Potential Associations Between Chronic Respiratory Disease and Periodontal Disease: Analysis of National Health and Nutrition Examination Survey III*

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Background: Associations between poor oral health and chronic lung disease have recently been reported. The present study evaluated these potential associations by analyzing data from the National Health and Nutrition Examination Survey III (NHANES III), which documents the general health and nutritional status of randomly selected United States subjects from 1988 to 1994.

Methods: This cross-sectional, retrospective study of the NHANES III database included a study population of 13,792 subjects ≥20 years of age with at least 6 natural teeth. A history of bronchitis and/or emphysema was recorded from the medical questionnaire, and a dichotomized variable combined those with either chronic bronchitis and/or emphysema, together considered as chronic obstructive pulmonary disease (COPD). Subject lung function was estimated by calculating the ratio of forced expiratory volume (FEV) after 1 second (FEV_1)/forced vital capacity (FVC). Oral health status was assessed from the DMFS/T index (summary of cumulative caries experience), gingival bleeding, gingival recession, gingival probing depth, and periodontal attachment level. Unweighted analyses were used for initial examination of the data, and a weighted analysis was performed in a final logistic regression model adjusting for age, gender, race and ethnicity, education, income, frequency of dental visits, diabetes mellitus, smoking, and alcohol use.

Results: The mean age of all subjects was 44.4 ± 17.8 years (mean ± SD): COPD = 51.2 ± 17.9 years and subjects without COPD = 43.9 ± 17.7 years. Subjects with a history of COPD had more periodontal attachment loss than subjects without COPD (1.48 ± 1.35 mm versus 1.17 ± 1.09 mm, $P = 0.0001$). Subjects with mean attachment loss (MAL) ≥3.0 mm had a higher risk of COPD than those having MAL <3.0 mm (odds ratio, 1.45; 95% CI, 1.02 to 2.05). A trend was noted in that lung function appeared to diminish with increasing periodontal attachment loss.

Conclusions: The findings of the present analysis support recently published reports that suggest an association between periodontal disease and COPD. *J Periodontol 2001;72:50-56.*

KEY WORDS

Lung diseases, obstructive; National Health and Nutrition Examination Survey III; oral health; periodontal diseases/complications; periodontal attachment loss/complications; risk factors; cross-sectional studies.

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Chronic obstructive pulmonary disease (COPD) is a condition in which there is chronic obstruction to airflow with excess production of sputum as a result of chronic bronchitis and or emphysema.[1] A recent report ranked COPD worldwide as the sixth leading cause of mortality (2.2 million deaths).[2] The cost of treating this condition amounts to billions of dollars annually in the United States alone. The most important established risk factor for COPD is a history of prolonged cigarette smoking.[3] Chronic exposure to toxic atmospheric pollutants (e.g., second-hand smoke) may also contribute to the disease. Genetic conditions including a defective alpha 1-antitrypsin gene, variant alpha 1-antichymotrypsin, alpha 2-macroglobulin, vitamin D-binding protein, and blood group antigen genes may also predispose subjects to COPD.[4] Identification of potential risk factors that contribute to the pathogenesis of COPD may suggest interventions that may prevent or delay the initiation or slow the progression of the disease.

Recent cross-sectional epidemiologic studies have suggested a potential association between poor oral health and respiratory diseases such as pneumonia[5-7] and COPD.[8,9] Potential mechanisms that may account for these associations have been recently

reviewed.[10] Lower respiratory tract infections, including exacerbation of COPD, depend on the initial colonization of microbial pathogens to oral/pharyngeal surfaces. The pathogens are subsequently shed into the salivary secretions, together with oral bacteria, hydrolytic enzymes, and proinflammatory cytokines. Thus, the contents of this secretion may contaminate and induce alterations of the respiratory epithelium.[10] Oral bacteria may modulate the adhesion of respiratory pathogens to mucosal surfaces by altering the environment of the upper airway to enhance the potential for respiratory pathogen colonization of the lower respiratory tract.[6] Enzymes within the aspirate may destroy macromolecules on the mucosal surface to expose receptors that permit adhesion and colonization of respiratory pathogens, or may destroy protective secretory molecules such as mucins, which clear bacteria from the mucosal surface. Finally, bacterial products or cytokines such as interleukin (IL)-1, IL-6, and IL-8 and tumor necrosis factor-α (TNF-α) in the aspirate may induce further cytokine production from respiratory epithelial cells, resulting in recruitment of inflammatory cells. The resulting inflamed mucosal epithelium may be more susceptible to infection by respiratory pathogens.[11,12]

It is therefore possible that accumulation of oral pathogens associated with periodontal disease may increase the risk for serious lower respiratory tract infection in susceptible subjects, including pneumonia in hospitalized subjects or exacerbation and progression of COPD. Periodontal disease may alter environmental conditions to permit mucosal colonization and infection by respiratory pathogens.[6-8,10,13] Oral conditions likely work in concert with other factors (continued smoking, environmental pollutants, viral infections, allergy, genetic factors, etc.) to contribute to progression of respiratory diseases.

The goal of the present study was to, therefore, evaluate potential associations between respiratory diseases and oral health status in the general population by analyzing data from the National Health and Nutrition Examination Survey III (NHANES III).

MATERIALS AND METHODS

Study Population

NHANES III, conducted by the National Center for Health Statistics,[14] documented the general health and nutritional status of individuals randomly selected from sampling areas that encompassed the continental United States from 1988 to 1994. Of these subjects, 13,792 who were at least 20 years old and had 6 natural teeth received a standardized dental examination, described by Drury et al.[15] The actual sample sizes for analysis varied depending on different analytical models. A description of the methods used to collect information concerning the oral health status of patients pertinent to the goals of this study is described in the Measures of Oral Health section below.

Population characteristics. Information regarding a subject's demographic, socioeconomic status (SES), and lifestyle was considered in this study. Demographic and medical histories obtained from questionnaires and direct physical examinations performed by a physician were analyzed.[16] Demographic variables included in this analysis were age in years, gender, race, and ethnicity (categorized as non-Hispanic white, non-Hispanic black, Mexican-American, and other races and ethnicity). SES variables considered included education (categorized as those who had 0 to 7, 8 to 11, 12, and more than 12 years of school education), household income (categorized as no income, <US $30,000, and ≥US $30,000) and frequency of dental visits (divided into 5 categories: more than once a year, once every 2 years, less than every 2 years, when needed to relieve pain, or not ever). Lifestyle characteristics examined included history of smoking (number of pack years estimated by multiplying the number of years each subject smoked by the average number of packs of cigarettes smoked per day) and alcohol consumption (dichotomized as non-drinker and drinker). A history of diabetes mellitus, known to be a risk factor for periodontitis,[17] was also considered in the analysis.

Respiratory disease/condition. A history of bronchitis and/or emphysema was obtained from responses to the questionnaire. A dichotomized variable was then constructed by combining those reporting having either chronic bronchitis and/or emphysema.

Information regarding the lung function of each subject was also estimated by calculating the ratio of forced expiratory volume (FEV) after 1 second (FEV1) /forced vital capacity (FVC) × 100. Trained technicians, who were supervised by licensed examining physicians,[16] performed lung function testing (by spirometry). A testing session consisted of repeated forced vital capacity (FVC) maneuvers. Each maneuver required the examinee to take the deepest possible breath and exhale into a spirometer as hard, fast, and completely as possible. The spirometer recorded the volume of air exhaled as a function of time from which a number of parameters were measured. Each examinee attempted to perform at least 5 FVC maneuvers. For a maneuver to be acceptable, it had to be a maximal exhalation free from a cough, excessive hesitation, a leak, an obstructed mouthpiece, variable effort, or early termination. An additional goal was that each examinee had a sufficient number of trials to demonstrate that the FVC and forced expiratory volume (FEV1) values were reproducible.

Measures of oral health. The oral health examination was performed on subjects by a licensed dentist specially trained in the use of specific epidemiologic

indices for oral health. The study operations plans include details of the methods and quality-control measures used to ensure data reliability.[16,18,19] The following data were analyzed for the present study. Dental caries was quantified using a mirror and a #23 explorer for the DMFS/T index which is the sum of the number of decayed, missing or filled permanent tooth surfaces/teeth and is, therefore, a summary of cumulative caries experience.

Periodontal health was measured around the teeth of one upper quadrant and one lower quadrant randomly selected at the beginning of each examination.[18,19] The buccal and mesial-buccal surfaces of each tooth were measured for gingival bleeding, gingival recession, and probing depth using a National Institutes of Health periodontal probe. Periodontal disease was measured by determination of:

1) Attachment level, which was obtained by subtracting the distance from the free gingival margin (FGM) to the cemento-enamel junction (CEJ) of each tooth, from the distance from the FGM to the bottom of the sulcus. Mean attachment loss (MAL) for each subject was then computed and dichotomized as those who had <1.5 mm MAL and those who had ≥1.5 mm MAL. This cutoff was determined by examination of the distribution of MAL for all teeth examined, where 53.3% of subjects had a MAL <1 mm. We therefore considered that subjects having over 1.5 mm MAL would have some degree of periodontal attachment loss. We also considered cutoff points of ≥2 MAL as well as ≥3 mm MAL to discern a relationship between MAL and lung disease. Both the continuous and categorical variables of MAL were used in separate analyses.

2) Gingival bleeding (GB) was dichotomized as 2 categories: GB <20% of sites that bled on probing, and GB ≥20% of sites that bled on probing.

3) A dental health index (DHI) was defined as the sum of the number of carious lesions and the number of teeth having a probing depth (PD) ≥5 mm.

Statistical Analysis

Preliminary analysis involved the identification of dependent and independent variables, as well as other covariates. Two dependent variables were used in this analysis: history of COPD and $(FEV_1)/(FVC) \times 100$. For the purpose of examining the relationship between respiratory disease and oral health, the independent variables considered included MAL, GB, and DHI. Furthermore, all demographic variables, SES, smoking, and alcohol consumption were each used as covariates in this analysis.

After all the dependent and independent variables and covariates were identified, descriptive statistics were used on unweighted data to examine possible associations among the general characteristics of the population. Student *t* test and ANOVA were also used to evaluate and compare the means of the parameters under study. Contingency table analysis and chi-square tests were employed to assess the proportions of subjects with COPD with respect to those categorical independent variables and covariates. However, due to the complex survey design and unequal probability of sample selections in NHANES III, weighted linear and logistic regression analyses using a software program† were utilized for the final analyses on lung function and COPD, respectively. All covariates, except pack year, were used in the regression model as dummy or indicator variables. Pack year was used as a continuous variable. Odds ratios and 95% confidence intervals were calculated from the logistic models.

RESULTS

Demographic data of the sample population are summarized in Table 1. The mean age of all subjects

† WesVar PC, v.2.11, Westat Inc., Rockville, MD.

Table 1.

Demographic Characteristics of Study Population

	COPD*		
	No	Yes	Totals (n)
Age (mean ± SD)	43.9 ± 17.7	51.2 ± 17.9	13792
Gender			
Female	6821	506	7327
Male	6161	304	6465
Race and ethnicity			
Non-Hispanic white	4775	432	5207
Non-Hispanic black	3723	208	3931
Mexican-American	3938	149	4087
Other	546	21	567
Education† (years)			
≤7	2063	125	2188
8-11	2632	217	2849
12	4115	250	4365
>12	4079	215	4294
Household income†			
No income	29	4	33
<US $30,000	7336	502	7838
≥US $30,000	4477	223	4700
Smoking (pack year)	7.3 ± 16.2	17.7 ± 28.4	13584
Alcohol consumption			
Never	2166	108	2274
Former	4267	340	4607

* COPD was defined as those subjects who had a history of either chronic bronchitis and/or emphysema (see the Materials and Methods section).
† Totals differ due to non-responses by some individuals to these questions.

was 44.4 ± 17.8 (data not shown). The mean age of subjects with COPD was 51.2 ± 17.9, while the mean age of subjects without this condition was 43.9 ± 17.7. Although there were slightly more non-diseased females than males in the sample (6,821 versus 6,161), two-thirds of the COPD group were females (506 of 810 subjects). This is consistent with previous reports of COPD in this population.[20] Non-Hispanic whites constituted the largest group of subjects based on ethnicity, followed by non-Hispanic blacks and Mexican-Americans. The majority of subjects had 12 or more years of education but had a household income of less than $30,000.

Oral health parameters between subjects with and without COPD are compared in Table 2. Those with COPD had, on average, more periodontal attachment loss and a higher oral health index than those without COPD. It is also interesting to note that the percentage of subjects with diabetes mellitus and COPD was significantly greater (84/783 = 10.7%) than that seen in subjects not having COPD (796/12,481 = 6.4%) (chi-square analysis, $P \leq 0.0001$). A statistically significant relationship was also noted between diabetes and COPD (crude odds ratio of 1.43, CI: 1.15 to 1.78), suggesting that diabetics had a higher risk of having COPD than non-diabetics. We therefore included diabetes in the final multiple regression model (see below).

To simultaneously control for multiple variables that may confound statistical analysis, gender, age, race, education, income, dental treatment history, alcohol consumption, diabetes status, and smoking status were considered in a logistic regression model against history of COPD. Calculated odds ratios for COPD in patients with varying degrees of periodontal attachment loss, as well as 95% confidence intervals, are presented in Table 3. No relationship was noted between gingival bleeding alone and a history of chronic bronchitis and/or emphysema, nor when the cut-off for MAL was ≥1.5 mm. However, the risk for COPD appeared to be significantly elevated when attachment loss was found to be severe (MAL ≥2.0 mm) when compared to the healthy (<2.0 mm MAL) group (odds ratio 1.35, 95% CI: 1.07-1.71). Furthermore, the odds ratio was 1.45 (95% CI: 1.02-2.05) for those who had ≥3.0 mm MAL.

The levels of lung function as related to periodontal status were also considered and are presented in

Table 2.

Dental Health in Study Population

	COPD*	
Clinical Parameter	No	Yes
Attachment loss (mean ± SD)	1.17 ± 1.09†	1.48 ± 1.35
Oral health index (mean ± SD)	6.45 ± 4.70	6.61 ± 4.73
Diabetes	796/12481 (6.4%)‡	84/783 (10.7%)
Gingival bleeding§		
<20% sites	9403	565
≥20% sites	2629	141
Total	12032	706
Mean attachment loss		
<1.5 mm	8804	436
≥1.5 mm	3210	267
Total	12014	703
<2.0 mm	10084	521
≥2.0 mm	1930	182
Total	12014	703
<3.0 mm	11198	616
≥3.0 mm	816	87
Total	12014	703

* COPD was defined as those subjects with a history of either chronic bronchitis and/or emphysema (see the Materials and Methods section).
† $P = 0.0001$ (Student t test).
‡ $P \leq 0.0001$, chi-square analysis.
§ Totals in these cells differ due to invalid dental data and to non-responses by some individuals to questions about a history of lung disease.

Table 3.

Relationship of COPD and Periodontal Disease

Periodontal Status	Total Number of Subjects With/Without COPD*	Odds Ratio†	95% CI
Gingival bleeding (≥20% of all sites)	381/7208	0.93	0.83-1.05
Mean attachment loss ≥1.5 mm	583/9810	1.11	0.89-1.38
Mean attachment loss ≥2.0 mm		1.35	1.07-1.71
Mean attachment loss ≥3.0 mm		1.45	1.02-2.05

* COPD was defined as those subjects who had a history of either chronic bronchitis and/or emphysema (see Materials and Methods section).
† Adjusted for age, gender, race and ethnicity, education, income, number of dental visits, pack years of smoking, alcohol consumption, and diabetes mellitus.

Table 4.

Levels of Lung Function (mean ± SD) by Dental Health Status

Status	$(FEV_1)/(FVC) \times 100$
Gingival bleeding	
<20% sites	79.31 ± 8.19
≥20% sites	79.25 ± 9.80
Mean attachment loss	
<1.5 mm*	81.26 ± 7.63
≥1.5 mm	75.28 ± 10.20
<2.0 mm*	80.04 ± 9.58
≥2.0 mm	73.88 ± 10.98
<3.0 mm*	79.64 ± 8.82
≥3.0 mm	72.26 ± 10.66

* Significantly greater lung function when compared to those with more mean attachment loss (P <0.0001, weighted t test).

Table 4. A trend was noted in that lung function appeared to diminish as the amount of attachment loss increased.

No other statistical associations were noted between any of the measures of oral health and acute respiratory diseases such as influenza or pneumonia.

DISCUSSION

The findings of the present analysis, together with other recently published studies,[8,9] support an association between poor oral health (defined here as periodontal disease) and COPD. Based on the calculated odds ratios, the association of periodontal attachment loss with the prevalence of COPD appears moderate (with an excess risk of 11% to 45%). However, a distinct trend was noted whereby the more severe the mean attachment loss, the greater association with COPD. It should be noted these findings are derived from retrospective analysis of cross-sectional data. Prospective epidemiologic studies will better assess the role of oral disease in COPD exacerbation and disease progression.

It is interesting to note the observed correlation between the severity of periodontal attachment loss and lung function. Our analysis indicated that subjects with more periodontal attachment loss had a higher prevalence of diminished lung function. This suggests the possibility that periodontal disease activity may contribute to COPD. One possible explanation for this finding may relate to the occurrence of COPD exacerbation. Periodic exacerbations of COPD are thought to be provoked in part by bacterial infection.[21,22] The organisms most closely associated with exacerbations are non-typable *Haemophilus influenzae, Streptococcus pneumoniae,* and *Moraxella catarrhalis*. Based on the results of the present and recent studies, it is possible that factors responsible for poor oral health may also play a provocative role in the process of infection of COPD patients by *H. influenzae, S. pneumoniae,* and/or *M. catarrhalis*. Further research defining the factors responsible for initiating the process of exacerbation, the underlying conditions that may modulate the progression of the disease, and methods to improve its management are clearly needed.

Although the potential mechanisms by which poor oral health may influence the course of COPD remain obscure, a number of mechanisms can be envisioned. The most direct means by which the oral cavity may influence lung disease is by aspiration of indigenous oral bacteria into the lower respiratory tract. Indeed, it is well known that anaerobic lung infections occur following aspiration of salivary secretions, especially in patients with periodontal disease.[23-30] Recently, it has been hypothesized that the oral cavity may also influence oral-pharyngeal colonization by recognized respiratory pathogens.[6,10,31-33] Dental plaque can serve as a reservoir for respiratory pathogens, especially in high-risk patients with poor oral hygiene. For example, institutionalized subjects appear to be more prone to substantial oral colonization by respiratory pathogens than ambulatory, non-institutionalized subjects.[5,34-36]

Periodontal disease, the localized chronic inflammatory condition caused by infection of the periodontal tissues by dental plaque bacteria, results in destruction of supporting bone and connective tissues. While periodontal attachment loss is thought to be episodic in nature,[37] periodontal inflammation can persist, in the absence of treatment, for years. During this time, oral bacteria may continuously stimulate periodontal tissues (epithelial cells, endothelial cells, fibroblasts, macrophages, white cells, peripheral mononuclear cells) to release cytokines such as IL-1α, IL-1β, IL-6, IL-8, and TNF-α.[38-40] A mechanism proposed for the gross airway epithelial damage observed in COPD involves cytokines (for example, IL-8) which recruit neutrophils to infiltrate airway parenchyma and to release proteolytic enzymes and toxic oxygen radicals.[41] The release of cytokines from the respiratory epithelium may follow binding of respiratory pathogens or their products to the respiratory epithelial cells. This mechanism has been demonstrated for pathogens such as *S. pneumoniae* and *H. influenzae*, which attach to mucosal receptors and stimulate IL-6 and IL-8 production by the underlying cells.[42,43] Oral bacteria in the secretions that adhere to the mucosal surfaces may bind to mucosal epithelium to stimulate cytokine production. It is also possible that cytokines originating from the oral tissues, for example from the gingival crevicular fluids,[44-46] enter whole saliva, which then contaminate distal respiratory epithelium. These cytokines may stimulate respiratory epithelial cells to release other cytokines to recruit inflammatory cells

(e.g., neutrophils) to the site. The release of hydrolytic enzymes from these inflammatory cells may result in damage of the epithelium, making it more susceptible to infection by respiratory pathogens.

In summary, the available evidence suggests that poor oral health, characterized by inadequate hygiene resulting in the formation of dental plaque or periodontal disease, is associated with serious pulmonary disease. It should be understood that we are not arguing that poor oral health alone is responsible for COPD. Rather, poor oral health may work in concert with other factors (such as continued smoking, environmental pollutants, viral infections, allergy, and/or genetic factors) to promote the progression and/or exacerbation of COPD. Further investigations will establish the role of oral health in the progression of COPD. It is conceivable that improved oral health may help prevent the progression of this disease.

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