Title

Correlation between the Number of Missing Teeth and Cognitive Function in Opioid Dependent and HIV + patients on antiretroviral medication, Methadone and Buprenorphine.

Author

Roitman, Igor

Publication Date

2011

Peer reviewed|Thesis/dissertation

Correlation between the Number of Missing Teeth and Cognitive Function in Opioid Dependent and HIV positive patients on antiretroviral medication, Methadone and Buprenorphine.

by

Igor Roitman

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in

Oral and Craniofacial Sciences

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Acknowledgments

I would like to thank my parents, Yaakov and Larisa, for giving me all they could, my wife, Inna, for supporting me along all along and encouraging me to pursue my dreams, my daughters, Shani and Zoe, for brightening my day every day and to all of my extensive family for believing in me all those years.

My special thanks to Mark and Steve for guiding and helping me in this project

Abstract

Introduction: The purpose of this study was to investigate Correlation between periodontal and cognitive status, determine influence of the medications on the periodontal status

Materials and Methods: The patient population was recruited from the community of San Francisco by advertisement and from the methadone clinic at San Francisco General Hospital and was divided into 4 groups: controls, opioid dependent receiving buprenorphine and antirethroviral medications, opioid dependent receiving Methadone with no antirethroviral and HIV+ opioid dependent receiving methadone and antirethroviral medications. Periodontal status, cognitive statuses were evaluated during the study period.

Results: Significant correlation between the number of missing teeth and decrease in cognitive function: Spearman rank correlation p value 0.02-0.07

Conclusion: we were able to demonstrate a significant correlation between the number of teeth and cognitive function. Since none of our patients were demented, dementia was not a confounding factor as it has been in studies looking at tooth loss and cognitive function in older adults.

.

Table of Contents

List of tables

Introduction

Emerging evidence suggests that a history of tooth loss may be associated with cognitive impairment in community-dwelling older adults. ([1] [2]. [3]). Cross-sectional analyses of nationally representative data from several countries using a variety of cognitive function tests show greater odds of impaired test performance or prevalence of dementia associated with a low number of teeth remaining. ([3]). Elderly women with nine or fewer teeth had twice the risk of developing dementia as those with 10 or more teeth [4]. While there is little published research on the oral health of injecting drug users (IDU), it is likely that their oral health will be compromised by the drugs they use as well as factors that characterize IDU lifestyles. IDU's lifestyles include tobacco use which are strongly associated with the incidence and prevalence of periodontal diseases, oral cancer and pre-cancerous conditions [[5]] IN addition IDU's often have poor nutrition and irregular eating patterns that have been associated with dental disease [6]. Suppression of pain responses to signs of decay by opiates, poor oral hygiene and limited access to dental care can also impact on the oral health of IDU's [7]. Higher levels of decay [Madinier I., Harrosch J., Dugourd M., Giraud-Morin C., Fosse T. [8]] and periodontal disease [9]and oro-facial/dental trauma [[9]] have been described in heroin and in-treatment methadone users. Higher levels of dental decay were found among IDU's than age-matched cohorts [10], [7] non-drug-using control groups [11 [8] and ex-drug-using control groups. Part of the reason for this increase in dental diseases in IDU's might be that opioids, amphetamines and alcohol cause xerostomia[[9], which

combined with poor oral hygiene and difficulty to access dental care becomes a significant risk factor for tooth loss.

Due to the poor oral hygiene, poor accessibility to treatment and financial constraints, missing teeth is a frequent finding among drug users. Besides affecting quality of life, tooth loss might also affect cognitive function. Emerging evidence suggests that a history of tooth loss may be associated with cognitive impairment in community-dwelling older adults. ([1] [2] [3]). Cross-sectional analyses of nationally representative data from several countries using a variety of cognitive function tests show a greater odds ratio of impaired test performance or prevalence of dementia associated with a lower number of remaining teeth ([3]). Edentulous persons aged 70 and older scored lower on a battery of cognitive tests than those with teeth, but the difference did not persist after adjusting for age and intelligence quotient.

The prospective findings from Grabe et al ([11]) suggest that the tooth loss precedes and plays a causal role in cognitive decline. Several causes related to oral health have been proposed for cognitive decline. For example, in fully or partially edentulous patients, low intake of Vit B has been proposed as one of the factors due to an inability to chew properly. In addition, inflammatory factors and LPS from periodontal disease can potentially cause vascular damage in the brain. Reports that cognitive function is related to measures of periodontal disease as well as tooth loss strengthen this latter hypothesis. In the NHANES 1988 to 1994 and 2001 to 2002 surveys, poor performance on the Digit Symbol Substitution Test or Serial Digit Learning Test was associated with clinical periodontal disease measures after adjusting for multiple confounding factor([3].

It is known that inflammation is a critical component of the pathogenesis of Alzheimer disease [12]). Although inflammation is not an initiator of this disorder, it nonetheless plays a pivotal role as a driving force that can modulate the neuropathology. Evidence from prospective studies demonstrates that elevation of pro-inflammatory serum markers [e.g. C-reactive protein, interleukin (IL)-1, TNF-a, IL-6 and a-1-antichymotypsin] may precede cognitive impairment [13], [14], [15]. In human autopsies, antigens from oral treponemes were more often found in samples from subjects with Alzheimer disease (14 of 16) than in samples from control subjects (4 of 18) ([16].).

IDU is also one of the major risk factors for HIV transmission. 12% of new HIV cases in the United States were among injection drug users ([17], according to Centers for Disease Control and Prevention people infected through injection drug use (IDU) accounted for 19% of all people living with HIV (204,600 persons). Sixteen percent of men (131,500 persons) and 26% of women (73,100 persons) living with HIV were infected through IDU ([18]. However, with the latest advancements in the treatment of HIV and wide use of antiretroviral medication, the mortality of HIV patients have declined significantly. A meta-analysis of studies from the mid-1990s to 2006 found that 72% of HIV-diagnosed persons in the United States entered HIV medical care within 4 months of diagnosis ([19]. Despite the success in reducing mortality from HIV due to the successful use of antiretroviral medication, HIV-associated neurocognitive disturbances are still an important clinical problem. Systematic evaluation of more than 1000 clinic patients in the CNS HIV Antiretroviral Effects Research (CHARTER) cohort demonstrated that neurologic impairment was present in 50% or more HIV positive subjects, a rate

comparable to that in the pre–antiretroviral era ([20]. The reasons for this might be ongoing viral replication and immune activation in the CNS, comorbid factors such as the use of both nonprescription and prescription drugs, perhaps including antiretroviral drugs, coinfections with other microbial agents such as hepatitis B and C, and genetic influences of both the virus and the host. [20]. There is a wide range of the reported results on the relationship between HIV and periodontal disease ([21],[22]. Most of the studies that reported correlations between HIV positive patients and increased risk for periodontal disease did not take into account some important covariants such as smoking. When smoking and other risk factor were included in the analysis, no significant differences were detected.[23] High but variable rates of smoking have been reported among individuals with HIV infection. Reports of smoking prevalence range from a low of 34% to as high as 74%. ([23, 24].

However, an argument can be made that older persons with cognitive impairment have poor compliance with oral hygiene and routine dental care because of their cognitive impairment, and that this is the reason for the correlation between loss of teeth and cognitive decline. We therefore were motivated to explore the correlation between tooth loss and cognitive function using serial cognitive exams in a much younger, non-demented patient population that suffers from tooth loss. Injection drug users (IDU) often experience tooth loss at a young age due to multiple factors, including poor oral hygiene, poor accessibility to treatment, and financial constraints. We thus hypothesized that tooth loss in injection drug users would be correlated with serial cognitive scores.

The purpose of this study was to investigate:

1. Correlation between periodontal and cognitive status
2. Determine influence of the medications on the periodontal status

Materials and Methods

The patient population was recruited from the community of San Francisco by advertisement and from the methadone clinic at San Francisco General Hospital and was divided into 4 groups: Group 1 (GR1) control group of healthy subjects, non-drug users and HIV-. Group 2 (GR2), 10 opiate dependent subjects, HIV-, group 3 (GR3) N opiate dependent, HIV – and Group 4 (GR4) N HIV+, opiate dependent subjects. GR1 was HIV-uninfected and received a two week course of daily ritonavir/darunavir (R/D) (100mg/800mg.) GR2 was HIV-uninfected and opiate-dependent. GR2 started buprenorphine opiate replacement therapy and after two weeks was given a two week course of daily ritonavir/darunavir (100mg/800mg). GR3 was HIV-uninfected and opiate dependent. GR3 received a 90-day course of methadone detoxification. GR4 was HIV-infected and opiate dependent. GR4 also received a 90-day course of methadone detoxification. GR1 and GR2 received two comprehensive periodontal exams, one exam before the administration of a two week course of ritonavir/darunavir, and a second exam approximately 2-3 weeks later after the ritonavir/darunavir administration had been completed. GR3 and GR4 received three comprehensive periodontal exams. The first exam was within one week of admission to the study, a second exam occurred approximately 35 days after admission to the study, and the third exam was approximately 90 to 120 days after admission to the study. At the initial screening visit, urine, blood and saliva samples were taken. Saliva samples were taken for proteomic analysis results of which will be reported later in another paper. The comprehensive periodontal exam was conducted on each subject which included number of teeth,

gingival index as described by Loe and Silness ([25], plaque index as described by Silness and Loe([26]. Probing depth and gingival recessions were measured using a University of North Carolina probe (UNC) (Hu Friedy) and Clinical Attachment Loss (CAL) was calculated according to Ramfjord, the distance from the Cemento Enamel Junction (CEJ) to the Free Gingival Margin was added to the pocket depth and CAL was calculated. In cases where free gingival margin was positioned above CEJ, negative [27]. Bleeding on Probing (BOP) was calculated as a percentage of the bleeding sites upon probing. The Cognitive score test was administered (Digit Symbol Substitution Test (DSST) during the baseline visit. The DSST is a pencil and paper test of psychomotor performance in which the subject is given a key grid of numbers and matching symbols and a test section with numbers and empty boxes (Wechsler Adult Intelligence Scale Revised. San Antonio, TX: Psychological Corporation, 1981.).

Group 1 and Group 2 were administered the DSST twice approximately two weeks apart - once before the administration of R/D and once after the administration of R/D.

Group3 and Group 4 were administered the DSST three times – the first was within one week of admission to the study, the second occurred approximately 35 days after admission to the study, and the third was approximately 90 to 120 days after admission to the study. No periodontal intervention was provided. Patients were referred to periodontal services when indicated.

43 patients were enrolled in the study, 29 males and 14 females. The average age was 42.2 y.o. Exclusion criteria included recent dental treatment, active antiretroviral

treatment, and inability to complete the follow up visits. The study was approved by Committee on Human Research (CHR) at UCSF.

Statistical Analysis

The Spearman rank correlation test was used to analyze the correlation between periodontal parameters, number of teeth and cognitive function. The difference between groups was analyzed by using Kruskal-Walis test. The effect of the drug intervention on periodontal status was tested by using Wicoxon Signed Rank test. The difference was calculated comparing visit 1 to visit 3 and visit 2 to visit 1. Regression analysis was done to see if there was an influence of other covariant such as smoking, age, gender.

Results

36 participants completed the study. 7 patients were lost to follow up or did not show for original examination due to various reasons. The mean age was 42.4 y.o. demographic data is presented in Table 1.

Table 1: Demographic data

	Group1	Group 2	Group3	Group4
Age (average)	43.27±2.97	46.27±2.58	40±2.97	39.6±2.98
Race	White 6 African American. 5	White 6 Latino 3 African American 1 Native American 1	White 7 Latino 2 African American 1 Native American 1	White 7 Latino 1 African American 2
Gender	Male 8 Female 3	Male 5 Female 6	Male 6 Female 5	Male 10 Female 0

There was no significant difference in clinical periodontal parameters between 1st and second exam in each group and between 2nd and 3rd exam in group 3 and 4. The initial and final data of clinical parameters is presented in tables 2 and 3.

Table 2: Initial Clinical Parameters

Group	# Teeth Present	Mean PII	Mean GI	Mean PD	Mean BOP	Mean GM	Mean CAL
1	25.5(3.83)	0.77(0.31)	0.61(0.29)	2.67(0.20)	0.41(0.21)	-0.24(0.55)	2.44(0.57)
2	18(8.18)	0.99(0.47)	0.94(0.35)	2.96(0.47)	0.47(0.2)	1.09(1.6)	4.05(1.99)
3	19.2(7.31)	0.95(0.28)	1.01(0.32)	2.88(0.47)	0.55(0.15)	0.47(1.36)	3.32(1.56)
4	16.7(10.56)	0.87(0.54)	0.85(0.51)	2.16(1.15)	0.29(0.23)	-0.08(0.56)	2.08(1.29)

Table 3: Final Clinical Parameters

Group	# Teeth Present	Mean PII	Mean GI	Mean PD	Mean BOP	Mean GM	Mean CAL
1	25.5(3.83)	0.84(0.45)	0.71(0.29)	2.66(0.23)	0.48(0.21)	-0.48(0.43)	2.17
2	17.9(7.7)	0.82(0.38)	0.85(0.43)	3.07(0.48)	0.45(0.28)	1.21(1.61)	4.21(1.72)
3	18(8.05)	1.14(0.37)	1.23(0.36)	2.86(0.41)	0.49(0.22)	0.64(1.36)	3.51(1.25)
4	16.6(10.6)	0.84(0.48)	0.81(0.44)	2.18(1.25)	0.32(019)	-0.11(0.49)	2.06(1.52)

The results are listed in Table 4,5,6,7 for each group

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	10	0.07	0.15	-0.04	0.18	0.07	-0.05	0.27	-0.21	0.33	0.13	0.18	0.76
Mean_CAL_diff21	10	-0.26	0.36	-0.52	-0.00	-0.18	-0.65	0.10	-0.80	0.29	0.084	0.048	0.67
Mean_GI_diff21	10	0.09	0.14	-0.01	0.20	0.10	-0.08	0.26	-0.08	0.28	0.090	0.068	0.18
Mean_GM_diff21	10	-0.24	0.34	-0.49	0.00	-0.18	-0.58	0.10	-0.76	0.20	0.084	0.051	0.27
Mean_PD_diff21	10	-0.02	0.12	-0.10	0.07	-0.04	-0.10	0.18	-0.18	0.19	0.49	0.67	0.12
Mean_PII_diff21	10	0.08	0.24	-0.09	0.24	0.00	-0.13	0.22	-0.14	0.65	0.38	0.34	0.031

Table 4: Group 1 Statistical analysis

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	8	0.02	0.21	-0.15	0.20	-0.01	-0.13	0.33	-0.29	0.33	0.84	0.78	0.91
Mean_CAL_diff21	7	0.28	0.52	-0.21	0.76	0.19	-0.42	1.04	-0.42	1.04	0.22	0.21	0.86
Mean_GI_diff21	8	-0.02	0.22	-0.20	0.17	-0.01	-0.20	0.36	-0.35	0.36	0.84	0.82	0.98
Mean_GM_diff21	7	0.18	0.47	-0.26	0.62	-0.01	-0.22	1.17	-0.22	1.17	0.81	0.35	0.036
Mean_PD_diff21	8	0.08	0.44	-0.29	0.45	0.01	-0.24	1.07	-0.33	1.07	0.95	0.62	0.039
Mean_PII_diff21	8	-0.13	0.29	-0.38	0.12	-0.23	-0.38	0.26	-0.50	0.26	0.25	0.25	0.22

Table 5: Group 2 Statistical analysis

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	9	0.02	0.11	-0.07	0.10	-0.01	-0.11	0.11	-0.13	0.20	0.82	0.66	0.74
Mean_CAL_diff21	9	0.20	1.07	-0.62	1.03	-0.04	-0.38	0.21	-0.61	2.98	0.65	0.59	0.0002
Mean_GI_diff21	9	0.07	0.28	-0.14	0.29	0.02	-0.21	0.47	-0.24	0.54	0.82	0.47	0.27
Mean_GM_diff21	9	-0.14	0.29	-0.36	0.08	-0.02	-0.38	0.10	-0.69	0.23	0.31	0.19	0.48
Mean_PD_diff21	9	-0.02	0.08	-0.08	0.04	-0.02	-0.10	0.08	-0.15	0.11	0.58	0.51	0.88
Mean_PII_diff21	9	0.02	0.22	-0.15	0.19	0.00	-0.14	0.25	-0.22	0.47	1.00	0.77	0.22

Table 6: Group 3 analysis

Table 7: Group 4 Statistical Analysis

There was little correlation within the groups between cognitive score and number of teeth present in the mouth, possibly due to a small sample. There was a tendency toward higher cognitive score in patients with greater number of teeth present. When the groups were collapsed, there was very strong correlation between the number of teeth and cognitive score (table 7)

Table 8: Correlations between cognitive function and number of teeth present

IVar	JVar	N	Pearson Correlation	Pearson 95% CI Lower	Pearson 95% CI Upper	Pearson P-Value	Spearman Rank Correlation	Spearman 95% CI Lower	Spearman 95% CI Upper	Spearman P-Value

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	7	-0.05	0.18	-0.22	0.11	-0.09	-0.28	0.31	-0.28	0.31	0.30	0.46	0.27
Mean_CAL_diff21	7	-0.11	0.42	-0.50	0.28	-0.30	-0.58	0.42	-0.58	0.42	0.58	0.51	0.16
Mean_GI_diff21	7	-0.22	0.36	-0.55	0.11	-0.15	-0.83	0.17	-0.83	0.17	0.30	0.16	0.49
Mean_GM_diff21	7	0.09	0.36	-0.25	0.42	0.18	-0.48	0.63	-0.48	0.63	0.58	0.54	0.96
Mean_PD_diff21	7	-0.20	0.34	-0.52	0.12	-0.10	-0.86	0.24	-0.86	0.24	0.11	0.17	0.42
Mean_PII_diff21	7	-0.14	0.36	-0.47	0.19	0.09	-0.67	0.17	-0.67	0.17	0.58	0.34	0.034

IVar	JVar	N	Pearson Correlation	Pearson 95% CI Lower	Pearson 95% CI Upper	Pearson P-Value	Spearman Rank Correlation	Spearman 95% CI Lower	Spearman 95% CI Upper	Spearman P-Value
Cognitive_score_1	Teeth_Present_1	39	0.362	0.052	0.608	0.024	0.448	0.155	0.669	0.0042
Cognitive_score_2	Teeth_Present_2	39	0.332	0.018	0.586	0.039	0.322	0.007	0.579	0.045
Cognitive_score_3	Teeth_Present_3	18	0.465	-.002	0.766	0.052	0.551	0.113	0.810	0.018

The regression analysis was done to analyze possible cofounders for correlation between cognitive score and number of missing teeth. Except race, no other cofounders were found as a significant factor (See table 8).

Table 9: Regression Analysis of Cognitive Function and Number of Missing Teeth

Model	Number of Obs	Dependent	Variable	Value	Estimate	Lower 95% CI	Upper 95% CI	Type 3 P-Value	P-Value	Quadratic P-Value	Normality P-Value
1	39	cognitive_score_1	TEETH_PRESENT_1		**0.536**	**0.076**	**0.997**	**0.024**		0.17	0.80
			TEETH_PRESENT_1 (per 10 units)		5.4	0.758	10.0				

				WHITE	NO	0.000					
				WHITE	YES	**7.9**	**0.168**	**15.7**	**0.045**		
2	39	cognitive_score_1	TEETH_PRESENT_1			**0.460**	**0.051**	**0.869**	**0.029**	**0.017**	0.99
			TEETH_PRESENT_1 (per 10 units)			4.6	0.511	8.7			
			RACE	W		0.000			**0.0018**		
			RACE	AA		**-13.05**	**-21.52**	**-4.588**	**0.0035**		
			RACE	L		-9.334	-19.36	0.693	0.067		
			RACE	N		**15.4**	**0.408**	**30**	**0.044**		
3	39	cognitive_score_1	TEETH_PRESENT_1			**0.655**	**0.160**	**1.150**	**0.011**	0.18	0.38
			TEETH_PRESENT_1 (per 10 units)			6.6	1.596	11.5			
			GENDER	M		0.000					
			GENDER	F		5.2	-4.072	14.5	0.26		
4	39	cognitive_score_1	TEETH_PRESENT_1			**0.521**	**0.031**	**1.011**	**0.038**	0.17	0.21
			TEETH_PRESENT_1 (per 10 units)			5.2	0.306	10.1			
			HIV	NO		0.000					
			HIV	YES		-4.595	-13.78	4.6	0.32		

5	39	cognitive_score_1	TEETH_PRESENT_1		**0.585**	**0.107**	**1.063**	**0.018**		0.31	0.83
			TEETH_PRESENT_1 (per 10 units)		5.8	1.068	10.6				
			SMOKE	NO	0.000						
			SMOKE	YES	5.6	-6.078	17.3	0.34			
6	39	cognitive_score_1	TEETH_PRESENT_1		**0.579**	**0.064**	**1.095**	**0.029**		0.23	0.59
			TEETH_PRESENT_1 (per 10 units)		5.8	0.636	11.0				
			AGE__YRS_		0.006	-0.467	0.478	0.98		0.073	
			AGE__YRS_ (per 10 units)		0.056	-4.671	4.8				
7	39	cognitive_score_1	TEETH_PRESENT_1		**0.537**	**0.033**	**1.040**	**0.037**		0.19	0.44
			TEETH_PRESENT_1 (per 10 units)		5.4	0.332	10.4				
			WEIGHT__KG_		0.097	-0.254	0.448	0.58		0.41	
			WEIGHT__KG_ (per 10 units)		0.970	-2.536	4.5				
8	39	cognitive_score_1	TEETH_PRESENT_1		0.462	-0.003	0.926	0.051		0.10	0.67

TEETH_PRESENT_ 1 (per 10 units)		4.6	-0.025	9.3	
HIV	NO	0.000			
HIV	YES	-5.822	-14.53	2.9	0.18
WHITE	NO	0.000			
WHITE	YES	**8.6**	**0.919**	**16.2**	**0.029**

Pink cells indicate effects with p<0.05

Red cells indicate evidence for violations of linearity assumptions.

Orange cells indicate evidence for violations of normality assumptions.

Discussion

The major finding of our study was the strong positive correlation between number of teeth and serial cognitive scores in a young, non-demented population. No covariates were found significant except race. There was no significant change in periodontal status in any group during the study. Our study failed to show any effect of antiretroviral medication on periodontal status. Since no periodontal treatment has been provided, we did not anticipate any changes in those parameters.

Several studies demonstrated correlation between the number of missing teeth and decrease in cognitive function. [28] Although the correlation between smoking, cognitive function and tooth loss was not seen in our study and this is in agreement with other studies [29], smoking cannot be ruled out as a causative factor for periodontitis and the tooth loss. Since the study population was from the lower socioeconomic level with history of drug abuse, some of the decrease in cognitive function can be a result of the drug damage. A study by Miitrovic showed impaired visual memory in heroin drug addicts that was correlated to the duration of the drug use and daily dose. [30] Soyka et al [31] showed in their study that long term methadone treatment slightly improves the executive and visual construction function.

Opioid-substitution treatment can possibly affect cognitive function. Rapeli et al [32] demonstrated poorer working memory performance comparing to controls in patients on methadone and buprenorphine. This might be another confounder in our results of decreased cognitive function.

Matthews et al [33] in their recent study used the data from Reasons for Geographic and Racial Differences in Stroke (REGARDS) to investigate the correlation between tooth loss and cognitive function. They also showed correlation between number of missing teeth and poorer cognitive function. They concluded that socio economic status might be a factor in tooth loss and they were unable to assess separately role of number of missing teeth and socio economic status on cognitive function. The same limitations apply to our study, since most of the participants were either homeless people, or

people with a lower socioeconomic status who were not able to afford dental treatment. The same limitations apply to our study.

Stein et al in their study in 2007 [34] analyzed the results of the Nun study, Participants in the Nun Study are Roman Catholic sisters who are members of the international congregation of the School Sisters of Notre Dame. Of the participants who did not have dementia at the first examination, those with few teeth (zero to nine) had an increased risk of developing dementia during the study compared with those who had 10 or more teeth. This study shows the potential correlation between the number of missing teeth and dementia regardless of socio economic status.

The increase in risk was found only in those without apoE4 allele, which is responsible for onset of Alzheimer disease. This study shows the potential correlation between the number of missing teeth and dementia regardless of socio economic status and genetic predisposition.

Gatz et al [4] used the data from the Swedish twin registry to find potential risk factors for dementia or Alzheimer disease in the future. They found that tooth loss and educational status were statistically significant in multivariate analysis. According to their study the twin with dementia was four times more likely to have poorer oral health. Poorer oral health was correlated with short adult height, less participation in mentally stimulating leisure activities, and history of cerebrovascular disease.[4] Unfortunately, in this study no intervention was provided for the study population, as it would be interesting to see if improvement in periodontal status and replacement of the missing teeth would influence cognitive function. Unfortunately, most of the

participants continued to use drugs during our study and we couldn't estimate the influence of the medications. The interesting finding that would be described in the other publication is that some of the proteins became expressed in the saliva only after administering antiretroviral medications, which may potentially lead to some explanation to the dementia in HIV patients who are on antiretroviral medication.

The small sample size and short follow up period are other limitations of our study. However, it was difficult to recruit more participants to the study in from this cohort. In addition and the compliance of the study population for a long period of time would be very unpredictable, which would result in the loss of many patients during the longer follow up period.

Although it seems biologically plausible that periodontal disease and tooth loss could influence cognitive function through inflammatory process, but it is also possible that lower number of teeth by itself is an indicator of underlying condition that can affect the cognition and are not accounted as a confounder.

Study Limitations

A small sample size is a limitation of our study. In addition, although it seems biologically plausible that periodontal disease and tooth loss could influence cognitive function through inflammatory processes and/or the direct effects of oral microbial toxins on the central nervous system, it is also possible that a lower number of teeth by itself is an indicator of an underlying condition that can affect cognition and that is not accounted for as a confounder.

Conclusion

There is an increased interest in the recent research in the link between the oral health and cognitive function. Our study is unique in that it was conducted in a young, non-demented group of subjects. Similar to previous studies in older adults, we were able to demonstrate a significant correlation between the number of teeth and cognitive function. Since none of our patients were demented, dementia was not a confounding factor as it has been in studies looking at tooth loss and cognitive function in older

adults. However, the direction of causation remains unclear. Future research should now focus on interventions that improve periodontal health, including replacement of missing teeth, to determine if cognition can be improved.

References

1. Stewart, R. and V. Hirani, *Dental health and cognitive impairment in an English national survey population.* J Am Geriatr Soc, 2007. **55**(9): p. 1410-4.
2. Kim, J.M., et al., *Dental health, nutritional status and recent-onset dementia in a Korean community population.* Int J Geriatr Psychiatry, 2007. **22**(9): p. 850-5.

3. Stewart, R., et al., *Oral health and cognitive function in the Third National Health and Nutrition Examination Survey (NHANES III).* Psychosom Med, 2008. **70**(8): p. 936-41.

4. Gatz, M., et al., *Potentially modifiable risk factors for dementia in identical twins.* Alzheimers Dement, 2006. **2**(2): p. 110-7.

5. Ylostalo, P., et al., *The relation of tobacco smoking to tooth loss among young adults.* Eur J Oral Sci, 2004. **112**(2): p. 121-6.

6. Zador, D., P.M. Lyons Wall, and I. Webster, *High sugar intake in a group of women on methadone maintenance in south western Sydney, Australia.* Addiction, 1996. **91**(7): p. 1053-61.

7. Scheutz, F., *Five-year evaluation of a dental care delivery system for drug addicts in Denmark.* Community Dent Oral Epidemiol, 1984. **12**(1): p. 29-34.

8. Madinier, I., et al., *[The buccal-dental health of drug addicts treated in the University hospital centre in Nice].* Presse Med, 2003. **32**(20): p. 919-23.

9. Abdollahi, M. and M. Radfar, *A review of drug-induced oral reactions.* J Contemp Dent Pract, 2003. **4**(1): p. 10-31.

10. Rosenstein, D.I., *Effect of long-term addiction to heroin on oral tissues.* J Public Health Dent, 1975. **35**(2): p. 118-22.

11. Grabe, H.J., et al., *Tooth loss and cognitive impairment.* J Clin Periodontol, 2009. **36**(7): p. 550-7.

12. Finch, C.E. and T.E. Morgan, *Systemic inflammation, infection, ApoE alleles, and Alzheimer disease: a position paper.* Curr Alzheimer Res, 2007. **4**(2): p. 185-9.

13. Yaffe, K., et al., *Inflammatory markers and cognition in well-functioning African-American and white elders.* Neurology, 2003. **61**(1): p. 76-80.

14. Dik, M.G., et al., *Serum inflammatory proteins and cognitive decline in older persons.* Neurology, 2005. **64**(8): p. 1371-7.

15. Tan, Z.S., et al., *Inflammatory markers and the risk of Alzheimer disease: the Framingham Study.* Neurology, 2007. **68**(22): p. 1902-8.

16. Riviere, G.R., K.H. Riviere, and K.S. Smith, *Molecular and immunological evidence of oral Treponema in the human brain and their association with Alzheimer's disease.* Oral Microbiol Immunol, 2002. **17**(2): p. 113-8.

17. Lansky, A., et al., *Epidemiology of HIV in the United States.* J Acquir Immune Defic Syndr. **55 Suppl 2**: p. S64-8.

18. Moore, R.D., *Epidemiology of HIV infection in the United States: implications for linkage to care.* Clin Infect Dis. **52 Suppl 2**: p. S208-13.

19. Marks, G., et al., *Entry and retention in medical care among HIV-diagnosed persons: a meta-analysis.* AIDS. **24**(17): p. 2665-78.

20. Clifford, D.B., *HIV-associated neurocognitive disease continues in the antiretroviral era.* Top HIV Med, 2008. **16**(2): p. 94-8.

21. Kroidl, A., et al., *Prevalence of oral lesions and periodontal diseases in HIV-infected patients on antiretroviral therapy.* Eur J Med Res, 2005. **10**(10): p. 448-53.

22. Pinheiro, A., et al., *Dental and oral lesions in HIV infected patients: a study in Brazil.* Int Dent J, 2004. **54**(3): p. 131-7.

23. Aichelmann-Reidy, M.E., D.L. Wrigley, and J.C. Gunsolley, *HIV infection and bone loss due to periodontal disease.* J Periodontol. **81**(6): p. 877-84.

24. Crothers, K., et al., *The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans.* J Gen Intern Med, 2005. **20**(12): p. 1142-5.

25. Loe, H. and J. Silness, *Periodontal Disease in Pregnancy. I. Prevalence and Severity.* Acta Odontol Scand, 1963. **21**: p. 533-51.

26. Silness, J. and H. Loe, *Periodontal Disease in Pregnancy. Ii. Correlation between Oral Hygiene and Periodontal Condtion.* Acta Odontol Scand, 1964. **22**: p. 121-35.

27. Goodson, J.M., *Diagnosis of periodontitis by physical measurement: interpretation from episodic disease hypothesis.* J Periodontol, 1992. **63**(4 Suppl): p. 373-82.

28. Shimazaki, Y., et al., *Influence of dentition status on physical disability, mental impairment, and mortality in institutionalized elderly people.* J Dent Res, 2001. **80**(1): p. 340-5.

29. Noble, J.M., et al., *Periodontitis is associated with cognitive impairment among older adults: analysis of NHANES-III.* J Neurol Neurosurg Psychiatry, 2009. **80**(11): p. 1206-11.

30. Mitrovic, S.M., et al., *The impact of heroin on visual memory.* Eur Rev Med Pharmacol Sci. **15**(5): p. 524-31.

31. Soyka, M., et al., *Cognitive function in short- and long-term substitution treatment: are there differences?* World J Biol Psychiatry. **11**(2 Pt 2): p. 400-8.

32. Rapeli, P., et al., *Memory function in opioid-dependent patients treated with methadone or buprenorphine along with benzodiazepine: longitudinal change in comparison to healthy individuals.* Subst Abuse Treat Prev Policy, 2009. **4**: p. 6.

33. Matthews, J.C., et al., *The association between self-reported tooth loss and cognitive function in the REasons for Geographic And Racial Differences in Stroke study: an assessment of potential pathways.* J Am Dent Assoc. **142**(4): p. 379-90.

34. Stein, P.S., et al., *Tooth loss, dementia and neuropathology in the Nun study.* J Am Dent Assoc, 2007. **138**(10): p. 1314-22; quiz 1381-2.

Table 1 Demographic Data

	Group1	Group 2	Group3	Group4
Age (average)	43.27±2.97	46.27±2.58	40±2.97	39.6±2.98
Race	White 6 African American. 5	White 6 Latino 3 African American 1 Native American 1	White 7 Latino 2 African American 1 Native American 1	White 7 Latino 1 African American 2
Gender	Male 8 Female 3	Male 5 Female 6	Male 6 Female 5	Male 10 Female 0

Table 2 Initial Clinical Parameter

Group	# Teeth Present	Mean PII	Mean GI	Mean PD	Mean BOP	Mean GM	Mean CAL
1	25.5(3.83)	0.77(0.31)	0.61(0.29)	2.67(0.20)	0.41(0.21)	-0.24(0.55)	2.44(0.57)
2	18(8.18)	0.99(0.47)	0.94(0.35)	2.96(0.47)	0.47(0.2)	1.09(1.6)	4.05(1.99)
3	19.2(7.31)	0.95(0.28)	1.01(0.32)	2.88(0.47)	0.55(0.15)	0.47(1.36)	3.32(1.56)
4	16.7(10.56)	0.87(0.54)	0.85(0.51)	2.16(1.15)	0.29(0.23)	-0.08(0.56)	2.08(1.29)

Table 3 Final Clinical Parametr

Group	# Teeth Present	Mean PII	Mean GI	Mean PD	Mean BOP	Mean GM	Mean CAL
1	25.5(3.83)	0.84(0.45)	0.71(0.29)	2.66(0.23)	0.48(0.21)	-0.48(0.43)	2.17
2	17.9(7.7)	0.82(0.38)	0.85(0.43)	3.07(0.48)	0.45(0.28)	1.21(1.61)	4.21(1.72)
3	18(8.05)	1.14(0.37)	1.23(0.36)	2.86(0.41)	0.49(0.22)	0.64(1.36)	3.51(1.25)
4	16.6(10.6)	0.84(0.48)	0.81(0.44)	2.18(1.25)	0.32(019)	-0.11(0.49)	2.06(1.52)

Table 4 Group 1 Statistical Analysis

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	10	0.07	0.15	-0.04	0.18	0.07	-0.05	0.27	-0.21	0.33	0.13	0.18	0.76
Mean_CAL_diff21	10	-0.26	0.36	-0.52	-0.00	-0.18	-0.65	0.10	-0.80	0.29	0.084	0.048	0.67
Mean_GI_diff21	10	0.09	0.14	-0.01	0.20	0.10	-0.08	0.26	-0.08	0.28	0.090	0.068	0.18
Mean_GM_diff21	10	-0.24	0.34	-0.49	0.00	-0.18	-0.58	0.10	-0.76	0.20	0.084	0.051	0.27
Mean_PD_diff21	10	-0.02	0.12	-0.10	0.07	-0.04	-0.10	0.18	-0.18	0.19	0.49	0.67	0.12
Mean_PII_diff21	10	0.08	0.24	-0.09	0.24	0.00	-0.13	0.22	-0.14	0.65	0.38	0.34	0.031

Table 5 Group 2 Statistical Analysis

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	8	0.02	0.21	-0.15	0.20	-0.01	-0.13	0.33	-0.29	0.33	0.84	0.78	0.91
Mean_CAL_diff21	7	0.28	0.52	-0.21	0.76	0.19	-0.42	1.04	-0.42	1.04	0.22	0.21	0.86
Mean_GI_diff21	8	-0.02	0.22	-0.20	0.17	-0.01	-0.20	0.36	-0.35	0.36	0.84	0.82	0.98
Mean_GM_diff21	7	0.18	0.47	-0.26	0.62	-0.01	-0.22	1.17	-0.22	1.17	0.81	0.35	0.036
Mean_PD_diff21	8	0.08	0.44	-0.29	0.45	0.01	-0.24	1.07	-0.33	1.07	0.95	0.62	0.039
Mean_PII_diff21	8	-0.13	0.29	-0.38	0.12	-0.23	-0.38	0.26	-0.50	0.26	0.25	0.25	0.22

Table 6: Group 3 Statistical

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	9	0.02	0.11	-0.07	0.10	-0.01	-0.11	0.11	-0.13	0.20	0.82	0.66	0.74
Mean_CAL_diff21	9	0.20	1.07	-0.62	1.03	-0.04	-0.38	0.21	-0.61	2.98	0.65	0.59	0.0002
Mean_GI_diff21	9	0.07	0.28	-0.14	0.29	0.02	-0.21	0.47	-0.24	0.54	0.82	0.47	0.27
Mean_GM_diff21	9	-0.14	0.29	-0.36	0.08	-0.02	-0.38	0.10	-0.69	0.23	0.31	0.19	0.48
Mean_PD_diff21	9	-0.02	0.08	-0.08	0.04	-0.02	-0.10	0.08	-0.15	0.11	0.58	0.51	0.88
Mean_PII_diff21	9	0.02	0.22	-0.15	0.19	0.00	-0.14	0.25	-0.22	0.47	1.00	0.77	0.22

Table 7 Group 4 Statistical analysis

Variable	N	Mean	SD	Mean 95% CI Lower	Mean 95% CI Upper	Median	Median 95% CI Lower	Median 95% CI Upper	Min	Max	Wilcoxon Signed-Rank P-Value	T-test P-Value	P-Value Normality
Mean_BOP_diff21	7	-0.05	0.18	-0.22	0.11	-0.09	-0.28	0.31	-0.28	0.31	0.30	0.46	0.27
Mean_CAL_diff21	7	-0.11	0.42	-0.50	0.28	-0.30	-0.58	0.42	-0.58	0.42	0.58	0.51	0.16
Mean_GI_diff21	7	-0.22	0.36	-0.55	0.11	-0.15	-0.83	0.17	-0.83	0.17	0.30	0.16	0.49
Mean_GM_diff21	7	0.09	0.36	-0.25	0.42	0.18	-0.48	0.63	-0.48	0.63	0.58	0.54	0.96
Mean_PD_diff21	7	-0.20	0.34	-0.52	0.12	-0.10	-0.86	0.24	-0.86	0.24	0.11	0.17	0.42
Mean_PII_diff21	7	-0.14	0.36	-0.47	0.19	0.09	-0.67	0.17	-0.67	0.17	0.58	0.34	0.034

Table 8: Correlations between cognitive function and number of teeth present

IVar	JVar	N	Pearson Correlation	Pearson 95% CI Lower	Pearson 95% CI Upper	Pearson P-Value	Spearman Rank Correlation	Spearman 95% CI Lower	Spearman 95% CI Upper	Spearman P-Value
Cognitive_score_1	**Teeth_Present_1**	**39**	0.362	0.052	0.608	0.024	0.448	0.155	0.669	0.0042
Cognitive_score_2	**Teeth_Present_2**	**39**	0.332	0.018	0.586	0.039	0.322	0.007	0.579	0.045
Cognitive_score_3	**Teeth_Present_3**	**18**	0.465	-.002	0.766	0.052	0.551	0.113	0.810	0.018

Table 9: Regression Analysis of Cognitive Function and Number of Missing Teeth

Model	Number of Obs	Dependent	Variable	Value	Estimate	Lower 95% CI	Upper 95% CI	P-Value	Type 3 P-Value	Quadratic P-Value	Normality P-Value
1	39	cognitive_score_1	TEETH_PRESENT_1		**0.536**	**0.076**	**0.997**	**0.024**		0.17	0.80
			TEETH_PRESENT_1 (per 10 units)		5.4	0.758	10.0				
			WHITE	NO	0.000						
			WHITE	YES	**7.9**	**0.168**	**15.7**	**0.045**			
2	39	cognitive_score_1	TEETH_PRESENT_1		**0.460**	**0.051**	**0.869**	**0.029**		**0.017**	0.99
			TEETH_PRESENT_1 (per 10 units)		4.6	0.511	8.7				
			RACE	W	0.000				**0.0018**		
			RACE	AA	**-13.05**	**-21.52**	**-4.588**	**0.0035**			
			RACE	L	-9.334	-19.36	0.693	0.067			
			RACE	N	**15.4**	**0.408**	**30**	**0.044**			
3	39	cognitive_score_1	TEETH_PRESENT_1		**0.655**	**0.160**	**1.150**	**0.011**		0.18	0.38

			TEETH_PRESENT _1 (per 10 units)		6.6	1.596	11.5				
			GENDER	M	0.000						
			GENDER	F	5.2	-4.072	14.5	0.26			
4	39	cognitive_score_1	TEETH_PRESENT _1		**0.521**	**0.031**	**1.011**	**0.038**		0.17	0.21
			TEETH_PRESENT _1 (per 10 units)		5.2	0.306	10.1				
			HIV	NO	0.000						
			HIV	YES	-4.595	-13.78	4.6	0.32			
5	39	cognitive_score_1	TEETH_PRESENT _1		**0.585**	**0.107**	**1.063**	**0.018**		0.31	0.83
			TEETH_PRESENT _1 (per 10 units)		5.8	1.068	10.6				
			SMOKE	NO	0.000						
			SMOKE	YES	5.6	-6.078	17.3	0.34			
6	39	cognitive_score_1	TEETH_PRESENT _1		**0.579**	**0.064**	**1.095**	**0.029**		0.23	0.59
			TEETH_PRESENT _1 (per 10 units)		5.8	0.636	11.0				
			AGE__YRS_		0.006	-0.467	0.478	0.98		0.073	

			AGE__YRS_ (per 10 units)		0.056	-4.671	4.8				
7	39	cognitive_score_1	TEETH_PRESENT_1		**0.537**	**0.033**	**1.040**	**0.037**		0.19	0.44
			TEETH_PRESENT_1 (per 10 units)		5.4	0.332	10.4				
			WEIGHT__KG_		0.097	-0.254	0.448	0.58		0.41	
			WEIGHT__KG_ (per 10 units)		0.970	-2.536	4.5				
8	39	cognitive_score_1	TEETH_PRESENT_1		0.462	-0.003	0.926	0.051		0.10	0.67
			TEETH_PRESENT_1 (per 10 units)		4.6	-0.025	9.3				
			HIV	NO	0.000						
			HIV	YES	-5.822	-14.53	2.9	0.18			
			WHITE	NO	0.000						
			WHITE	YES	**8.6**	**0.919**	**16.2**	**0.029**			

Pink cells indicate effects with p<0.05

Red cells indicate evidence for violations of linearity assumptions.

Orange cells indicate evidence for violations of normality assumptions.

Publishing Agreement

It is the policy of the University to encourage the distribution of all theses, dissertations, and manuscripts. Copies of all UCSF theses, dissertations, and manuscripts will be routed to the library via the Graduate Division. The library will make all theses, dissertations, and manuscripts accessible to the public and will preserve these to the best of their abilities, in perpetuity.

Please sign the following statement:
I hereby grant permission to the Graduate Division of the University of California, San
Francisco to release copies of my thesis, dissertation, or manuscript to the Campus
Library to provide access and preservation, in whole or in part, in perpetuity.

Author Signature

12/08/2011

Date