is dependent on unobserved information. MNAR is a non-ignorable missingness and can result in biased estimates.

Incompleteness of data in our study could have happened due to two reasons. One, clinician at that given visit did not take BW radiographs for the patient, which would result in MAR. Or two, the patient did not show up due to unobserved information such as associated morbidity or mortality to CVD, which would result in MNAR.

Mixed-effect models have the ability to account for MAR but not for MNAR and hence two models were conducted as part of the sensitivity analysis, one for complete data for all 145 patients that were followed for two years only and is presented in the appendix, and the other for all patients followed over four years (main analysis used in this study) with time variable specified in the model to estimate the difference at two points, one at the two years interval, and the other at the four years interval.

We decided to choose the later model since estimates at the two years interval did not differ between the two models emphasizing that estimates after four years may be biased due to the fewer number of patients in both groups.

Conclusion:

CVD patients had higher rate of annual bone loss compared to patients who did not have any CVD. This observation indicates that targeting high-risk patients for risk assessment is fundamental to provide the best healthcare possible to those who are the most in need. Periodic examination and assessment of periodontal health is essential for everyone, however, it has to

be more emphasized and prioritized for individuals that are more prone to the diseases.

It is also apparent that socioeconomic status plays a very important role in determining the severity of periodontitis. This would suggest an inequality of access to healthcare. However, preventive measures can be implemented. Reaching out to communities with low socioeconomic status and establishing preventive care centers can help in reducing adverse outcomes of the disease. An assessment of healthcare centers in low socioeconomic status areas is required to address this observation.

Collaborations between clinicians and public health professionals are essential to establish and maintain optimal clinical care and community awareness by successfully implementing treatments and approaches to control or even eliminate preventable chronic diseases such as periodontitis.

Chapter 5:

Aim 3:

Predict annual alveolar bone loss in a subpopulation of elderly patients who were taking oral bisphosphonate adjusting for systemic diseases and associated risk factors

Introduction:

Although several studies raised the question of whether increased alveolar bone loss is a natural consequence of aging,[20,22,23] higher prevalence of periodontitis and bone loss in general, have been consistently addressed and reported in the literature to be associated with aging.[17,19,93]

Periodontitis was also reported in the literature to be associated with age-related diseases such as osteoporosis especially in postmenopausal women.[94–96] In 2018, Mashalkar et al published a study on postmenopausal women to investigate the correlation between periodontitis and osteoporosis.[97] Authors of the study concluded that there was significant association between osteoporosis in postmenopausal women and the severity of periodontitis.

Multiple studies also assessed the effect of bisphosphonate (BIS) administration on alveolar bone loss.[98–100] Bisphosphonates were introduced to clinical practice decades age.[101,102] They are structurally related to inorganic pyrophosphate, as they contain a core phosphate-carbon-phosphate structure with highest affinity for the bone relative to other tissues. Bisphosphonates inhibit enzymatic degradation, hinder calcification and

suppress bone resorption. They are utilized in conditions where there is an imbalance between osteoblast-mediated bone formation and osteoclast bone resorption.

Bisphosphonates are the mainstay of therapy for skeletal disorders, particularly osteoporosis due to skeletal remodeling because they achieve high concentration to active bone remodeling sites such as conditions with accelerated skeletal turnover.[101–103] They increase the density of the bone, reduce markers of bone turnover and ultimately reduce fractures.[101] In addition, bisphosphonates are utilized to resolve hypercalcemia among cancer patients.[101–103] Other clinical implications include; primary hyperparathyroidism, osteogenersis imperfecta and paget's disease of bone.[103]

Due to its marked efficacy in prevention of bone loss in susceptible populations, alendronate (generic name of BIS) had been proposed as a useful agent to prevent alveolar bone loss.[104] One systematic review assessed 8 clinical studies that evaluated the efficacy of bisphosphonate therapy in the management of periodontitis, particularly as an adjunct to scaling and root planing.[105] Alendronate was utilized as either a topical application or oral

therapy option. The study concluded that there was a statically significant reduction in probing depth and bone defect suggesting the clinical effectiveness of bisphosphonate in the management of periodontitis.

Another group investigated the potential outcomes of alendronate among postmenopausal women with periodontal disease.[106] Postmenopausal women are at highest risk for osteoporosis due to estrogen deficiency. Authors of the study concluded that oral alendronate improved periodontal health and alveolar bone turnover in postmenopausal women.

Moreover, El-Shinnawi et al in 2003 published a clinical trial on 24 adults with periodontitis that had been followed for six months.[107] 12 patients were administered oral alendronate and were compared to a control group that did not receive any drug. Although clinical parameters (attachment level, pocket depth, and gingival index) of the alendronate group showed no difference compared to the control group, alendronate group showed significant change in bone density compared to the control group, favoring patients who received oral bisphosphonate.

Methods:

The sample of this aim was drawn from the main sample of 1131 patients used in aim 1. We identified all subjects that reported receiving oral BIS from 2008 – 2015 (N=30). We examined the electronic health records of each patient to identify suitable radiographs for analysis. Exclusion criteria were similar to those discussed in Chapter 1.

For longitudinal data analysis, we required that eligible subjects for inclusion to have at least two exposures of CMS or repeated BW radiographs with at least one-year interval. We identified 26 patients out of the 30 identified earlier that satisfied these criteria. This group is the exposure group; patients who reported taking oral BIS. The 26 patients who were taking BIS were then matched on age and sex to another 26 patients who did not report receiving BIS at any point of their life. Radiographs of a total of 52 patients (26 patients of each group) were analyzed over a two-year period.

Statistical Analyses:

Analyses for this aim were carried out in similar fashion of the previous two aims. Mixed-effect linear regression model with multi-level design has been

conducted to estimate the difference of change in mean bone level in mm. We included the time term to the model to assess the amount of change across the years of follow up for both groups.

Primary predictor:

The main difference in this specific aim is that our primary predictor was whether the subjects had reported taken oral BIS or not. Other variables were included in the model to adjust for any type of confounding expected. Theses variables included age, sex (although we did not expect any confounding by age or sex since the two groups were matched on them, we included them to account for any residual confounding), race, median house income, smoking status, diabetes, and hypertension. The criteria identifying each variable were similar to the criteria of specific aim 1 and 2. However, the population of this sample was older and the youngest subject was 57-year-old, hence, age was used as a continuous predictor. Furthermore, the numbers across the 5 groups were scarce; hence we categorized BMI into two groups of Underweight/Normal weight and Overweight/Obese with the former group as the reference group.

Large number of patients did not have their SBP and DBP measured or reported. Hence, hypertension was coded based on the reported condition by the patient at their visit by coding it 1 if the patient reported a history of hypertension and 0 if they had not.

In this sample, no one had reported as being current smoker so we created binary smoking variable for analysis by coding everyone who have ever smoked (former smoker) as ever smoker (=1) and those who had never smoked as never smoker (=0).

Primary outcome:

The primary outcome is the difference of mean alveolar bone level in millimeters between the group that were taking oral BIS and the group that were not, comparing mean bone level measurements at the follow up visits to the baseline mean of both groups. Same case definition criteria of periodontitis severity used in previous aims were also used to create mild, moderate, and severe periodontitis variables to estimate the proportion of each for descriptive statistics and analysis.

Results:

Descriptive statistics of baseline characteristics (Univariate Analysis):

In descriptive statistics, the term bone level will be used as a description of the readings.

A total of 52 matched subjects were included for analysis. Subjects' age ranged between 57 to 88 years old. Mean age of the sample was almost 71-year-old (±0.19) with 92% of the subjects being females (Table 1.3). BIS group mean alveolar bone level at baseline was 1.90 mm (±0.040) and 1.99 mm (±0.036) for the group who are not taking BIS. 54% of the sample was White. Table 2.3 presents different racial groups and other predictors with their measured mean bone levels. 21% of the subjects were former smokers and none of the subjects have reported themselves as current smokers.

Severity of the disease and proportions of case definitions:

Overall mild periodontitis prevalence for the sample was 94.2% (±3.2%) while moderate periodontitis prevalence was 50% (±7.0%). Severe periodontitis was the least prevalent by an estimate of 7.7% (±3.7) for the whole sample (Table 2.3). Mild periodontitis was higher in the BIS group compared to the no BIS group; however, moderate periodontitis was higher in the no BIS group (Table 1.3). Moderate and severe periodontitis were also

higher among individuals with lower than median house income (Figure 1.3).

Unadjusted estimates overtime (Bivariate Analysis):

The term bone loss will be used to describe the change of bone level between the two groups in this bivariate and the following multi-variable analyses.

After the two-year interval, the group with no history of receiving oral BIS did not experience significant change in mean bone level. On the other hand, the BIS group had experienced 0.087 mm mean bone loss after two years with marginally statistical significance compared to the group with no BIS intake baseline (95% CI: -0.0002, 0.175. P-value = 0.051). Table 3.3 presents the bivariate analysis and its unadjusted estimates of mean bone loss at baseline and over time.

Adjusted estimates overtime (Multi-variable Analysis):

Since subjects were matched on age and sex, we did not expect adding these two variables to the model would affect the outcome significantly. However, we included them to control for any residual confounding by age or sex.

None of the variables included in the model showed significant association with the outcome. For the group who did not take oral BIS, change over time was not significant after the two-year period. However, BIS group had experienced 0.088 mm more bone loss compared to no BIS group (95% CI: 0.001, 0.176. P-value = 0.048), adjusting for all other variables included in the model. Table 4.3 presents the estimates at baseline and over time, in addition to the estimates of all other variables. Figure 2.3 presents the change of bone loss comparing BIS group to no BIS group over the two-year period of time. Although it does not achieve statistical significance, we can notice a reduction of the mean alveolar bone loss for no BIS group over time. A possible explanation of this observation is that the no BIS group received double the number of periodontal treatments (scaling and root planing) compared to BIS group (Table 5.3).

Random-effect estimates:

For the random effect part, we found that estimates (mean change) vary between individuals and teeth by 0.14 mm (95% CI: 0.10, 0.17) and 0.12

mm (95% CI: 0.10, 0.13), respectively. Random-effect coefficients are also provided in Table 4.3.

Discussion:

Results of this study indicate that, after two years of follow up, oral administration of BIS did not have a protective effect on the mean alveolar bone loss. Although a recent systematic review and meta-analysis on the effect of BIS used as an adjunctive treatment of periodontal diseases indicated beneficial effect of BIS administration, the authors concluded that due to short periods of follow up in the eight studies identified in the literature, as well as the potential adverse effect of BIS in the oral cavity– osteonecrosis of the jaws, its use as an adjunctive treatment for managing periodontal diseases is debatable.[105]

Another study, that was not included in the previously mention systematic review, was published by Jeffcoat et al in 2007 to investigate the effectiveness of oral alendronate.[100] 335 patients were randomized into two groups of alendronate and no drug groups and were followed over 24 months. After two years of follow up, the group receiving oral alendronate

did not show any significant change in either alveolar bone density or alveolar bone loss compared to the control group.

Only patients that were having low mandibular bone mineral density at baseline showed significant reduction of bone loss compared to control group. The authors of the study concluded that administering oral alendronate over two years for patients with periodontitis had no effect on alveolar bone loss except for the subpopulation of patients who had low mandibular bone mineral density.

Although studies that examined the effect of oral BIS disagreed on its effect on periodontal health,[98–100,104,106] route of administration may play an integral role of the effectiveness of bisphosphonate on alveolar bone loss.

Local delivery of 1% alendronate gel was also examined on patients with aggressive periodontitis, a more severe form of periodontal disease,[108] and diabetic patients with chronic periodontitis, a systemic disease with higher risk of developing periodontal diseases,[109] as an adjunct to scaling and root planing for the treatment of intrabony defects. The researchers of both studies found a significant reduction in probing depth, greater gain of

clinical attachment level, and bone reforming of intrabony defects. Moreover, an animal study conducted by Price et al, found that local delivery of a simvastatin-alendronate-β-cyclodextrin was statistically associated with reduced bone loss as a consequence of periodontitis.[110]

Limitations of this study are similar to limitations of the two previous aims; partial mouth periodontal examination would result in underestimating the true change in mean bone loss. However, we did not have missing outcomes related to loss to follow up (lack of radiographs); all 52 patients were followed for two years. Nevertheless, the sample size was relatively small having only 26 patients in each group. Moreover, the BIS group maybe exhibited underlying factors affected their bone biology and resulted in an increased risk of bone loss that was observed even on this small group of patients.

Conclusion:

Bisphosphonate medications are indicated for several bone related diseases. In our study, we found that the group who reported receiving oral bisphosphonates showed no improvement in maintaining alveolar bone

level– on the contrary, our results suggest that the use of oral BIS may not be effective in reducing annual alveolar bone loss.

Route of administration of bisphosphonate, on the other hand, could play an important role for its effectiveness to be achieved. Emerging evidence of several studies indicate that local delivery of bisphosphonate can help in maintaining periodontal health and alveolar bone level for patients who are more prone to the disease.

Chapter 6:

Overall Conclusion:

Several predictors included in our study showed significant association with mean alveolar bone level changes. Of theses predictors, older age (65+ years old), male, Asian racial group, and smoking experience have had the highest prediction of increased annual mean alveolar bone loss. However, median house income was significantly associated with decreased annual mean alveolar bone loss. This effect of high house income protectively influenced the association of other risk factors that were reported to put the patient at higher risk of periodontal diseases such as obesity and hypertension.

Furthermore, patients who reported having cardiovascular diseases experienced higher annual mean alveolar bone loss (0.062 mm per year) compared to patients with no cardiovascular diseases (0.022 mm per year). The best quality of healthcare is fundamental right to every human being, however, patients with conditions that put them at increased risk that might jeopardize their well being is further more necessary to maintain.

Finally, we did not find any protective effect of oral bisphosphonate on the annual mean alveolar bone loss, however, emerging evidence is promising

for the use of bisphosphonate as an adjunctive local delivery medication for management of periodontal diseases.

Public health professionals and clinicians collaboration is a mandate to achieve and sustain high quality of healthcare for everyone. Addressing and evaluating areas with low house income for further investigation is necessary to attain and sustain equality of access to the healthcare system.

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Tables:

Table 1.0 Intra and inter examiner reliability

Examiner	Site/Tooth	ICC Individual (95% CI)	ICC Average (95% CI)	P value
Intra M	M3	0.92 (0.87-0.95)	0.96 (0.93-0.97)	P < 0.0001
Intra H	M3	0.92 (0.86-0.95)	0.95 (0.92-0.97)	P < 0.0001
Inter M & H	M3	0.80 (0.68-0.87)	0.88 (0.81-0.93)	P < 0.0001
Inter M & H	D13	0.95 (0.92-0.97)	0.97 (0.95-0.98)	P < 0.0001

Table 2.0 Count of procedures and periodontal treatment codes for the whole sample (*N*=1131)

Code	Description	N (%)
D4240	Gingival flap for four teeth or more	**1 (0.09)**
D4241	Gingival flap for one to three teeth	**1 (0.09)**
D4260	Osseous surgery for four teeth or more	**1 (0.09)**
D4261	Osseous surgery for one to three teeth	**7 (0.6)**
D4263	Bone replacement graft	**32 (2.83)**
D4265	Biologic materials – tissue regeneration	**24 (2.12)**
D4266	Guided tissue regeneration	**2 (0.18)**
D4341	Scaling/root planing for 4 teeth or more	**76 (6.72)**
D4342	Scaling/root planing for 1-3 teeth	**97 (8.58)**

Table 1.1 Prevalence of mild, moderate, and severe periodontitis among different groups of patients visiting HSDM

		Percentage (%)[§]							
	N (%)	Mild[§]	SE	Moderate[§]	SE	Severe[§]	SE	Mean Bone Level (mm)	SE

Total	1131 (100.0)	55.5	1.4	20.7	1.2	2.8	0.5	1.30	0.006
Age Groups (yrs)									
< 30	247 (21.8)	17.0	2.3	1.2	0.7	0.0	n/a	0.77	0.006
30-34	108 (9.5)	33.3	4.5	3.7	1.8	0.9	0.9	0.90	0.012
35-49	305 (27.0)	51.8	2.8	12.7	1.9	1.9	0.8	1.24	0.010
50-64	300 (26.5)	80.6	2.2	37.3	2.8	4.3	1.1	1.80	0.013
65+	171 (15.1)	86.5	2.6	44.5	3.8	7.0	1.9	2.04	0.019
Gender									
Male	508 (44.9)	57.0	2.2	24.1	1.9	4.3	0.9	1.34	0.009
Female	623 (55.1)	54.1	1.9	18.0	1.5	1.6	0.5	1.26	0.008
Race									
White	413 (36.5)	56.1	2.4	20.3	1.9	2.6	0.7	1.30	0.009
African American	100 (8.8)	53.0	5.0	27.0	4.4	9.0	2.8	1.36	0.028
Asian	85 (7.5)	62.3	5.2	29.4	4.9	1.1	1.1	1.43	0.020
Other	250 (22.1)	58.0	3.1	20.0	2.5	1.6	0.7	1.29	0.012
Unknown	283 (25.0)	48.2	3.2	15.1	2.3	3.0	1.1	1.24	0.013
Median House Income									
Lower than median	510 (45.1)	55.1	2.2	22.1	1.8	3.9	0.8	1.32	0.009
Higher than median	621 (54.9)	55.5	1.9	19.4	1.6	1.9	0.5	1.28	0.007
Body Mass Index									
Underweight	27 (2.4)	18.5	7.6	11.1	6.1	0.0	n/a	0.92	0.031
Normal	413 (36.5)	52.5	2.4	19.1	1.9	2.6	0.8	1.23	0.009
Overweight	263 (23.2)	60.8	3.0	23.2	2.6	2.2	0.9	1.40	0.013
Obese	137 (12.1)	59.1	4.2	23.4	3.6	3.6	1.6	1.45	0.021
Not reported	291 (25.7)	56.0	2.9	20.3	2.3	3.4	1.0	1.30	0.011
Smoking Status									
Never smoker	668 (59.0)	49.5	1.9	15.8	1.4	2.3	0.6	1.19	0.007
Former smoker	141 (12.4)	70.2	3.8	41.1	4.1	4.2	1.7	1.72	0.021
Current Smoker	82 (7.2)	58.5	5.4	19.5	4.4	2.4	1.70	1.41	0.023
Not Reported	240 (21.2)	61.6	3.1	22.5	2.7	3.3	1.1	1.38	0.013
Diabetes									
Yes	60 (5.3)	75.0	5.6	40.0	6.3	6.7	3.2	1.81	0.038
No	1071 (94.7)	54.2	1.5	19.6	1.2	2.6	0.5	1.28	0.006
CVD									
Yes	132 (11.7)	79.5	3.5	32.6	4.1	3.0	1.5	1.66	0.020
No	999 (88.3)	52.1	1.5	19.1	1.2	2.8	0.5	1.26	0.006
Hypertension									
Normal	346 (30.6)	46.8	2.6	15.6	1.9	1.4	0.6	1.18	0.009
Elevated	157 (13.9)	54.1	3.9	21.6	3.2	3.8	1.5	1.35	0.016
Stage 1	281 (24.9)	59.7	2.9	24.5	2.5	2.1	0.8	1.37	0.012
Stage 2	125 (11.0)	70.4	4.1	31.2	4.1	8.0	2.4	1.61	0.023

Not reported	222 (19.6)	55.4	3.3	17.1	2.5	2.2	0.9	1.23	0.013

Table 2.1 Procedures and periodontal treatment codes

City	N	%	Cum %
Cambridge	92	8.95	8.95
Boston	89	8.66	17.61
Brookline	67	6.52	24.12
Somerville	36	3.5	27.63
Dorchester	34	3.31	30.93
Brighton	31	3.02	33.95
Jamaica Plain	31	3.02	36.96
East Boston	24	2.33	39.3
Malden	21	2.04	41.34
Lynn	20	1.95	43.29
Revere	20	1.95	45.23
Everett	18	1.75	46.98
Roslindale	18	1.75	48.74
Roxbury Crossing	18	1.75	50.49
Dorchester Center	17	1.65	52.14
Hyde Park	16	1.56	53.7
Quincy	14	1.36	55.06
Chelsea	13	1.26	56.32
Allston	12	1.17	57.49
Arlington	12	1.17	58.66
Chestnut Hill	12	1.17	59.82
Quincy	11	1.07	60.89

Table 3.1 Unadjusted mean alveolar bone loss (mm) with different predictors included (bivariate analysis)

Variables	Unadjusted MABL (mm)*	95% CI	*p*-value
Age Groups (yrs)			
< 30 (reference)			
30-34	0.22	(0.18-0.26)	< 0.001
35-49	0.47	(0.44-0.50)	< 0.001
50-64	1.03	(1.01-1.06)	< 0.001

65+	1.27	(1.23-1.31)	< 0.001
Gender			
Female (reference)			
Male	0.08	(0.05-0.10)	< 0.001
Race			
White (reference)			
African American	0.06	(0.01-0.10)	0.006
Asian	0.13	(0.09-0.18)	< 0.001
Other	-0.004	(-0.03-0.02)	0.786
Unknown	-0.05	((-0.08)-(-0.02))	0.001
Median House Income*			
Low (reference)			
High	-0.04	((-0.06)-(-0.01))	0.001
Body Mass Index**			
Underweight	-0.30	((-0.38)-(-0.23))	< 0.001
Normal (reference)			
Overweight	0.16	(0.13-0.19)	< 0.001
Obese	0.21	(0.03-0.09)	< 0.001
Smoking Status			
Never smoker (reference)			
Former smoker	0.52	(0.48-0.56)	0.009
Current Smoker	0.21	(0.17-0.26)	< 0.001
Diabetes			
No (reference)			
Yes	0.53	(0.47-0.59)	< 0.001
Hypertension			
Normal (reference)			
Elevated	0.166	(0.12-0.20)	< 0.001
Stage 1	0.186	(0.15-0.21)	< 0.001
Stage 2	0.422	(0.37-0.46)	< 0.001
CVD			
No (reference)			
Yes	0.40	(0.36-0.44)	< 0.001

N= 1131 patients (20,760 sites from 12,965 teeth)
*Mean alveolar bone loss in millimeter

Table 4.1 Adjusted mean alveolar bone loss (mm) with different predictors included in the model (multi-variable analysis)

Variables	Adjusted MABL (mm)*	95% CI	*p*-value
Age Groups (yrs)			
< 30 (reference)			
30-34	0.20	(0.11-0.30)	< 0.001
35-49	0.43	(0.36-0.50)	< 0.001
50-64	0.87	(0.79-0.95)	< 0.001
65+	1.09	(0.99-1.18)	< 0.001
Gender			
Female (reference)			
Male	0.096	(0.04-0.14)	< 0.001
Race			
White (reference)			
African American	0.003	(-0.09-0.10)	0.949
Asian	0.23	(0.13-0.33)	< 0.001
Other	0.08	(0.01-0.15)	0.024
Unknown	0.016	(-0.05-0.08)	0.641
Median House Income*BMIcat			
Low Underweight	0.05	(-0.22-0.32)	0.709
Low Normal (reference)			
Low Overweight	-0.02	(-0.12-0.08)	0.659
Low Obese	-0.07	(-0.19-0.05)	0.241
HIgh Underweight	-0.22	((-0.442)-(-0.009))	0.041
High Normal	-0.04	(-0.13-0.03)	0.272
High Overweight	-0.15	((-0.25)-(-0.05))	0.004
High Obese	-0.25	((-0.38)-(-0.12))	< 0.001
Smoking Status			
Never smoker (reference)			
Former smoker	0.154	(0.07-0.23)	< 0.001
Current Smoker	0.157	(0.05-0.25)	0.002
Diabetes			
No (reference)			
Yes	0.020	(-0.10-0.14)	0.742
Hypertension			
Normal (reference)			
Elevated	0.063	(-0.019-0.14)	0.137

Stage 1	-0.012	(-0.08-0.06)	0.739
Stage 2	-0.008	(-0.10-0.08)	0.860
CVD			
No (reference)			
Yes	0.013	(-0.07-0.10)	0.757
D4341**			
No (reference)			
Yes	0.21	(0.10-0.31)	< 0.001
Random effect			
Between Individuals	0.164	(0.15-0.18)	n/a
Between Teeth	0.066	(0.060-0.072)	n/a
Between Sites	0.17	(0.16-0.17)	n/a

N= 1131 patients (20,760 sites from 12,965 teeth)
*Mean alveolar bone loss in millimeter
** Scaling and root planing for 4 teeth or more code.

Table 1.2 Systemic diseases distribution between the two groups

Distribution of systemic diseases among CVD group N(%)						
Group	**Only CVD**	**CVD+Diabetes**	**CVD+Hypertension**	**C+D+H***	**Free of all**	**Total**
CVD	19 (32.7)	1 (1.7)	31 (53.5)	7 (12.1)	0 (0)	58 (100)
Distribution of systemic diseases among control group N(%)						
	CVD	**Diabetes**	**Hypertension**	**D+H****	**Free of all**	**Total**
Control	0 (0)	13 (15)	13 (15)	1 (1)	60 (69)	87(100)

N= 145 patients
*The patient has CVD, diabetes, and hypertension
**The patient has diabetes and hypertension

Table 2.2 Prevalence of mild, moderate, and severe periodontitis comparing both groups of patients at baseline

	Percentage (%)§											
	N (%)	**Mean Age**	**SE**	**Age Range**	**Females§**	**SE**	**Mild§**	**SE**	**Moderate§**	**SE**	**Severe§**	**SE**
Total	145 (100)	71.7	3.7	18-94	63.4	0.7	71.7	3.7	26.9	3.6	2.7	1.3
CVD												
Yes	58 (40)	64.8	0.3	29-94	58.6	1.1	70.6	6.0	20.6	5.3	3.4	2.4

No	87 (60)	58.3	0.2	18-78	66.7	0.9	72.4	4.8	31.0	4.9	2.3	1.6

Table 3.2 Descriptive statistics and prevalence of mild, moderate, and severe periodontitis of the whole sample at baseline

		Percentage (%)[§]							
	N (%)	Mild[§]	SE	Moderate[§]	SE	Severe[§]	SE	MABL (mm)*	SE
Total	145 (100)	71.7	3.7	26.9	3.6	2.7	1.3	1.49	0.015
Age Groups (yrs)									
< 30	3 (2)	0.0	n/a	0.0	n/a	0.0	n/a	0.53	0.039
30-34	2 (1.4)	0.0	n/a	0.0	n/a	0.0	n/a	0.57	0.072
35-49	22 (15.2)	31.8	10.1	4.5	4.5	0.0	n/a	1.09	0.023
50-64	63 (43.4)	74.6	5.5	20.6	5.1	1.5	1.5	1.49	0.022
65+	55 (38)	90.9	3.9	45.4	6.7	5.4	3.1	1.81	0.027
Gender									
Male	53 (36.5)	67.9	6.4	24.5	5.9	1.8	1.8	1.42	0.026
Female	92 (63.5)	73.9	4.6	28.2	4.7	3.2	1.8	1.54	0.019
Race									
White	75 (51.7)	82.6	4.4	32.0	5.4	4.0	2.2	1.61	0.021
African American	9 (6.2)	77.8	14.7	22.3	14.7	0.0	n/a	1.42	0.059
Asian	7 (4.8)	85.7	14.2	42.8	20.2	0.0	n/a	1.71	0.087
Other	21 (14.5)	47.6	11.1	19.0	8.7	0.0	n/a	1.20	0.035
Unknown	33 (22.7)	64.7	11.9	17.6	9.5	0.0	n/a	1.38	0.030
Median House Income									
Low	57 (39.3)	70.1	6.1	36.8	6.4	3.5	2.4	1.53	0.027
High	88 (60.7)	72.7	4.7	20.4	4.3	2.3	1.6	1.47	0.018
Body Mass Index									
Underweight	2 (1.4)	100.0	0.0	50.0	50.0	0.0	n/a	1.86	0.116
Normal	35 (24.1)	71.4	7.7	34.2	8.1	5.7	3.9	1.57	0.031
Overweight	37 (25.5)	67.5	7.8	21.6	6.8	0.0	n/a	1.48	0.031
Obese	33 (22.7)	63.6	8.5	18.2	6.8	3.0	3.0	1.33	0.031
Not reported	38 (26.2)	81.5	6.3	31.6	7.6	2.6	2.6	1.56	0.031
Smoking Status									
Never smoker	75 (51.7)	64.0	5.5	16.0	4.2	1.3	1.3	1.32	0.019
Former smoker	16 (11)	87.5	8.5	56.2	12.8	6.2	6.2	1.97	0.078
Current Smoker	7 (4.8)	85.7	14.2	42.8	20.2	0.0	n/a	1.68	0.053
Not reported	47 (32.4)	76.6	6.2	32.0	6.8	4.2	2.9	1.60	0.027
Diabetes									
Yes	22 (15.2)	68.1	10.1	9.1	6.2	4.5	4.5	1.34	0.042
No	123 (84.8)	72.3	4.0	30.0	4.1	2.4	1.4	1.52	0.016

CVD									
Yes	58 (40)	70.6	6.0	20.6	5.3	3.4	2.4	1.45	0.024
No	87 (60)	72.4	4.8	31.0	4.9	2.3	1.6	1.52	0.020
Hypertension									
Yes	52 (35.9)	63.4	6.7	19.2	5.5	3.8	2.7	1.44	0.027
No	93 (64.1)	76.3	4.4	31.1	4.8	2.1	1.5	1.52	0.018

*Mean alveolar bone level in millimeters

Table 4.2 Unadjusted mean alveolar bone loss (mm) for both groups over time

Variables	Unadjusted MABL (mm)*	95% CI	*p*-value
Year*CVD			
0 * No CVD (reference)			
2 * No CVD	0.044	(0.014-0.075)	0.004
4 * No CVD	0.120	(0.081-0.159)	< 0.001
0 * CVD+	-0.010	(-0.192-0.172)	0.911
2 * CVD+	0.122	(0.072-0.172)	< 0.001
4 * CVD+	0.130	(0.061-0.200)	< 0.001

N= 145 patients (6,945 sites from 1,923 teeth)
*Mean alveolar bone loss in millimeter

Table 5.2 Adjusted mean alveolar bone loss (mm) for both groups over time

Variables	Adjusted MABL (mm)*	95% CI	*p*-value
Year*CVD			
0 No CVD (reference)			
2 No CVD	0.045	(0.014-0.075)	0.004
4 No CVD	0.121	(0.021-0.160)	< 0.001
0 CVD+	-0.022	(-0.187-0.141)	0.784
2 CVD+	0.121	(0.071-0.172)	< 0.001
4 CVD+	0.131	(0.060-0.199)	< 0.001

Age Groups (yrs)			
<= 34 (reference)			
35-49	0.408	(0.01-0.80)	0.044
50-64	0.889	(0.50-1.27)	< 0.001
65+	1.161	(0.76-1.56)	< 0.001
Gender			
Female (reference)			
Male	0.026	(-0.12-0.17)	0.720
Race			
White (reference)			
African American	0.026	(-0.261-0.314)	0.854
Asian	0.129	(-0.19-0.45)	0.429
Other	-0.123	(-0.33-0.09)	0.263
Unknown	-0.082	(-0.25-0.08)	0.348
Median House Income (before interaction)			
Low (reference)			
High	-0.157	((-0.305)-(-0.009))	0.037
Body Mass Index			
Underweight	0.026	(-0.26-0.31)	0.854
Normal (reference)			
Overweight	0.129	(-0.19-0.45)	0.429
Obese	-0.123	(-0.33-0.09)	0.263
Smoking Status			
Never smoker (reference)			
Ever smoker	0.237	(0.037-0.4371)	0.020
Diabetes			
No (reference)			
Yes	-0.140	(-0.35-0.07)	0.194
Median House Income*Hypertension			
Low Not Hypertensive (reference)			
Low Hypertensive	-0.126	(-0.36-0.11)	0.294
High Not Hypertensive	-0.110	(-0.29-0.07)	0.244
High Hypertensive	-0.361	((-0.58)-(-0.13))	0.002
Hypertension (before interaction)			
No (reference)			
Yes	-0.195	((-0.36)-(-0.02))	0.024
D4341**			
No (reference)			
Yes	0.283	(0.07-0.49)	0.007
Random effect			
Between Individuals	0.13	(0.10-0.17)	n/a
Between Teeth	0.12	(0.10-0.13)	n/a

Between Sites	0.20	(0.19-0.21)	n/a

N= 145 patients (6,945 sites from 1,923 teeth)
*Mean alveolar bone loss in millimeter
** Scaling and root planing for 4 teeth or more code.

Table 6.2 Proportion of patients received periodontal procedures including scaling and root planing comparing CVD and no CVD groups

		N(%)	
Code	**Description**	**CVD=1**	**CVD=0**
D4240	Gingival flap for four teeth or more	0 (0)	0 (0)
D4241	Gingival flap for one to three teeth	1 (1.7)	0 (0)
D4260	Osseous surgery for four teeth or more	0 (0)	0 (0)
D4261	Osseous surgery for one to three teeth	3 (5.17)	0 (0)
D4263	Bone replacement graft	4 (6.9)	5 (5.7)
D4265	Biologic materials – tissue regeneration	2 (3.4)	4 (4.6)
D4266	Guided tissue regeneration	0 (0)	0 (0)
D4341	Scaling/root planing for 4 teeth or more	9 (15.5)	12 (13.8)
D4342	Scaling/root planing for 1-3 teeth	16 (27.6)	12 (13.8)
None		23 (39.6)	54 (62)
Total		58 (100)	87 (100)

N= 145 patients

Table 1.3 Prevalence of mild, moderate, and severe periodontitis comparing both groups of patients at baseline

					Percentage (%)[§]							
	N	**Mean Age**	**SE**	**Age Range**	**Females[§]**	**SE**	**Mild[§]**	**SE**	**Moderate[§]**	**SE**	**Severe[§]**	**SE**
Total	52	70.8	0.19	57-88	92.3	0.6	94.2	3.2	50.0	7.0	7.7	3.7
BIS												
Yes	26	70.9	0.3	57-88	92.3	0.9	96.1	3.8	38.4	9.7	7.7	5.3
No	26	70.7	0.3	57-87	92.3	0.9	92.3	5.3	61.5	9.7	7.7	5.3

Table 2.3 Descriptive statistics and prevalence of mild, moderate, and severe periodontitis of the whole sample at baseline

		Percentage (%)[§]							
	N	Mild[§]	SE	Moderate[§]	SE	Severe[§]	SE	MABL (mm)*	SE
Total	52 (100)	94.2	3.2	50.0	7.0	7.7	3.7	1.94	0.027
Age Groups (yrs)									
< 30	0	0.0	n/a	0.0	n/a	0.0	n/a	0.00	n/a
30-34	0	0.0	n/a	0.0	n/a	0.0	n/a	0.00	n/a
35-49	0	0.0	n/a	0.0	n/a	0.0	n/a	0.00	n/a
50-64	14 (26.9)	100.0	0.0	50.0	13.8	7.1	7.1	2.02	0.050
65+	38 (73.1)	92.1	4.4	50.0	8.2	7.9	4.4	1.91	0.032
Gender									
Male	4 (7.7)	100.0	0.0	25.0	25.0	0.0	n/a	1.76	0.067
Female	48 (92.3)	93.7	3.5	52.1	7.2	8.3	4.0	1.96	0.029
Race									
White	28 (53.9)	96.4	3.5	53.5	9.6	7.1	4.9	1.98	0.035
African American	1 (1.9)	100.0	0.0	100.0	0.0	0.0	n/a	2.45	0.232
Asian	6 (11.5)	100.0	0.0	83.3	16.6	33.4	21.1	2.19	0.106
Other	4 (7.7)	100.0	0.0	25.0	25.0	0.0	n/a	1.50	0.074
Unknown	13 (25)	88.9	11.1	33.4	16.7	0.0	n/a	1.83	0.047
Median House Income									
Low	16 (30.7)	87.5	8.5	68.7	11.9	12.5	8.5	2.08	0.051
High	36 (69.3)	97.2	2.7	41.7	8.3	5.5	3.8	1.88	0.031
Body Mass Index									
Underweight	2 (3.8)	100.0	0.0	100.0	0.0	0.0	n/a	2.29	0.119
Normal	18 (34.6)	100.0	0.0	50.0	12.1	5.6	5.6	1.91	0.043
Overweight	10 (19.2)	80.0	13.3	30.0	15.2	10.0	10.0	1.68	0.064
Obese	4 (7.7)	75.0	25.0	25.0	25.0	0.0	n/a	1.57	0.070
Not reported	18 (34.6)	100.0	0.0	61.1	11.8	11.1	7.6	2.16	0.048
Smoking Status									
Never smoker	13 (25)	84.6	10.4	46.1	14.4	7.7	7.7	1.73	0.047
Former smoker	11 (21.1)	100.0	0.0	45.5	15.7	18.2	12.2	2.05	0.064
Current Smoker	0	0.0	n/a	0.0	n/a	0.0	n/a	0.0	n/a
Not reported	28 (53.9)	96.4	3.5	53.5	9.6	3.5	3.5	2.0	0.037
Bisphosphonate intake									
Yes	26 (50)	96.1	3.8	38.4	9.7	7.7	5.3	1.90	0.040

No	26 (50)	92.3	5.3	61.5	9.7	7.7	5.3	1.99	0.036
Diabetes									
Yes	2 (3.9)	100.0	0.0	0.0	n/a	0.0	n/a	1.54	0.102
No	50 (96.1)	94.0	3.4	52.0	7.1	8.0	3.8	1.95	0.027
CVD									
Yes	15 (28.9)	93.4	6.6	40.0	13.1	6.7	6.7	1.91	0.048
No	37 (71.1)	94.6	3.7	54.0	8.3	8.1	4.5	1.95	0.032
Hypertension									
Yes	35 (67.3)	94.1	5.8	35.3	11.9	11.7	8.0	1.85	0.047
No	17 (32.7)	94.2	3.9	57.1	8.4	5.7	3.9	1.98	0.033

*Mean alveolar bone level in millimeters

Table 3.3 Unadjusted mean alveolar bone loss (mm) for both groups over time

Variables	Unadjusted MABL (mm)*	95% CI	*p*-value
Year*BIS			
0 No BIS (reference)			
2 No BIS	-0.027	(-0.08-0.03)	0.383
0 BIS+	-0.059	(-0.27-0.15)	0.594
2 BIS+	0.087	(-0.0002-0.175)	0.051

N= 52 patients (XXX sites from 658 teeth)
*Mean alveolar bone loss in millimeter

Table 4.3 Adjusted mean alveolar bone loss (mm) for both groups over time

Variables	Adjusted MABL (mm)*	95% CI	*p*-value
Year*BIS			
0 No BIS (reference)			
2 No BIS	-0.027	(-0.08-0.03)	0.374
0 BIS+	0.084	(-0.16-0.033)	0.515
2 BIS+	0.088	(0.001-0.176)	0.048
Age (continious yrs)			

1 year increase	-0.002	(-0.016-0.012)	0.764
Gender			
Female (reference)			
Male	-0.312	(-0.830-0.204)	0.236
Race			
White (reference)			
African American	0.476	(-0.244-1.198)	0.195
Asian	0.092	(-0.246-0.432)	0.591
Other	-0.289	(-0.708-0.129)	0.176
Unknown	-0.108	(-0.348-0.130)	0.373
Median House Income*			
Low (reference)			
High	-0.153	((-0.405)-0.098)	0.233
Body Mass Index**			
Underweight/Normal (reference)			
Overweight/Obese	-0.235	(-0.476-0.004)	0.055
Smoking Status			
Never smoker (reference)			
Former smoker	0.153	(-0.199-0.505)	0.394
Current Smoker	n/a	n/a	n/a
CVD			
No (reference)			
Yes	0.133	(-0.165-0.433)	0.381
Hypertension			
No (reference)			
Yes	-0.118	(-0.388-0.150)	0.388
D4341			
No (reference)			
Yes	0.113	(-0.169-0.396)	0.433
Random effect			
Between Individuals	0.14	(0.10-0.17)	n/a
Between Teeth	0.12	(0.10-0.13)	n/a
Between Sites	0.21	(0.19-0.22)	

N= 52 patients (2,307 sites from 658 teeth)
*Mean alveolar bone loss in millimeter

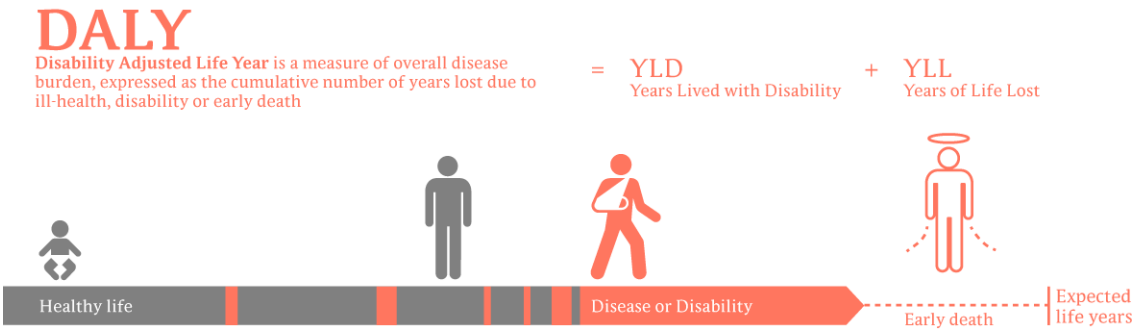
Table 5.3 Proportion of patients received periodontal procedures including scaling and root planing comparing BIS and no BIS groups

		N(%)	
Code		**BIS=1**	**BIS=0**
D4240	Gingival flap for four teeth or more	0 (0)	0 (0)
D4241	Gingival flap for one to three teeth	0 (0)	0 (0)
D4260	Osseous surgery for four teeth or more	0 (0)	0 (0)
D4261	Osseous surgery for one to three teeth	2 (7.7)	0 (0)
D4263	Bone replacement graft	3 (11.5)	4 (15.4)
D4265	Biologic materials – tissue regeneration	3 (11.5)	3 (11.5)
D4266	Guided tissue regeneration	1 (3.8)	0 (0)
D4341	Scaling/root planing for 4 teeth or more	2 (7.7)	6 (23)
D4342	Scaling/root planing for 1-3 teeth	6 (23)	10 (38.4)
None		9 (34.6)	3 (11.5)
Total		26 (100)	26 (100)

N= 52 patients

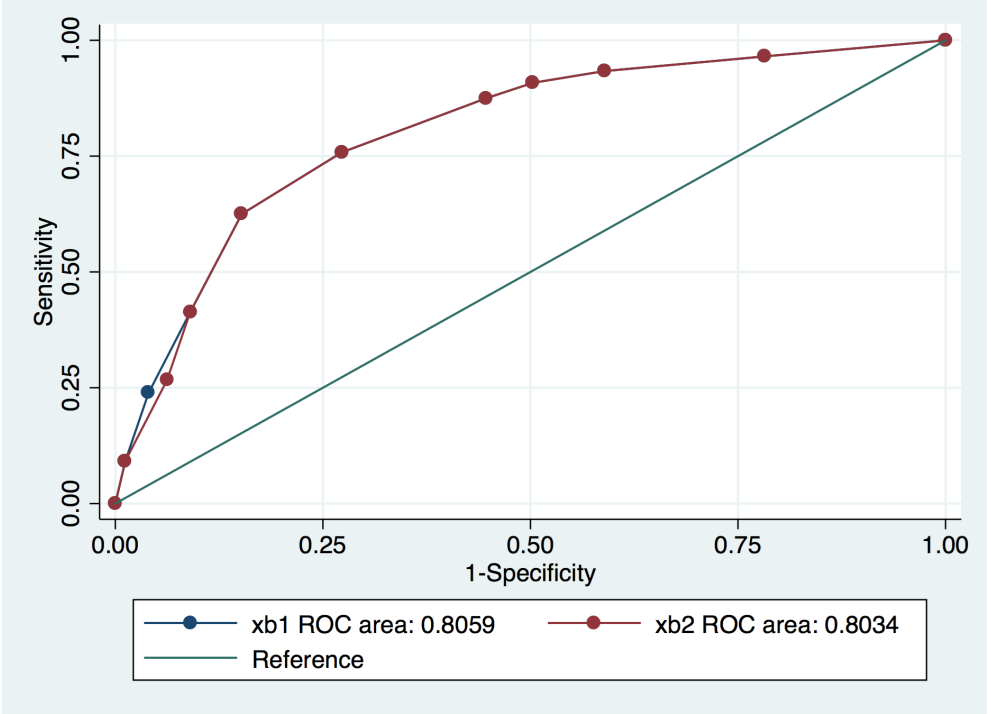
Figures:

Figure 1.0



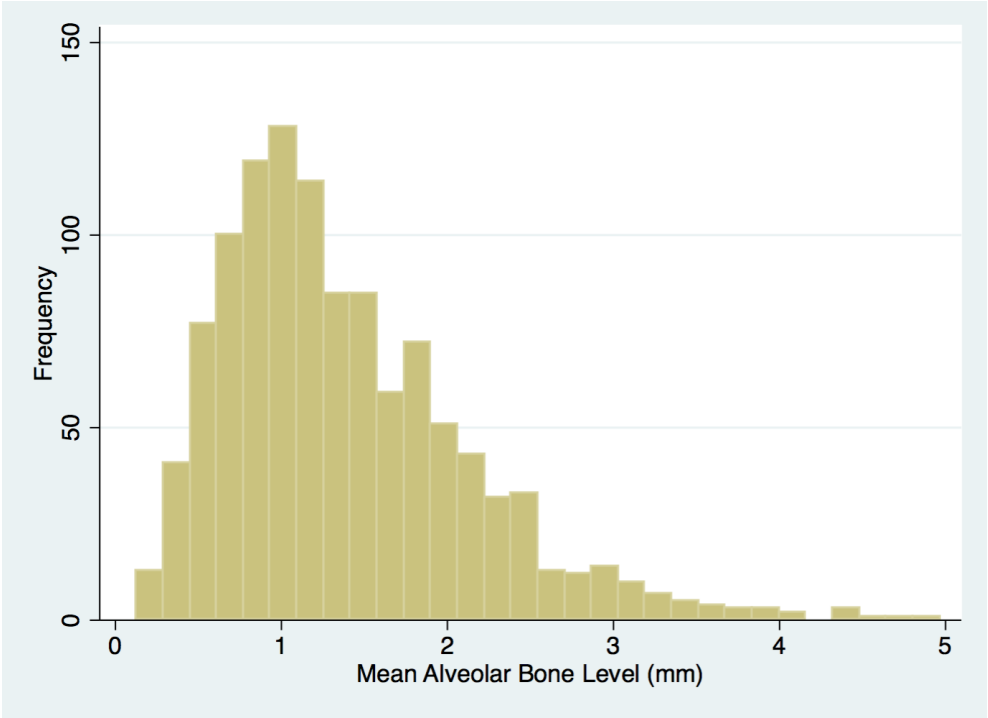
Infographic for disability adjusted life year
*Source: Own work by Planemad

Figure 2.0 ROC curve of comparing CDC-AAP case definitions of periodontitis to 15% corrected measurements for radiographic magnification



*xb1= recommended guidelines using CDC-AAP case definitions
*xb2= measurements corrected for radiographic discrepancy

Figure 1.1 Histogram of Mean Alveolar Bone Level Distribution - Outliers Included



*Distribution shows some degree of skewedness to the right

Figure 2.1 Boxplot of Mean Alveolar Bone Level Distribution - Outliers Included

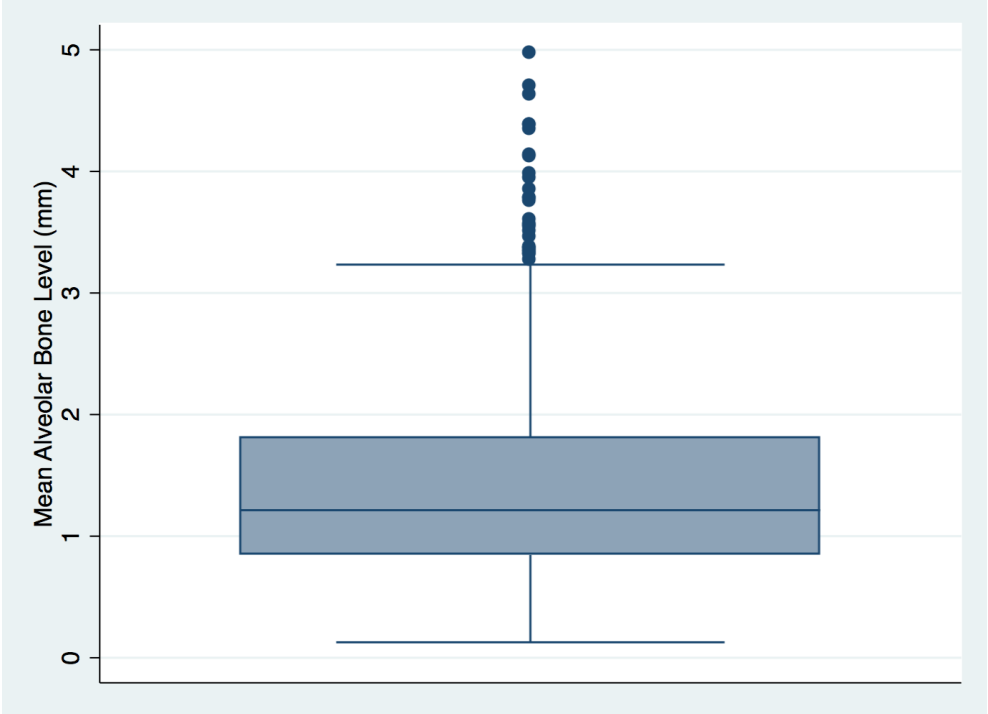
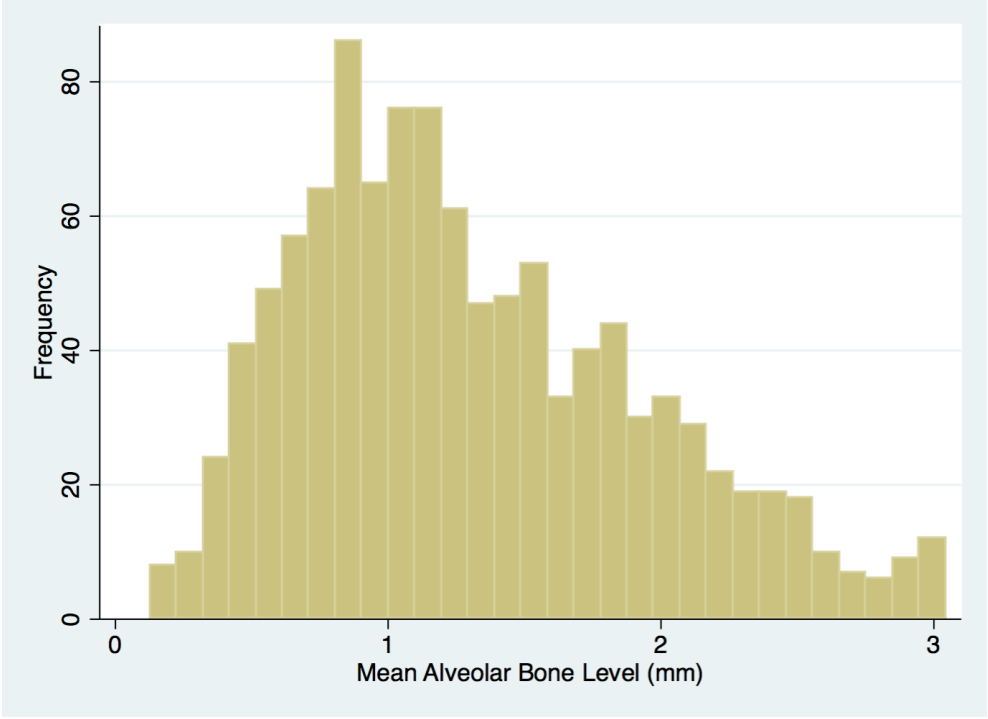


Figure 3.1 Histogram of Mean Alveolar Bone Level Distribution - Outliers Removed



*Distribution shows more normality and less skewedness

Figure 4.1 Boxplot of Mean Alveolar Bone Level Distribution - Outliers Removed

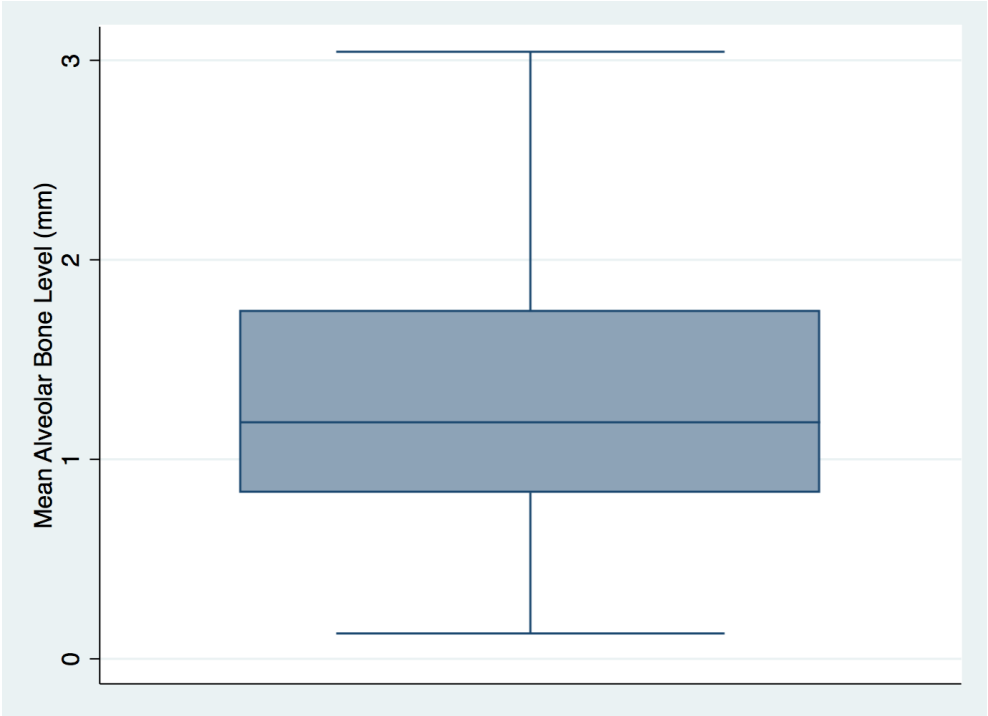


Figure 5.1 Distribution of observed values around fitted values of simple linear regression model using age as primary predictor - Outliers Included

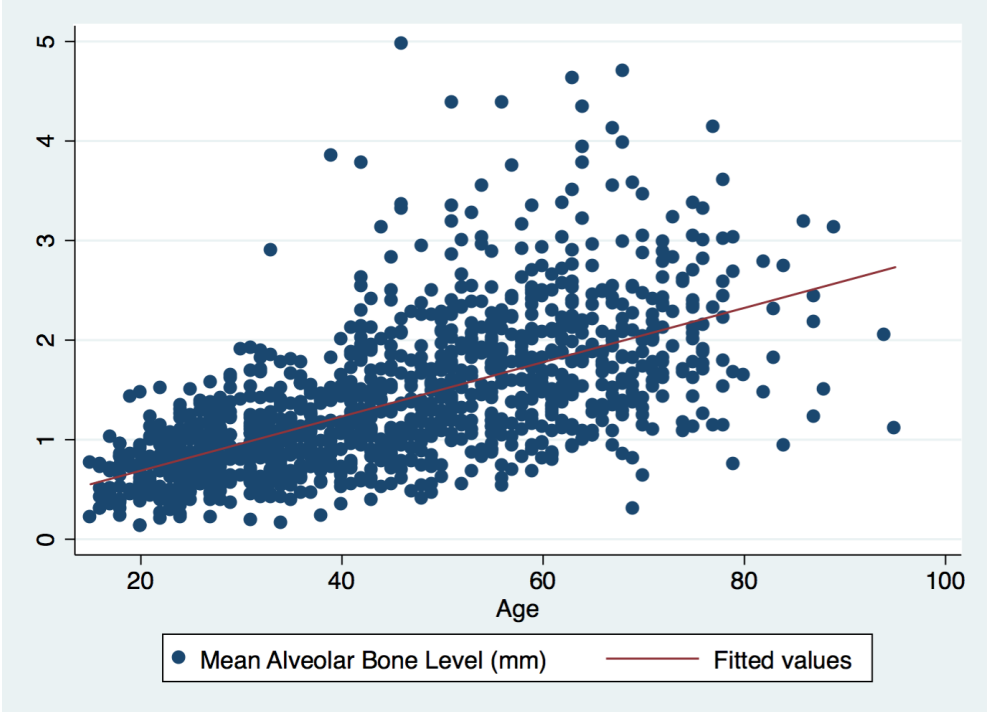


Figure 6.1 Distribution of observed values around fitted values of simple linear regression model using age as primary predictor - Outliers Removed

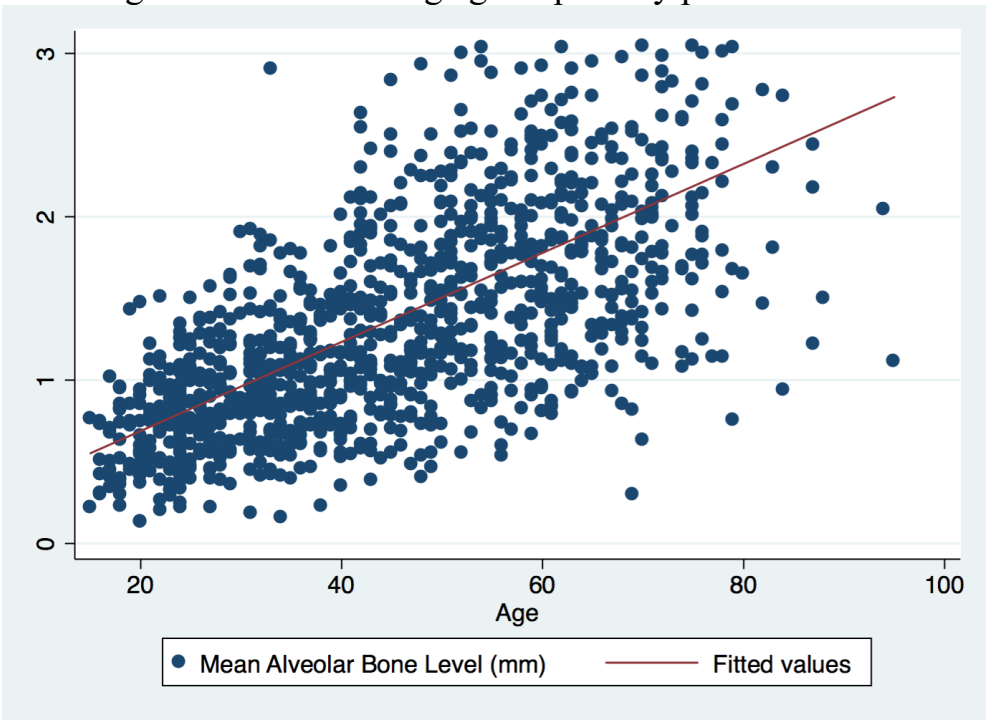


Figure 7.1 Residuals distribution after removing outliers

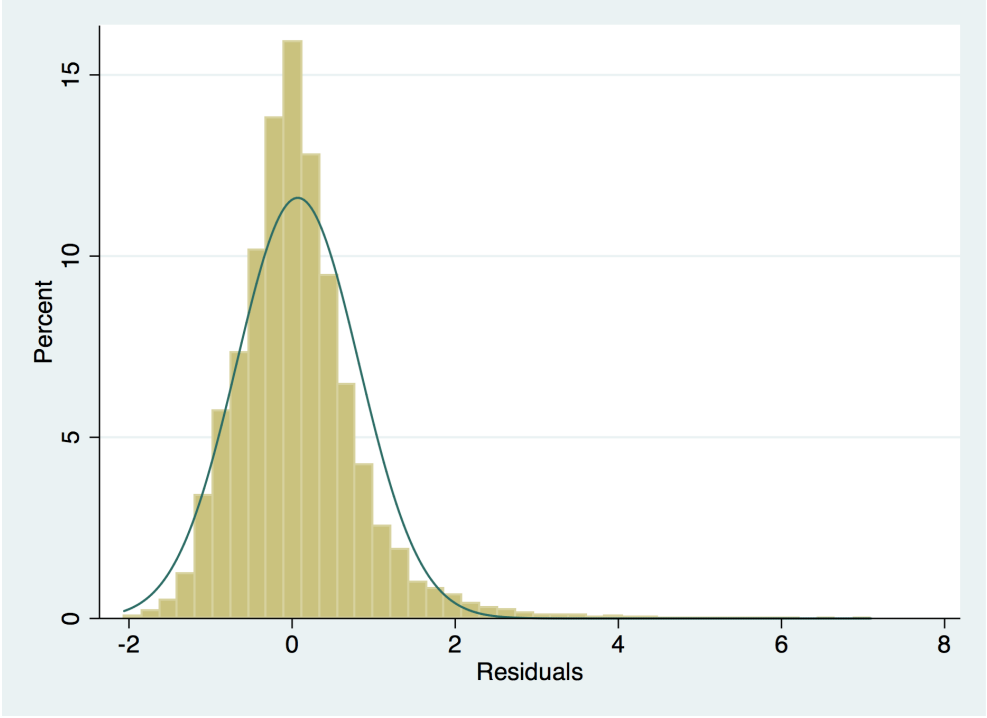
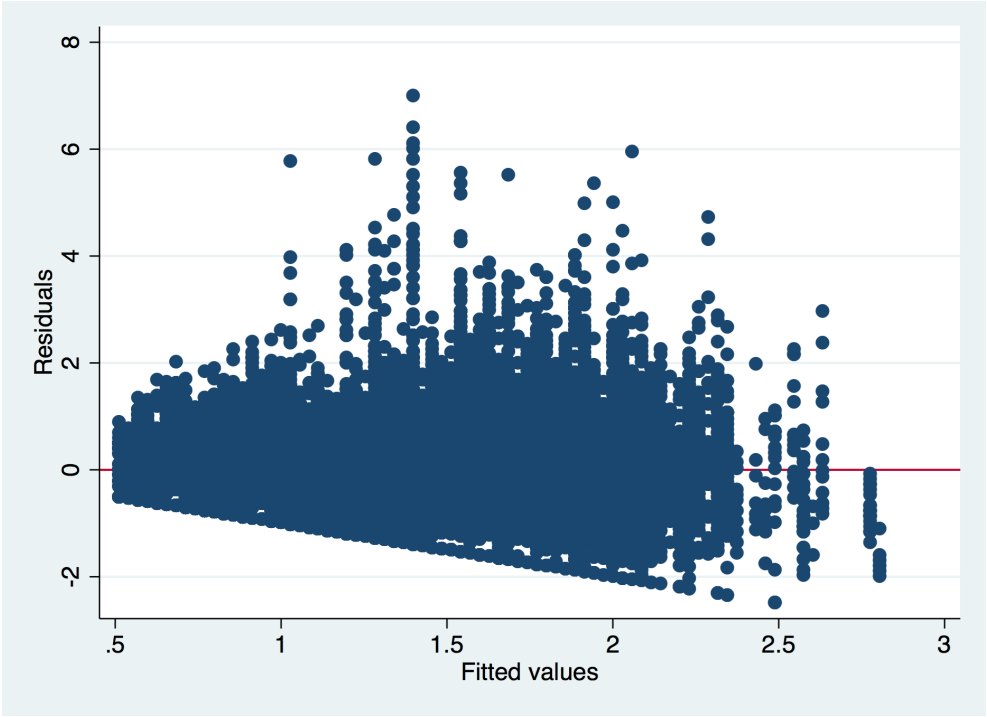
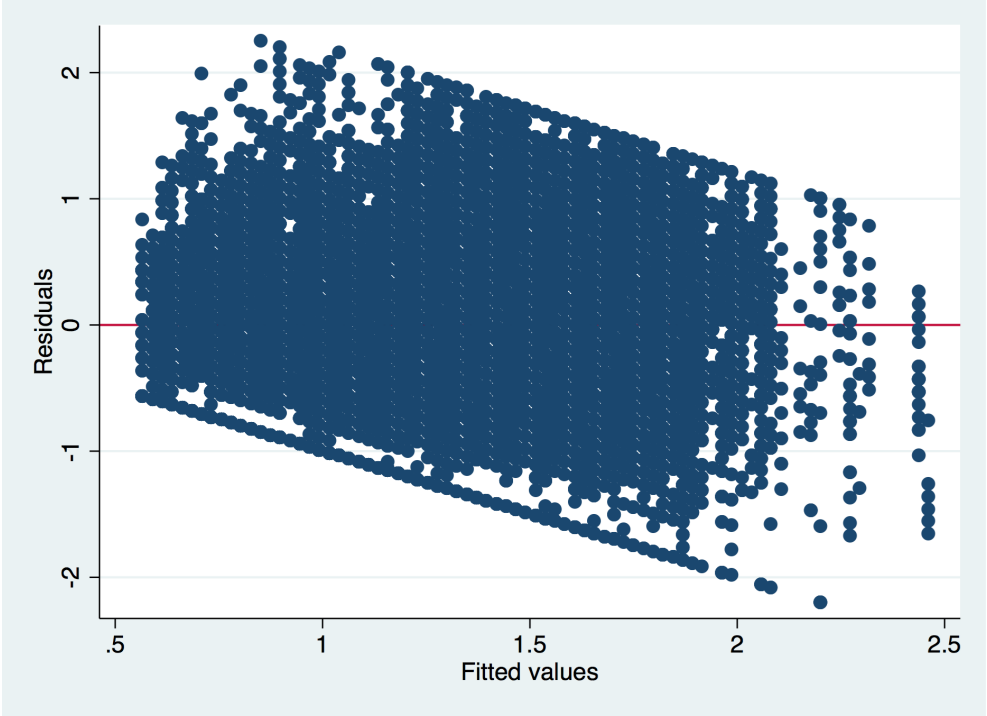


Figure 8.1 Residuals versus fitted values of linear regression model – Outliers Included



*Fanning out of residuals as fitted values increases

Figure 9.1 Residuals versus fitted values of linear regression model – Outliers Removed



*No sign of fanning out of residuals as fitted values increases

Figure 10.1 Distribution of Median House Income

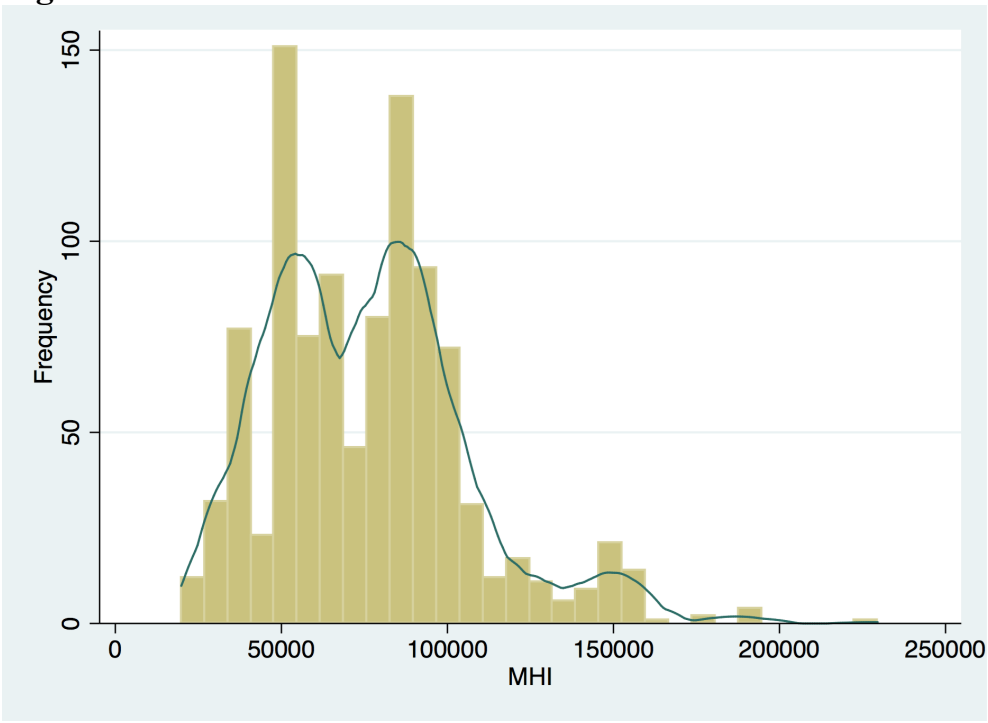


Figure 11.1 The 20 areas with highest median house income

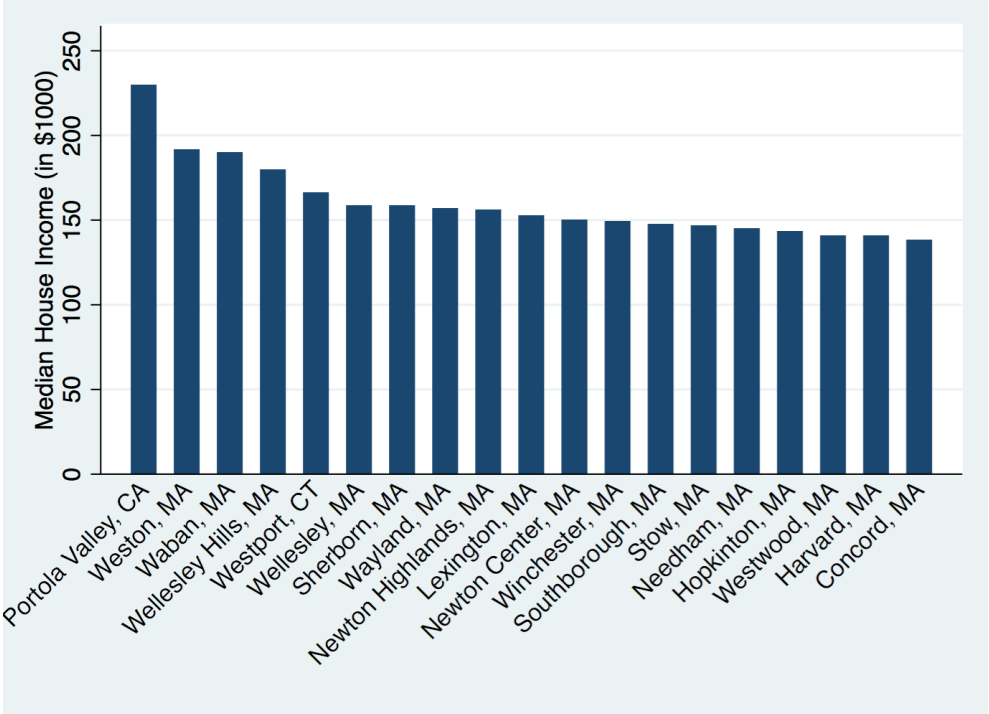


Figure 12.1 The 20 areas with lowest median house income

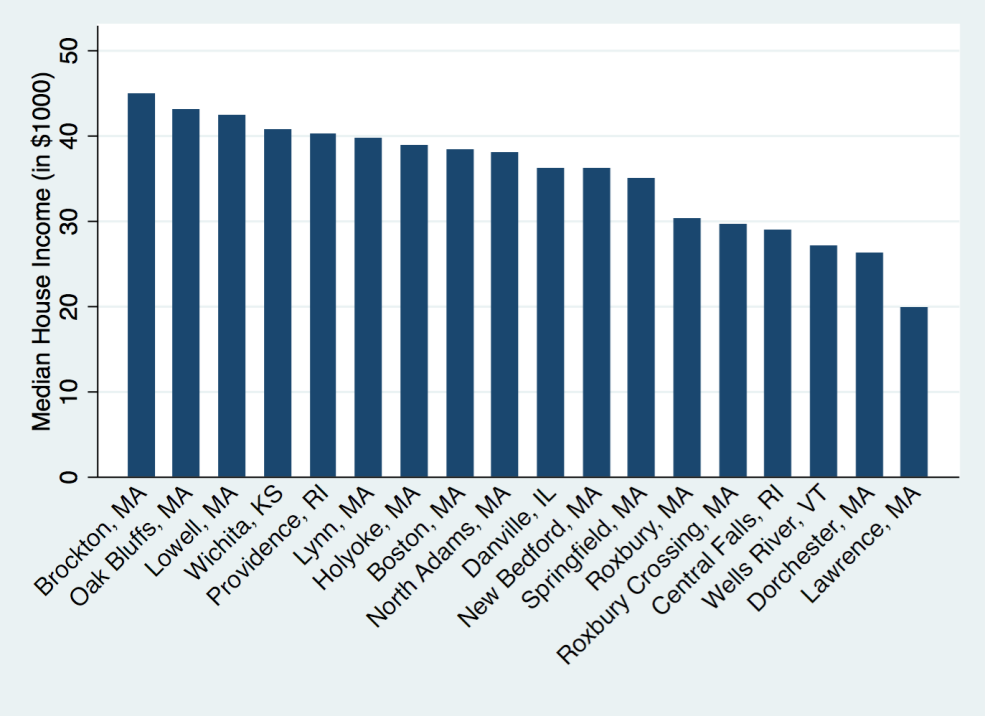


Figure 13.1 Prevalence of mild, moderate, and severe periodontitis over different age groups and gender – Aim 1

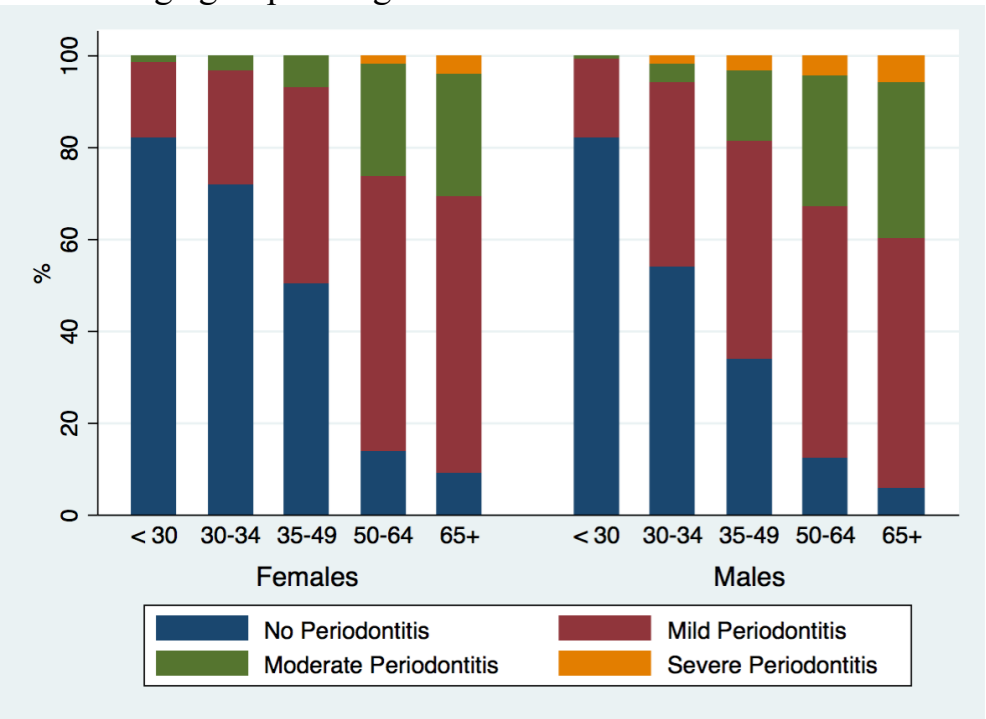


Figure 14.1 Mean alveolar bone level (mm) over different age groups and gender – Aim 1

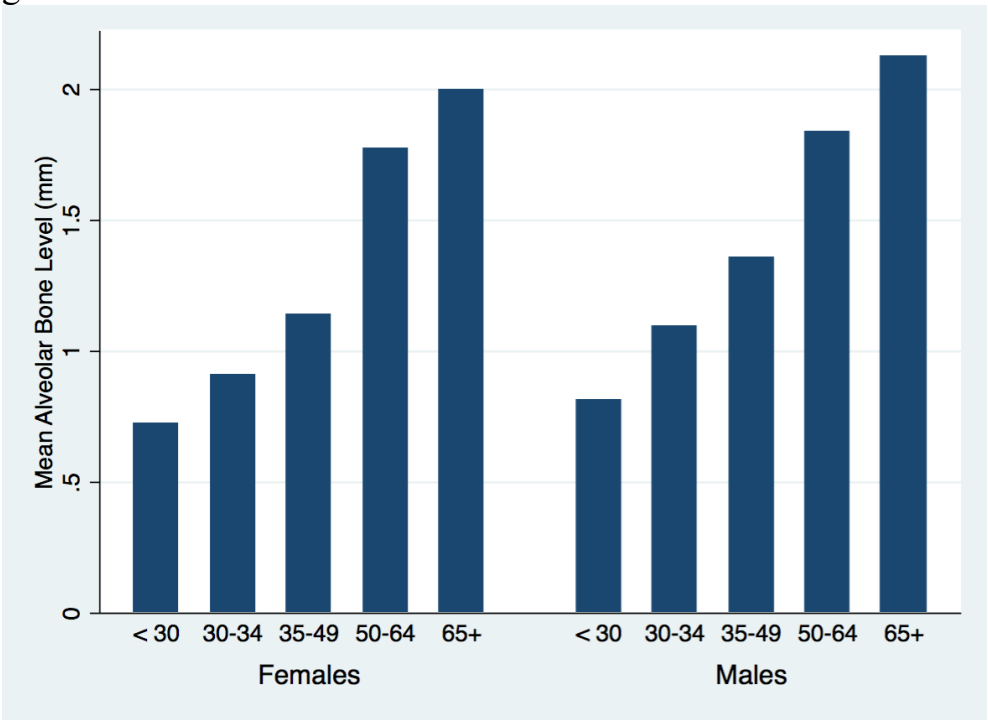


Figure 1.2 Prevalence of mild, moderate, and severe periodontitis by median house income – Aim 2

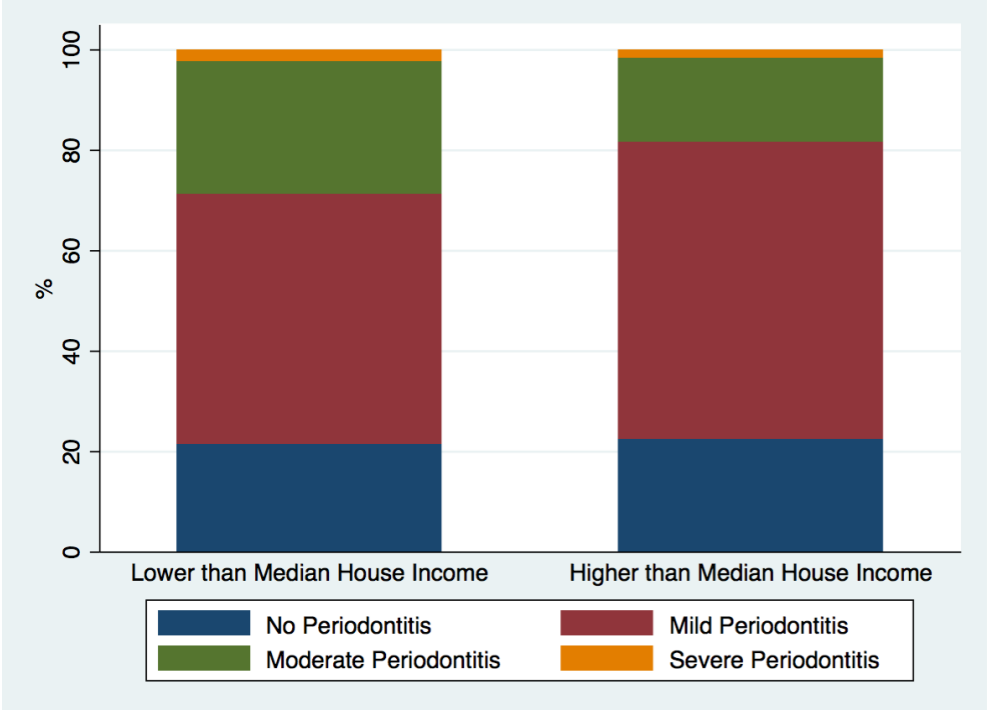


Figure 2.2 Mean alveolar bone level difference over time comparing CVD group to no CVD group – Aim 2

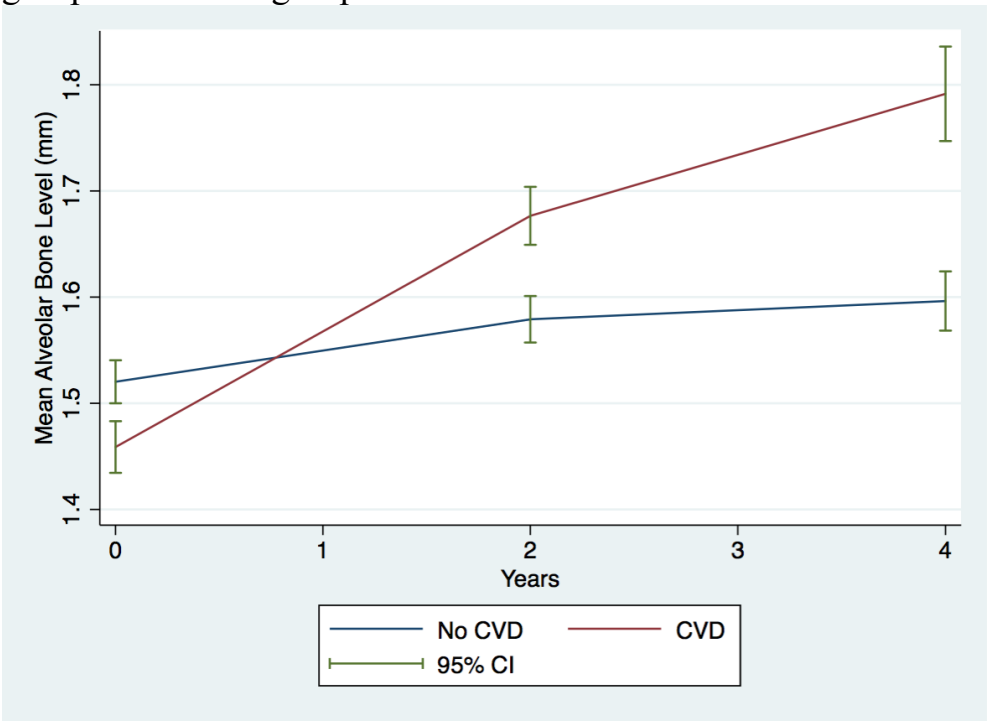


Figure 1.3 Prevalence of mild, moderate, and severe periodontitis by median house income – Aim 3

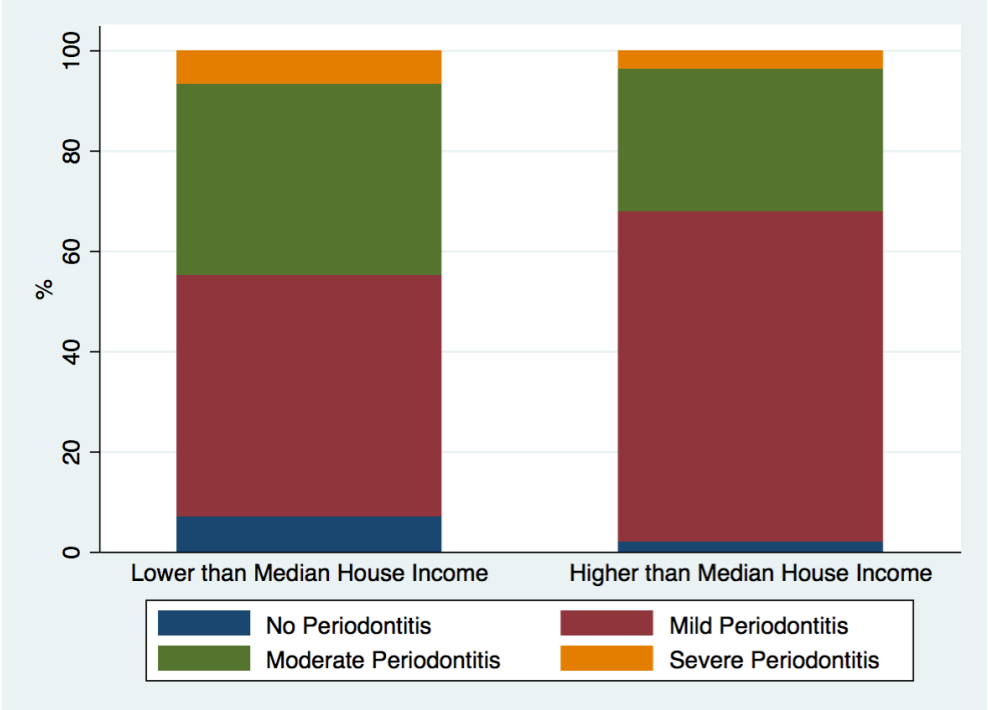
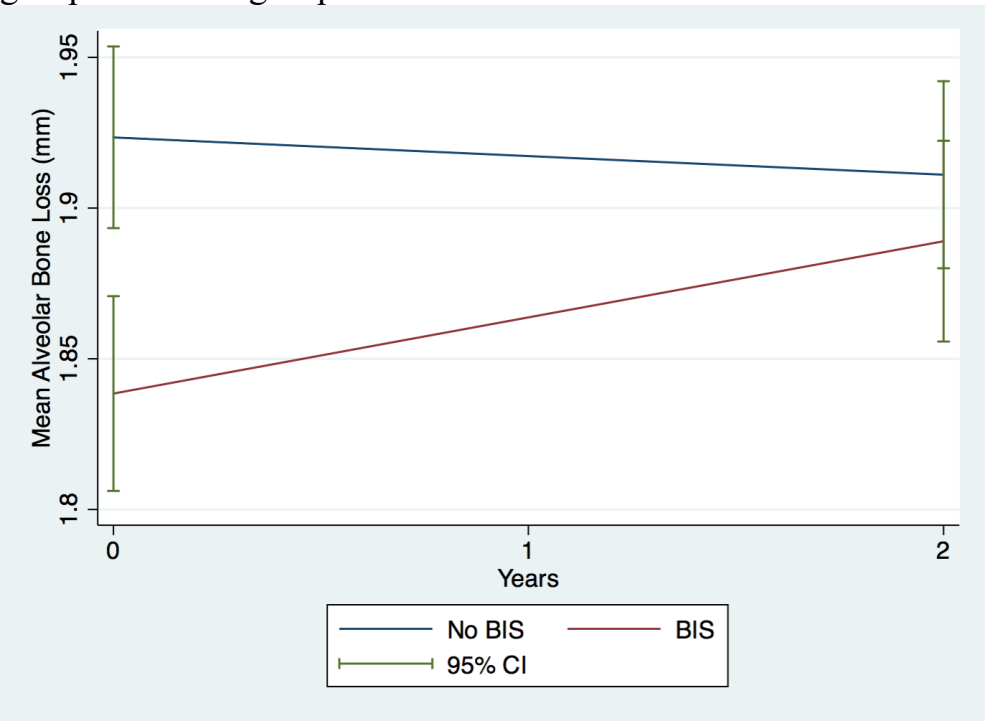
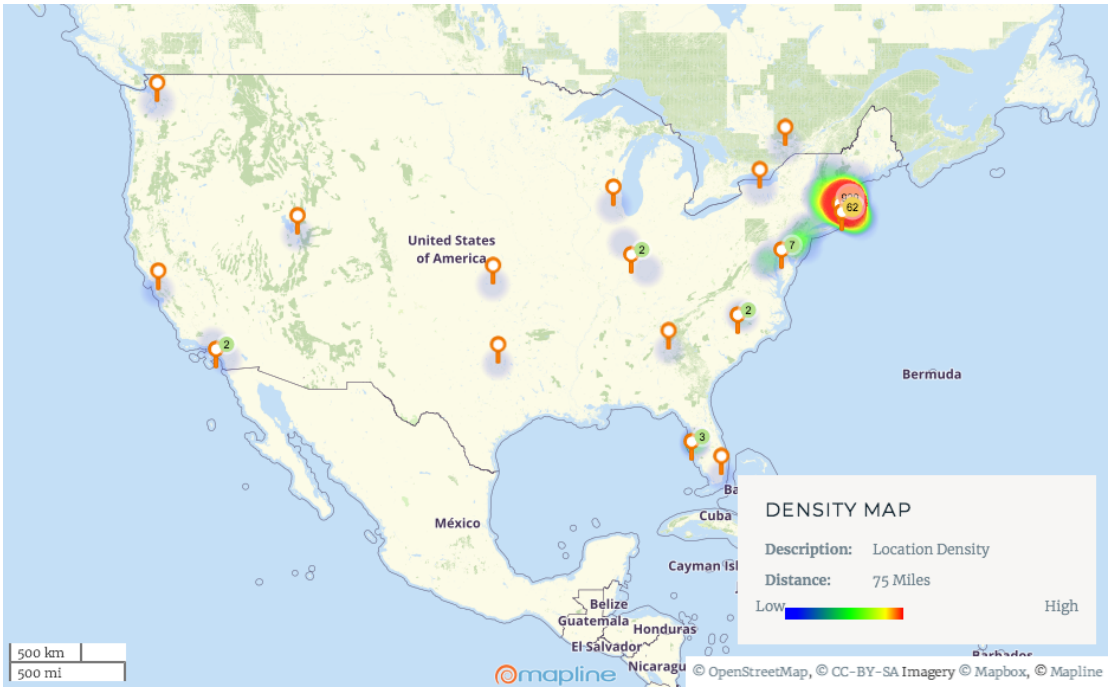


Figure 2.3 Mean alveolar bone level difference over time comparing BIS group to no BIS group – Aim 3

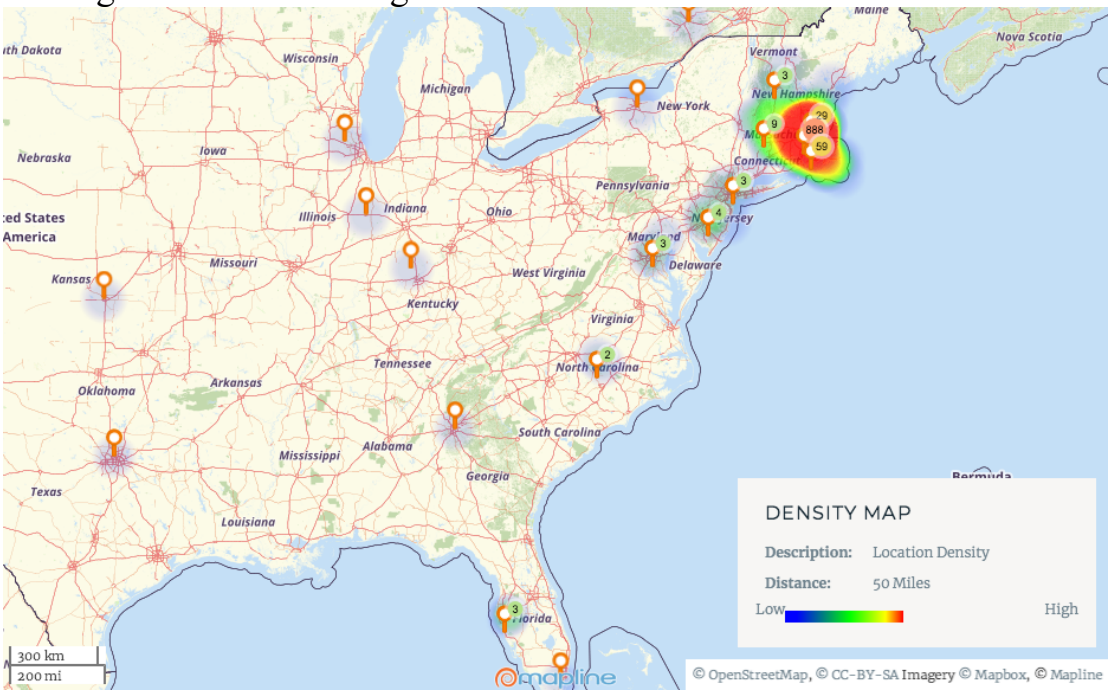


Maps:

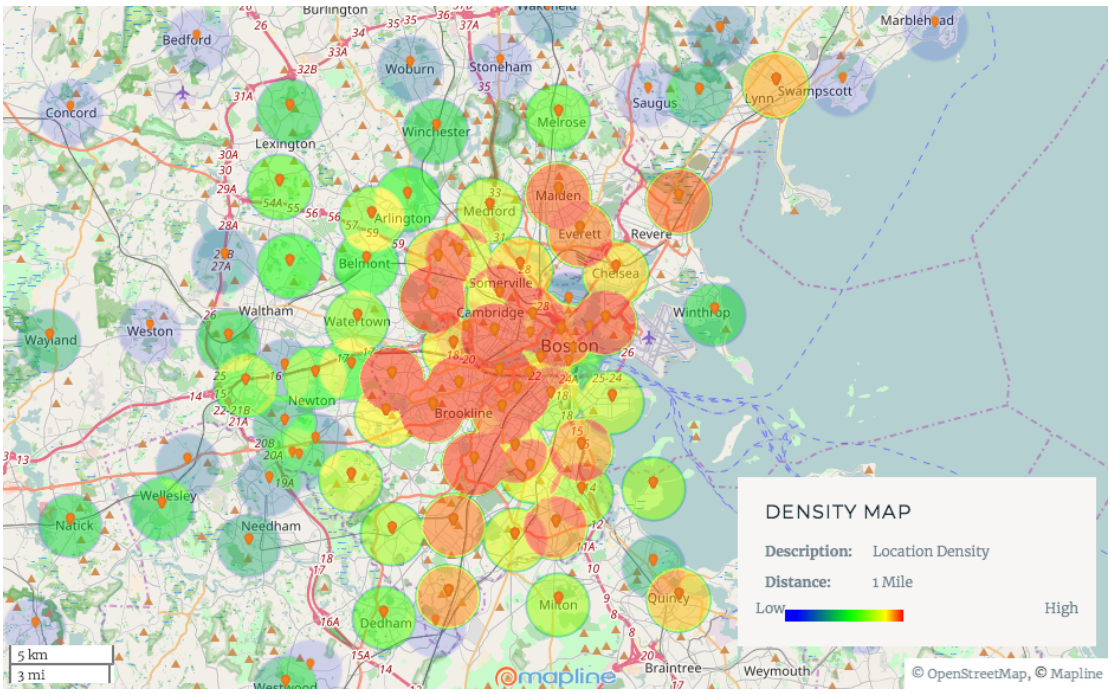
Map 1.1 Density of areas (frequency of visiting) from where patients visiting HSDM are coming from – 75 Miles



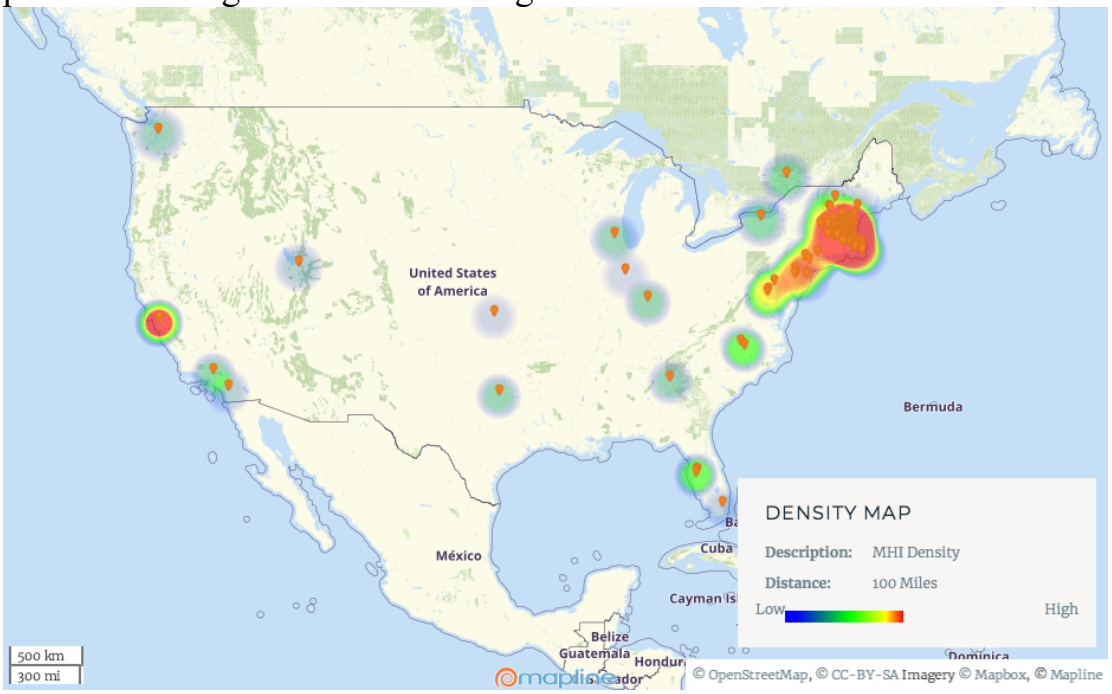
Map 2.1 Density of areas (frequency of visiting) from where patients visiting HSDM are coming from – 50 miles



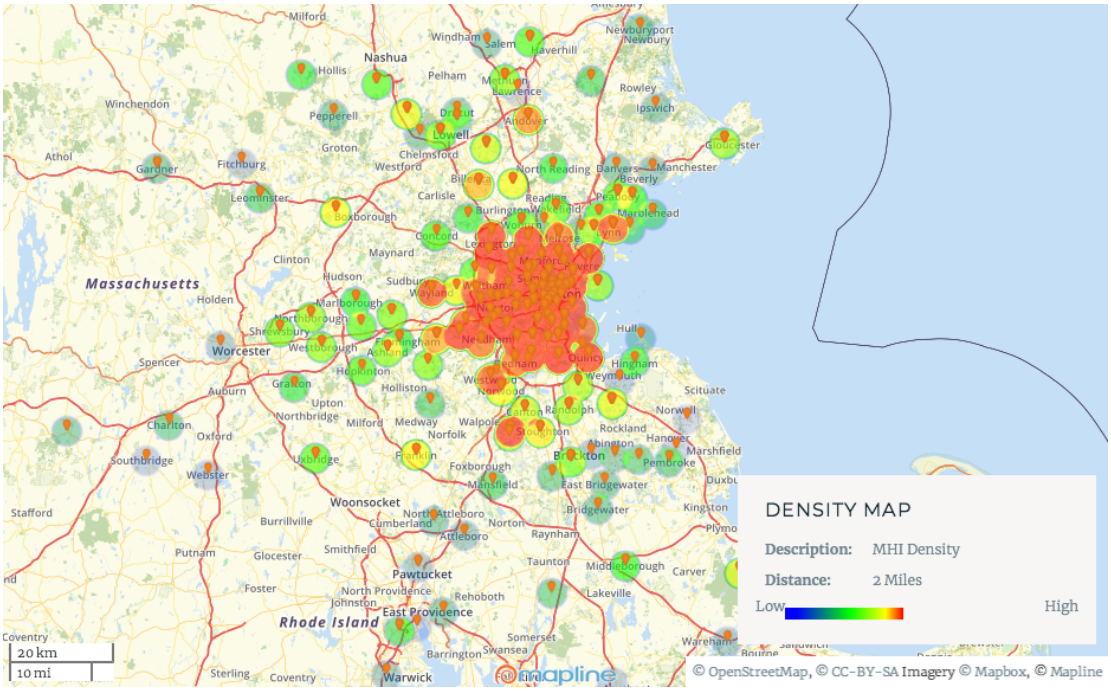
Map 3.1 Density of areas (frequency of visiting) from where patients visiting HSDM are coming from – 1 mile



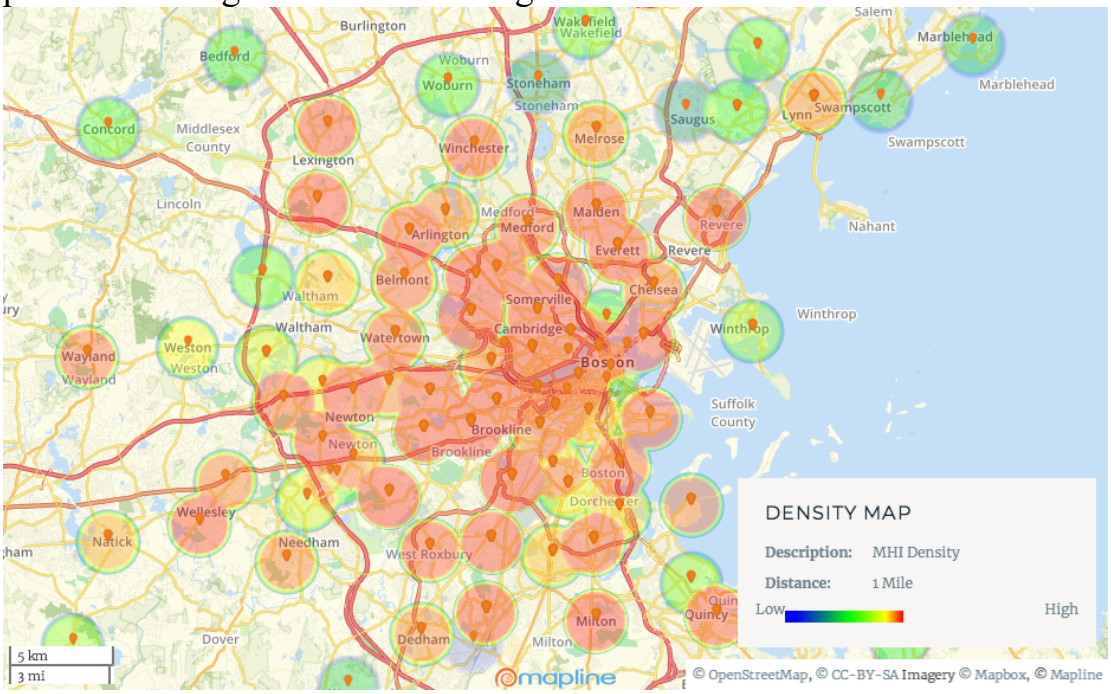
Map 4.1 Density of areas based on median house income from where patients visiting HSDM are coming from – 100 miles



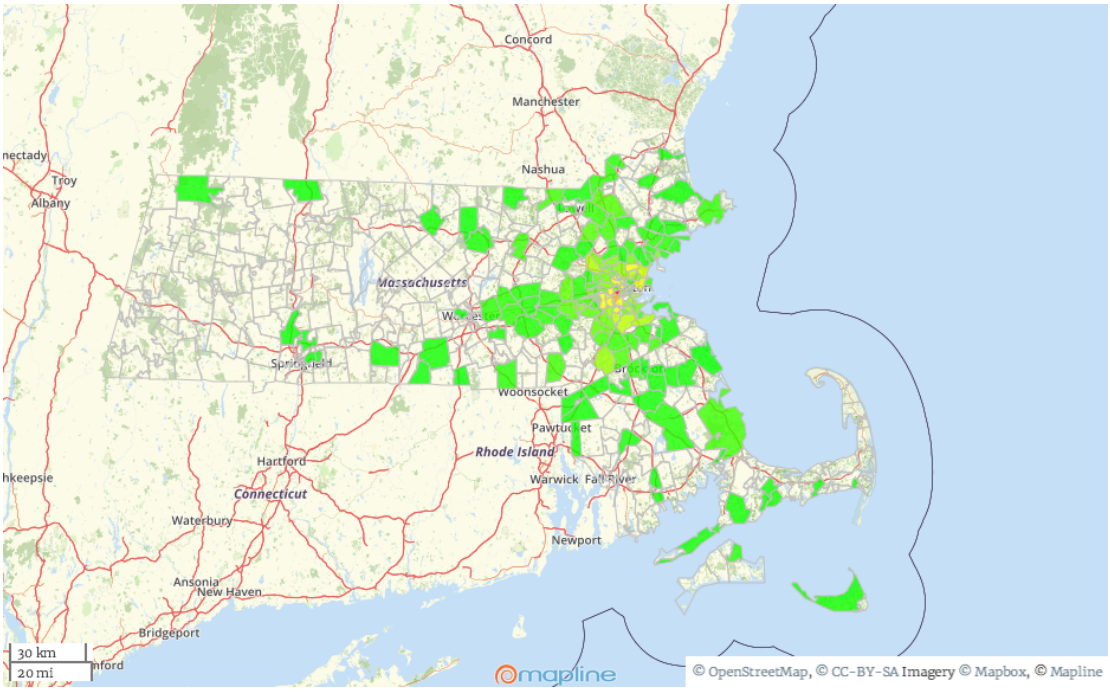
Map 5.1 Density of areas based on median house income from where patients visiting HSDM are coming from – 2 miles



Map 6.1 Density of areas based on median house income from where patients visiting HSDM are coming from – 1 mile



Map 7.1 ZIP cods areas from where patients visiting HSDM are coming from – Massachusetts


Concord
Manchester
Nashua
Troy
Albany
Massachusetts
Springfield
Woonsocket
Pawtucket
Rhode Island
Hartford
Connecticut
Warwick
Waterbury
Newport
Ansonia
New Haven
Bridgeport
30 km
20 mi
mapline
© OpenStreetMap, © CC-BY-SA Imagery © Mapbox, © Mapline

Appendix:

Sensitivity analysis:

The models below were used to assess the sensitivity of the models selected for out main analyses. Tables and graphs for sensitivity analysis are all presented below.

Radiographic case definition of periodontal diseases:

We corrected radiographic magnification error by 15% of all readings based on the fraction of error we obtained from the radiographs calibration study. We analyzed the corrected measurements for its sensitivity and specificity against the recommendation of radiographic evaluation of bone loss by the AAP Task Force Report 2015, which did not include any recommendations to correct for radiographic discrepancies expected from using non-standardized radiographs. We used the corrected measurements, however, we wanted to check of how much difference there is, and whether it is significant, between the corrected measurements and the non-corrected ones. The corrected model exhibited a very small increase in false positive rate (Figure 1.4), however, we tested the difference in area under ROC curve (Test statistic= 1.33. P-value= 0.25) and concluded that the area under the ROC curve is equal (Table 1.4).

Figure 1.4

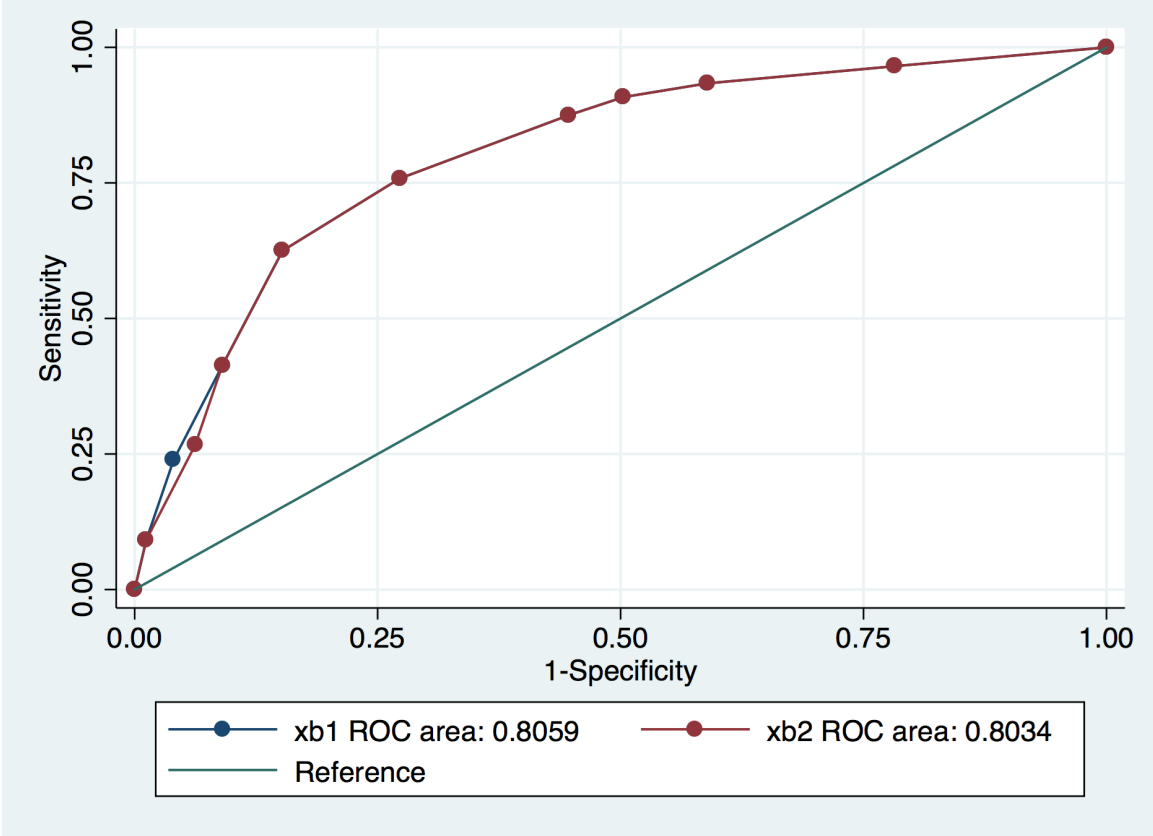


Table 1.4

	Obs	ROC Area	Std. Err.	-Asymptotic Normal-- [95% Conf.	Interval]
xb1	1,131	0.8059	0.0130	0.78038	0.83145
xb2	1,131	0.8034	0.0132	0.77756	0.82929

Ho: area(xb1) = area(xb2)
chi2(1) = 1.33 Prob>chi2 = 0.2491

Models including outliers versus models including no outliers:

We also restricted our main analyses to observations with no outliers. However, here we present the two models, main model with no outliers (Table 2.4) and sensitivity analysis model with outliers (Table 3.4).

No outliers (main model):

Table 2.4

```
Mixed-effects ML regression                     Number of obs     =     20,760

------------------------------------------------------------------
                |     No. of       Observations per Group
 Group Variable |     Groups    Minimum    Average    Maximum
----------------+-------------------------------------------------
             ID |      1,129          1       18.4         32
          Tooth |     12,965          1        1.6          2
------------------------------------------------------------------

                                                Wald chi2(28)     =    1038.33
Log likelihood = -15550.392                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
           T |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  AgeCATnew3 |
           2 |   .2080651   .0497248     4.18   0.000     .1106063     .305524
           3 |   .4343311   .0376541    11.53   0.000     .3605304    .5081317
           4 |   .8734157   .0396229    22.04   0.000     .7957562    .9510752
           5 |    1.08464   .0486555    22.29   0.000     .9892772    1.180003
             |
         Sex |   .0960202    .027008     3.56   0.000     .0430855     .148955
             |
     RaceNew |
           2 |   .0032116   .0498324     0.06   0.949     -.094458    .1008813
           3 |   .2325756   .0520403     4.47   0.000     .1305784    .3345728
           4 |   .0809488   .0359093     2.25   0.024     .0105678    .1513298
           5 |   .0160581   .0344259     0.47   0.641    -.0514154    .0835316
             |
MHIbinary#BMIcat |
         0 1 |   .0518657   .1390045     0.37   0.709     -.220578    .3243095
         0 3 |   -.023318   .0528328    -0.44   0.659    -.1268683    .0802324
         0 4 |  -.0742831   .0634016    -1.17   0.241     -.198548    .0499817
```

0 5	-.0944092	.0519034	-1.82	0.069	-.1961381	.0073197
1 1	-.2258872	.1102989	-2.05	0.041	-.4420692	-.0097052
1 2	-.0482535	.0439516	-1.10	0.272	-.1343971	.0378901
1 3	-.1503994	.0515832	-2.92	0.004	-.2515006	-.0492982
1 4	-.2508445	.067011	-3.74	0.000	-.3821835	-.1195054
1 5	-.0406966	.0512375	-0.79	0.427	-.1411202	.059727
Smoking						
1	.1577658	.0515956	3.06	0.002	.0566403	.2588913
2	.1541177	.042702	3.61	0.000	.0704234	.2378121
3	.0466398	.0349166	1.34	0.182	-.0217955	.1150751
Diabetes	.0204449	.0621396	0.33	0.742	-.1013465	.1422362
Hypertension1						
2	.0625629	.0420737	1.49	0.137	-.0199001	.1450259
3	-.0123376	.0370908	-0.33	0.739	-.0850342	.060359
4	-.0087108	.0495504	-0.18	0.860	-.1058277	.0884061
5	.0159106	.0390871	0.41	0.684	-.0606988	.0925199
CVDHeartProblem	.0137731	.0444365	0.31	0.757	-.0733207	.100867
D4341	.2092995	.0539127	3.88	0.000	.1036326	.3149665
_cons	.6992609	.0494292	14.15	0.000	.6023815	.7961404

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.1647159	.0078773	.1499781	.1809018
Tooth: Identity				
var(_cons)	.0660112	.0029403	.0604926	.0720332
var(Residual)	.171359	.0027587	.1660364	.1768523

LR test vs. linear model: chi2(2) = 7885.46 Prob > chi2 = 0.0000

Outliers included (sensitivity analysis model):

Table 3.4

Mixed-effects ML regression Number of obs = 21,484

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	1,131	1	19.0	32
Tooth	13,284	1	1.6	2

Wald chi2(28) = 883.48
Log likelihood = -18931.695 Prob > chi2 = 0.0000

T	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
AgeCATnew3						
2	.2216989	.0645283	3.44	0.001	.0952257	.348172
3	.4794195	.0488109	9.82	0.000	.3837518	.5750871
4	1.002505	.0511886	19.58	0.000	.9021766	1.102832
5	1.258523	.0625321	20.13	0.000	1.135963	1.381084
Sex	.1426341	.0348072	4.10	0.000	.0744132	.2108551
RaceNew						
2	.0909381	.0641428	1.42	0.156	-.0347794	.2166557
3	.2612739	.0672537	3.88	0.000	.1294591	.3930888
4	.0793286	.0463768	1.71	0.087	-.0115683	.1702255
5	.0407525	.0444056	0.92	0.359	-.0462809	.1277859
MHIbinary#BMIcat						
0 1	.0613645	.1803183	0.34	0.734	-.2920529	.4147819
0 3	-.0292375	.0680428	-0.43	0.667	-.162599	.104124
0 4	-.0219392	.0816242	-0.27	0.788	-.1819197	.1380413
0 5	-.0761211	.066808	-1.14	0.255	-.2070624	.0548202
1 1	-.2466236	.1428323	-1.73	0.084	-.5265698	.0333226
1 2	-.0596853	.0567898	-1.05	0.293	-.1709913	.0516207
1 3	-.2023698	.0666439	-3.04	0.002	-.3329894	-.0717501
1 4	-.3513553	.0865413	-4.06	0.000	-.520973	-.1817375
1 5	-.0470306	.0661659	-0.71	0.477	-.1767133	.0826522
Smoking						
1	.1664418	.0665775	2.50	0.012	.0359523	.2969313
2	.1965299	.0547305	3.59	0.000	.0892601	.3037998
3	.0442297	.0450498	0.98	0.326	-.0440663	.1325257
Diabetes	.0511445	.0794554	0.64	0.520	-.1045853	.2068742
Hypertension1						
2	.0836288	.0542317	1.54	0.123	-.0226634	.189921
3	-.037678	.047889	-0.79	0.431	-.1315387	.0561827
4	.0141981	.0636993	0.22	0.824	-.1106502	.1390465
5	.0368891	.0505246	0.73	0.465	-.0621373	.1359156
CVDHeartProblem	-.0363522	.0570598	-0.64	0.524	-.1481874	.0754829
D4341	.3686036	.068487	5.38	0.000	.2343714	.5028357
_cons	.6566019	.0639297	10.27	0.000	.531302	.7819018

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.2827256	.0130135	.2583362	.3094175
Tooth: Identity				
var(_cons)	.0952631	.0036917	.0882955	.1027805
var(Residual)	.2131684	.0033312	.2067383	.2197984

LR test vs. linear model: chi2(2) = 11043.98 Prob > chi2 = 0.0000

Main and sensitivity analysis models did not differ in regard to significance of predictor variables. However, we can notice that on the whole, the model with outliers included increased strength of association estimates for all variables. We preferred to use the model with no outliers to account for any overestimation that might arise from outliers.

Parametric versus non-parametric tests:

We compared parametric tests to non-parametric tests to check if outliers are still influencing our estimates. Non-parametric tests have the ability to handle not normally distributed data since they rely on the median, which is less influenced by outliers, compared to parametric tests as they rely on the mean, which can be easily influenced by outliers. The purpose of this sensitivity analysis was to check if running these two models would alter our findings and whether p-values of the same variables would change significance.

Comparing mean alveolar bone level, with categorical age as primary predictor, using ANOVA test (parametric) we hade a test statistic = 163.42 (df=4) and p-value < 0.001 and using Kruskal-Wallis test (non-parametric)

we had a test statistic = 499.46 (df=4) and p-value < 0.001 indicating that the two tests were capable of detecting a difference of mean alveolar bone level across the age groups.

We also compared the two statistical models using two-sample t-test (parametric, test statistic = -6.7 with a p-value < 0.001) and Wilcoxon rank-sum test (non-parametric, test statistic = -5.2 with a p-value < 0.001) using sex as a predictor and we found similar results.

We decided to conduct the main analyses using parametric tests since we wanted to have an exact estimate of the amount of mean alveolar bone change that cannot be detected by non-parametric tests.

Aim 1 - Logistic regression to estimate the odds of developing moderate to severe periodontitis:

We had two models to estimate relative risk of periodontal diseases. The first one was linear regression model to predict the amount of change in mean alveolar bone level (primary model used in main document). The second one was logistic regression model (secondary model, Table 4.4) with

the outcome being categorized as 0 for no sign of periodontal disease and mild periodontitis, and 1 for moderate and severe periodontitis. The later model was categorized in such a manner due to the shared properties of moderate and severe periodontitis as they impose higher risk of tooth loss and are more severe forms of the disease that we desired to measure compared to mild periodontitis.

Table 4.4

Logistic regression — Number of obs = 1,114; LR chi2(27) = 296.55; Prob > chi2 = 0.0000; Log likelihood = -424.35329; Pseudo R2 = 0.2589

Perio1SiteNomildModsevere	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
AgeCATnew3						
2	3.654459	2.920318	1.62	0.105	.7631652	17.49958
3	13.37188	8.470396	4.09	0.000	3.86367	46.27908
4	64.48708	40.59501	6.62	0.000	18.77743	221.4671
5	88.59552	57.27717	6.94	0.000	24.95217	314.5685
Sex	1.851501	.3361654	3.39	0.001	1.29711	2.642843
RaceNew						
2	1.837711	.5835161	1.92	0.055	.9862817	3.424156
3	3.239986	1.11656	3.41	0.001	1.648933	6.366241
4	1.331948	.3249571	1.17	0.240	.8256931	2.148602
5	1.186601	.2874083	0.71	0.480	.7381317	1.907548
MHIbinary#BMIcat						
0 1	7.318861	6.928659	2.10	0.036	1.14452	46.80191
0 3	.7599015	.2610255	-0.80	0.424	.3875881	1.489856
0 4	.5749023	.2388156	-1.33	0.183	.2546849	1.297732
0 5	.495684	.1851453	-1.88	0.060	.2383793	1.030721
1 1	1	(empty)				
1 2	.774628	.2391818	-0.83	0.408	.4229292	1.418792
1 3	.4246085	.1501229	-2.42	0.015	.2123446	.8490557
1 4	.3274209	.1441924	-2.54	0.011	.138117	.7761858
1 5	.6763885	.2372429	-1.11	0.265	.3401243	1.3451
Smoking						
1	1.233497	.4298353	0.60	0.547	.6230475	2.442054
2	2.155509	.5247895	3.15	0.002	1.337558	3.473658
3	1.198201	.2771846	0.78	0.434	.7614084	1.885565
Diabetes	1.255128	.4146753	0.69	0.492	.6568464	2.398347
Hypertension1						
2	1.233069	.3568753	0.72	0.469	.6992499	2.174415
3	1.0764	.2735984	0.29	0.772	.6540572	1.77146
4	1.006317	.3045578	0.02	0.983	.5560607	1.821158

5	1.033611	.2938448	0.12	0.907	.5920648	1.80445
CVDHeartProblem	.8942507	.2197966	-0.45	0.649	.5523873	1.447688
D4341	3.091883	.8810821	3.96	0.000	1.768721	5.404888
_cons	.0061591	.0041924	-7.48	0.000	.0016223	.0233836

Different race groups showed higher risk of periodontal disease compared to White race. African American race showed higher risk of developing moderate to severe periodontitis with marginal significance (OR=1.83, 95%CI: 0.98-3.42. P-value=0.055). In our study we had only 21 Hispanic subjects, hence, they were added to Other race category. Moreover, our results showed that Asian race had a higher risk of developing moderate to severe periodontitis compared to White (OR=3.23, 95%CI: 1.64-6.36. P-value=0.001).

Furthermore, obese subjects with high house income had 70% lower odds of developing moderate to severe periodontitis (OR=0.32, 95%CI: 0.13-0.77. P-value=0.011). Overall smoking experience was positively associated with increased risk of developing moderate to severe periodontitis compared to never smokers (OR=2.15, 95%CI: 1.33-3.47. P-value=0.002).

Aim 2 - Control group free of all diseases versus control group free from CVD only:

In aim 2, the control group (N=87) contained 27 patients with diabetes, hypertension, or both. We conducted two models, main model that was used for main analysis (Table 5.4) and sensitivity analysis model (Table 6.4), to assess the need of removing these 27 patients to check if they are influencing the outcome significantly.

Main model (N=145, CVD group=58 and control group=87):

Table 5.4

Mixed-effects ML regression — Number of obs = 6,945

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	145	9	47.9	90
Tooth	1,923	1	3.6	6

Log likelihood = -5494.5251 — Wald chi2(24) = 280.44; Prob > chi2 = 0.0000

T	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Visit						
2	.045214	.0155793	2.90	0.004	.0146792	.0757488
3	.1212712	.0198274	6.12	0.000	.0824102	.1601322
1.CVDHeartProblem	-.024333	.0836552	-0.29	0.771	-.1882941	.139628
Visit#CVDHeartProblem						
2 1	.1219177	.0255562	4.77	0.000	.0718285	.1720068
3 1	.1309908	.0352899	3.71	0.000	.0618238	.2001577
AgeCATnew3						

3	.4084322	.2030576	2.01	0.044	.0104466	.8064179
4	.8890243	.1962077	4.53	0.000	.5044642	1.273584
5	1.161596	.2038729	5.70	0.000	.7620122	1.561179
Sex	.0149784	.0763612	0.20	0.844	-.1346869	.1646436
RaceNew						
2	.0113325	.1476287	0.08	0.939	-.2780145	.3006795
3	.1261462	.1633677	0.77	0.440	-.1940487	.4463411
4	-.1160776	.1102038	-1.05	0.292	-.3320732	.0999179
5	-.0902348	.0874976	-1.03	0.302	-.2617269	.0812573
BMIcat						
1	.201812	.295785	0.68	0.495	-.3779159	.7815399
3	-.0570877	.1016588	-0.56	0.574	-.2563353	.1421598
4	-.140493	.1099199	-1.28	0.201	-.3559319	.074946
5	-.1310242	.1003812	-1.31	0.192	-.3277676	.0657193
Smoking						
1	.2532677	.1039247	2.44	0.015	.049579	.4569564
3	.1321845	.085304	1.55	0.121	-.0350083	.2993772
Diabetes	-.1365553	.1077013	-1.27	0.205	-.347646	.0745353
MHIbinary#Hypertension						
0 1	-.1238494	.1200261	-1.03	0.302	-.3590963	.1113974
1 0	-.1089137	.0944331	-1.15	0.249	-.2939991	.0761718
1 1	-.3587922	.1135388	-3.16	0.002	-.5813242	-.1362602
D4341	.2853078	.1042553	2.74	0.006	.0809712	.4896444
_cons	.7427116	.199102	3.73	0.000	.3524789	1.132944

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.1368015	.0179468	.1057847	.1769126
Tooth: Identity				
var(_cons)	.1201924	.0064554	.1081833	.1335346
var(Residual)	.1996477	.0040103	.1919404	.2076644

LR test vs. linear model: chi2(2) = 2892.50 Prob > chi2 = 0.0000

Sensitivity analysis model (N=118, CVD group=58 and control group=60):

Table 6.4

Mixed-effects ML regression Number of obs = 5,823

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	118	9	49.3	90
Tooth	1,584	1	3.7	6

Log likelihood = -4584.5827

Wald chi2(24) = 227.99
Prob > chi2 = 0.0000

T	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Visit						
2	.0419479	.0179444	2.34	0.019	.0067775	.0771183
3	.0952595	.0227982	4.18	0.000	.0505758	.1399432
1.CVD	-.126203	.1045993	-1.21	0.228	-.3312138	.0788078
Visit#CVD						
2 1	.1249653	.0270824	4.61	0.000	.0718848	.1780459
3 1	.1559132	.0370731	4.21	0.000	.0832513	.228575
AgeCATnew3						
3	.4213968	.4079553	1.03	0.302	-.3781809	1.220975
4	.9389055	.4048501	2.32	0.020	.1454138	1.732397
5	1.194667	.4092519	2.92	0.004	.3925479	1.996786
Sex	.0116985	.0819303	0.14	0.886	-.1488819	.172279
RaceNew						
2	.2336273	.1840216	1.27	0.204	-.1270484	.594303
3	.3605965	.2034875	1.77	0.076	-.0382316	.7594247
4	-.0425417	.1238876	-0.34	0.731	-.2853569	.2002735
5	-.010729	.0916285	-0.12	0.907	-.1903176	.1688596
BMIcat						
1	.2621155	.2877278	0.91	0.362	-.3018205	.8260516
3	.0022208	.1074288	0.02	0.984	-.2083358	.2127775
4	-.0680153	.1206463	-0.56	0.573	-.3044777	.168447
5	-.1148128	.105736	-1.09	0.278	-.3220515	.0924259
Smoking						
1	.2823768	.1174216	2.40	0.016	.0522347	.512519
3	.2139495	.0881523	2.43	0.015	.0411743	.3867248
Diabetes	.1095879	.1574492	0.70	0.486	-.1990068	.4181827
MHIbinary#Hypertension						
0 1	-.1265243	.1613838	-0.78	0.433	-.4428307	.1897822
1 0	-.0717284	.0992687	-0.72	0.470	-.2662915	.1228347
1 1	-.3261354	.1411095	-2.31	0.021	-.602705	-.0495659
D4341	.3220538	.1150325	2.80	0.005	.0965943	.5475133
_cons	.6275389	.4088969	1.53	0.125	-.1738843	1.428962

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.1243089	.0182403	.09324	.1657303
Tooth: Identity				
var(_cons)	.1158104	.0068626	.1031117	.1300731
var(Residual)	.2003774	.0043756	.1919823	.2091396

LR test vs. linear model: chi2(2) = 2288.34 Prob > chi2 = 0.0000

We notice that after removing the 27 patients (sensitivity analysis model), estimates of no CVD group (control) decreased, and estimates of CVD group increased. However, we decided to use the main model with the inclusion of all 87 patients of the control group since we are controlling for diabetes in the main model and its effect was statistically not significant. Furthermore, estimates of the interaction term between median house income and hypertension were significant in both models and differed only by 0.032 mm.

Aim 2 – two-year interval versus four-year interval:

For aim 2, we had loss to follow up (radiographs unavailability) over the four years period; however, all patients were followed for two years. Presented here are the two models; model of analyzing the whole sample over four years (Table 7.4), and a model of analyzing only two years of follow up including all patients (Table 8.4).

Follow up over 4 years (main model used in the study):

Table 7.4

Mixed-effects ML regression — Number of obs = 6,945

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	145	9	47.9	90
Tooth	1,923	1	3.6	6

Log likelihood = -5494.5251 — Wald chi2(24) = 280.44; Prob > chi2 = 0.0000

T	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Visit						
2	.045214	.0155793	2.90	0.004	.0146792	.0757488
3	.1212712	.0198274	6.12	0.000	.0824102	.1601322
1.CVDHeartProblem	-.024333	.0836552	-0.29	0.771	-.1882941	.139628
Visit#CVDHeartProblem						
2 1	.1219177	.0255562	4.77	0.000	.0718285	.1720068
3 1	.1309908	.0352899	3.71	0.000	.0618238	.2001577
AgeCATnew3						
3	.4084322	.2030576	2.01	0.044	.0104466	.8064179
4	.8890243	.1962077	4.53	0.000	.5044642	1.273584
5	1.161596	.2038729	5.70	0.000	.7620122	1.561179
Sex	.0149784	.0763612	0.20	0.844	-.1346869	.1646436
RaceNew						
2	.0113325	.1476287	0.08	0.939	-.2780145	.3006795
3	.1261462	.1633677	0.77	0.440	-.1940487	.4463411
4	-.1160776	.1102038	-1.05	0.292	-.3320732	.0999179
5	-.0902348	.0874976	-1.03	0.302	-.2617269	.0812573
BMIcat						
1	.201812	.295785	0.68	0.495	-.3779159	.7815399
3	-.0570877	.1016588	-0.56	0.574	-.2563353	.1421598
4	-.140493	.1099199	-1.28	0.201	-.3559319	.074946
5	-.1310242	.1003812	-1.31	0.192	-.3277676	.0657193
Smoking						
1	.2532677	.1039247	2.44	0.015	.049579	.4569564
3	.1321845	.085304	1.55	0.121	-.0350083	.2993772
Diabetes	-.1365553	.1077013	-1.27	0.205	-.347646	.0745353
MHIbinary#Hypertension						
0 1	-.1238494	.1200261	-1.03	0.302	-.3590963	.1113974
1 0	-.1089137	.0944331	-1.15	0.249	-.2939991	.0761718
1 1	-.3587922	.1135388	-3.16	0.002	-.5813242	-.1362602
D4341	.2853078	.1042553	2.74	0.006	.0809712	.4896444
_cons	.7427116	.199102	3.73	0.000	.3524789	1.132944

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.1368015	.0179468	.1057847	.1769126
Tooth: Identity				
var(_cons)	.1201924	.0064554	.1081833	.1335346
var(Residual)	.1996477	.0040103	.1919404	.2076644

LR test vs. linear model: chi2(2) = 2892.50 Prob > chi2 = 0.0000

Follow up over 2 years only (sensitivity analysis model):

Table 8.4

Mixed-effects ML regression Number of obs = 5,619

Group Variable	No. of Groups	Observations per Group Minimum	Average	Maximum
ID	145	9	38.8	64
Tooth	1,900	1	3.0	4

Log likelihood = -4548.2251 Wald chi2(22) = 205.66
Prob > chi2 = 0.0000

T	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
2.Visit	.0416907	.0156233	2.67	0.008	.0110697	.0723117
1.CVDHeartProblem	-.0213355	.0858904	-0.25	0.804	-.1896775	.1470065
Visit#CVDHeartProblem						
2 1	.1259916	.0256194	4.92	0.000	.0757785	.1762047
AgeCATnew3						
3	.4274645	.2090355	2.04	0.041	.0177625	.8371665
4	.9097906	.2019568	4.50	0.000	.5139626	1.305619
5	1.186836	.2099038	5.65	0.000	.7754317	1.59824
Sex	.0146998	.0786305	0.19	0.852	-.1394132	.1688127
RaceNew						
2	.0048405	.1516851	0.03	0.975	-.2924569	.3021379
3	.1557496	.1681678	0.93	0.354	-.1738531	.4853524
4	-.1090754	.1133402	-0.96	0.336	-.331218	.1130673
5	-.0786822	.0899956	-0.87	0.382	-.2550703	.097706
BMIcat						
1	.159688	.3040545	0.53	0.599	-.436248	.7556239
3	-.0505971	.1046115	-0.48	0.629	-.255632	.1544377
4	-.1543223	.1131891	-1.36	0.173	-.3761689	.0675242
5	-.1332257	.1032676	-1.29	0.197	-.3356266	.0691751
Smoking						
1	.2438545	.1069377	2.28	0.023	.0342604	.4534485
3	.1114694	.0878301	1.27	0.204	-.0606745	.2836133

Diabetes	-.1467831	.1106913	-1.33	0.185	-.363734	.0701678
MHIbinary#Hypertension						
0 1	-.1532815	.1234217	-1.24	0.214	-.3951836	.0886207
1 0	-.1276232	.0970562	-1.31	0.189	-.3178498	.0626034
1 1	-.3961518	.1168763	-3.39	0.001	-.6252252	-.1670785
D4341	.2856728	.1071744	2.67	0.008	.075615	.4957307
_cons	.7474608	.2049443	3.65	0.000	.3457774	1.149144

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
ID: Identity				
var(_cons)	.1446761	.019035	.1117904	.1872359
Tooth: Identity				
var(_cons)	.119276	.0069034	.1064848	.1336036
var(Residual)	.1991663	.0046496	.1902586	.2084911

LR test vs. linear model: chi2(2) = 2274.75 Prob > chi2 = 0.0000

We can notice that the difference of mean alveolar bone loss after two years changed from 0.121 mm in the main model to 0.125 mm in the sensitivity analysis model. All other variables did not change significantly, and hence we preferred to use the model with four years of follow up with the reported estimates at two years and at four years.