Tooth Loss Positively Predicts Cardiovascular Disease Risk in Adult Filipino Women

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Abstract

Cardiovascular disease (CVD) is a growing global epidemic. Recent studies have shown that CVD is negatively associated with oral health, likely reflecting the propensity of oral fauna to cause systemic inflammation, which in turn thickens the arterial walls. As globalization increases, populations in some developing countries adopt dietary and activity patterns that increase the risk of CVD while retaining poor oral hygiene habits, the main factor in high rates of tooth loss. This study's primary objective was to investigate the association between tooth loss and CVD controlling for relevant covariates related to lifestyle, and to evaluate the possible mediating role of C-reactive protein (CRP), an inflammatory marker. Measures of tooth loss, anthropometry, disease history, pathogen exposure, income, and urbanicity ranking were evaluated as predictors of CVD in 1,619 women participating in the Cebu Longitudinal Health and Nutrition Survey in the Philippines. A series of maximum likelihood logistic regression models were used to predict CVD risk in women who developed CVD after age 20. Extreme tooth loss, defined as greater than 25 teeth missing, was the strongest predictor of elevated CVD risk \[ \text{OR}= 2.11; p< 0.018 \]. Two candidate pathways were considered, a) inflammation, which is caused by bacteria entering the bloodstream from oral lesions; b) obesity, which may occur due to edentulous individuals eating softer, higher caloric foods. First, waist circumference, a measure of obesity, was tested as a possible mediator but did not appear to be a significant predictor of CVD. Next, when CRP was taken into account, the association between tooth loss and CVD became stronger and more significant \[ \text{OR}= 2.17; p<0.015 \]. Nonetheless, tooth loss
was not predictive of CRP, and CRP was positively, but not significantly, associated with CVD risk. These results underscore the need for additional research on the potential mediating role of inflammatory markers to determine how tooth loss is associated with elevated CVD risk in the Philippines.

Introduction

Cardiovascular disease (CVD) is characterized by any of a number of specific diseases that affect the heart and/or the blood vessel system. The veins and arteries leading to and from the heart are especially vulnerable to the buildup of fatty substances in the arteries, a condition called atherosclerosis. Extra strain on the heart from atherosclerosis may result in chest pain, angina pectoris, and other symptoms. When one or more of the coronary arteries are completely blocked, a heart attack, or myocardial infarction, may occur (Mayo Clinic 2010). Poor oral hygiene and inflammation have been shown to correspond to CVD risk. This study aims to investigate this hypothesis in middle-aged Filipino women.

CVD has become a common cause of morbidity and mortality in most countries around the world. However, the incidence of disease is not uniform on a global scale. In industrialized countries, there has been a recent decline of CVD, which has been well documented (Thom 1989; Reddy and Yusuf 1998). In the United States, Canada and France, for example, CVD-related mortality fell by approximately 50% from 1965 to 1990 (Lopez 1993). The rate of CVD increase is greater in many developing countries than developed countries due to the modern epidemiological transition, a phenomenon in which a decline in deaths from infectious disease juxtaposes an increase in deaths from chronic disease (Yusuf et al. 2001). The epidemiological transition continues because of the rise in life expectancy. In the Asia-Pacific region, mortality attributed to CVD has increased nearly 300% from 1957 to 1990 (Khor 2001). Increasing longevity provides longer periods of exposure to the risk factors of CVD, including obesity,
tobacco, high blood pressure, diets high in saturated fat and a sedentary life-style (Howson et al. 1998). The Philippines is one country which faces a paradigm of both chronic and infectious disease. During the 1980s, CVD entered the Philippines' top ten list of causes of morbidity. Today, it is number seven on the list, behind respiratory tract infections, bronchitis, influenza, and diarrhea (Philippines Department of Health).

Both factors of diet and infection can impact the prevalence of CVD. Fats in the diet can contribute to high cholesterol and atherosclerosis while sugars contribute to the formation of dental caries. In South Asian countries, diet of rice, fruit, and fish has been replaced in part or supplemented by sugar and starch-containing foods and confections. Drewnowski and Popkin report that between 1962 and 1994, there was a major shift in the global diet that caused the classic relationship between income and fat intake to decouple. Greater fat consumption in low-income countries has arisen from the global availability of cheap vegetable oils and fats. Thus the nutrition transition now occurs at lower socioeconomic levels than it did previously, fueled by the evolutionarily-derived human preference for fats and sugars in the diet (Drewnowski and Popkin 2009).

Although economic development may have led to higher quality of life and better health for part of the population, the adverse health effects include the greater incidence of overweight and obese individuals as a result of an overall increase in total energy intake in developing countries undergoing urbanization (Popkin 1994). A study based on data from the Cebu Longitudinal Health and Nutrition Survey (CLHNS) found that the prevalence of overweight increased significantly among mothers and a cohort of their offspring between 1994 and 2005 (Kelles and Adair 2009). This period also coincided with rapid urban inflight and the migration of worker to cities (Quisumbing and McNiven 2005). Although under-nutrition is generally declining while over-nutrition is increasing, many Asian countries have the challenge of dealing
with a double burden of nutritional diseases (Mendez et al. 2005). As a typical example in the region, the Philippines followed predicted trends associated with demographic changes, economic development and the nutrition transition. Dietary macronutrient composition in the city of Manila has been increasing in fat content, animal products and sugars while decreasing in fiber, vegetables and fruits (Florentino et al. 1992). Here, the term “fat(s)” refers to both saturated and unsaturated lipids, and “sugars” refers to all monosaccharides and disaccharides.

One influence on diet choice is the availability of food items. The number of fast-food restaurants is rising as well as processed foods on store shelves. In addition, non-hunger based motivations for eating provides an important influence on diet. These motivations include environmental, social, and emotional cues. A 2006 study of women in Bacalod and Manila, the Philippines, showed that urban females were significantly more likely than their rural counterparts to eat due to emotional and environmental reasons (Hawks et al. 2006). As unhealthy fast foods become more accessible physically and economically, the Philippines will likely experience an escalation in problems with overweight and obesity as well as downstream effects such as CVD.

The shift in diet towards more fat and sugar content has brought a large portion of the population into greater risk for tooth decay. There is a wealth of evidence from human studies and animal experiments that show the role of dietary sugars in the etiology of dental caries (WHO 2003). Not only do sugars promote dental caries and eventually tooth loss, but also people with poor oral health tend to eat softer, high caloric and sugar-filled foods, which in turn promotes further oral health and cardiovascular health issues. With the Filipino urban population increasing more than two million people each year (Bridges 2007), the nutrition transition has the potential to drastically change the relationship between people and their environment for large populations.
Another factor that influences the burden of CVD is the environmental level of pathogens. There are no direct measures of pathogen levels in the Philippines, but general practices suggest that pathogenicity is significantly greater compared to more economically advanced countries. In urban areas, untreated discharges of industrial and municipal wastewater result in extremely poor water quality. Untreated effluent is indiscriminately disposed of in the Pasig River, which is one of the world’s most polluted rivers. Furthermore, less than 4% of the population of Manila, the capital city of the Philippines, is connected to the sewer network (Bridges 2007). In rural areas, pathogenicity results from farmyard animals that enter the house, water taken directly from the source without treatment, and the haphazard disposal of human waste since toilets are rare. In 1991, 25.1 percent of households did not have access to basic sanitation. This number rose to 30.6 percent in 1998 (United Nations 2004). Outbreaks such as diarrhea and cholera are not uncommon in the Philippines due to the lack of access to basic water services. The continuous presence of infectious disease agents and microbial contaminants can induce chronic inflammation, which has consequences on long-term health. Chronic inflammation can occur due to autoimmune diseases, frequent bouts of diarrhea or constipation, arthritis, heartburn, cancer, hypertension, hyperglycemia as well as cigarette smoking and pro-inflammatory foods (Gan et al. 2004).

Inflammation is a biological response elicited by the body in response to both acute and chronic physiological states. A marker of inflammation is c-reactive protein, or CRP, which is a protein produced by the liver in response to infection. As a marker, CRP can be measured to determine the current extent of infection. Elevated CRP levels for long periods of time occur as a result of chronic low-grade inflammation (Sun et al. 2005). Inflammation has been recognized as a risk factor for atherogenesis and thromboembolic events by triggering endothelial injury and inducing plaque formation on the arterial walls (Mehra et al. 2005). In doing so, inflammatory
molecules can infiltrate the lining of major blood vessels, causing vascular fatty degeneration and intravascular coagulation (Beck et al. 2000). In this way, inflammatory molecules contribute to atherosclerotic lesions and plaques, according to a statement by the American Heart Association (Pearson et al. 2003). In fact, virtually every step in atherogenesis is believed to involve immune-regulating cytokines and cells, such as macrophages, that are involved in the body’s inflammatory response (Desvarieux et al. 2004). As a sensitive systemic inflammatory marker, CRP has been shown to predict cardiovascular events among middle-aged and elderly subjects through the inflammatory pathways outlined above (Tracy et al. 1997; Vasović et al. 2010). In 2008, a clinical trial called the JUPITER study, or “Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin,” announced that CRP predicted heart events independent of cholesterol levels. The results of the study, which had 17,802 participants, suggested that CRP is a promising predictive test for the likelihood of myocardial infarction, half of which occur in people with normal plasma lipid levels (Ridker et al. 2008; Michos and Blumenthal 2009). Thus CRP may be a valuable predictor of cardiovascular risk, even for individuals with no other major risk factor.

Oral infections are a common source of chronic inflammation. Infection of the oral cavity can cause a dentate person, defined in this study as one who possesses all natural teeth not including third molars, to lose teeth and eventually become edentulous, the condition of possessing no natural teeth. The infections are initiated by invasive gram-negative bacteria that colonize dental plaque biofilms on the root surface of the tooth. Infections that affect the periodontal tissues supporting the tooth - including the alveolar bone, periodontal ligament, cementum, and gingiva – are periodontitis and gingivitis, both considered forms of periodontal disease (Armitage 1999). Studies show that periodontal disease is a progressive disease that can last many years (Lang et al. 1986) and tends to change the ratio of harmless and harmful
bacterial fauna in the mouth (Närhi et al. 1993; Närhi et al. 1998; Loesche et al. 1995). Previous research has found that oral bacteria can travel through the bloodstream from the oral cavity to other areas of the body including the heart (Khodaii et al. 2010; Desvarieux et al. 2005). While the bacterium stimulates a systemic inflammatory response, it can also trigger local inflammation in cardiac tissues and blood vessels. Thus inflammation in response to bacterial infection can cause great damage to the cardiovascular system.

Increasing problems with oral hygiene in the Philippines are augmented by poor health care infrastructure and lack of compliance with modern oral standards. The national prevalence for permanent as well as deciduous dental caries, or cavities, is 97.5% in rural areas and 96.7% in urban areas. In terms of DMFT (Decayed, Missing, Filled Teeth) Index, the Philippines ranked the highest amongst 17 countries according to the Global Oral Health Data Bank (WHO 2003). In a 1998 survey with the members of the Philippine Dental Association, 88.4 percent of dental practices were based in an urban area, 10.9 percent were in suburban centers while 0.7 percent were in a rural area. Furthermore, there was a 30.2 percent increase in the prevalence of periodontal disease from 1992 to 1998 (Philippines Department of Health 2005). It is possible that some of this increase is attributed to better reporting and diagnosis of oral health in the 1998 survey. From 1998 to 2005, no additional surveys were taken. Despite this information, we can infer from data of dental caries and periodontal disease that usage of toothbrushes, floss, and fluoride toothpaste was not high. The Filipino government itself has recognized this fact which led to the 2003 National Policy on Oral Health statement and forthcoming programs (Philippines Department of Health 2003). According to a 1994 WHO survey, brushing instruction and mouth rinsing only covered 30 percent of the population (Deong 1994). Traditionally, the twigs of guava trees were used as rudimentary toothbrushes. Another method was to use one’s finger as the toothbrush with sand as toothpaste (Severino 2005). The
effectiveness and continuation of these methods have not been studied, although they may be limited to rural areas or an impoverished demographic. In addition, a 2004 report, approximately 8 percent of the Filipino population is served by fluoridated water, considering both natural and artificially-enhanced water sources (The British Fluoridation Society 2004). The combination of poor oral healthcare and dietary habits points to downstream consequences such as cardiovascular disease.

The relationship between oral health and CVD has been a subject of mounting research (Mustapha et al. 2007; Desvarieux 2001; Nikawa et al. 1998). Studies on transient bacteremia and elevated inflammatory markers (Ebersole et al. 1997) show that poor oral hygiene in the form of a long-term infection can result in chronically elevated levels of CRP, which has a significant impact on the vascular system and cardiovascular health. However, the nature of the relationship between oral health, CRP, and cardiovascular health has yet to be determined. Investigating the association between tooth loss and biological, social, and demographic factors can help in the development of targeted and effective interventions for at-risk populations in a context where CVD is becoming an increasing public health concern.

The CLHNS is a longitudinal birth cohort study where women around the rural and urban Cebu metropolitan area were enrolled while pregnant. The present research focuses on these women, who are representative of the population from which they were drawn, twenty-two years later at ages 35 to 69 years (n = 1,691). This study was designed as a first attempt at evaluating predictors of heart disease in the original mothers of the CLHNS study, and it aims to explore the value of tooth loss for predicting heart disease by evaluating whether a woman’s socioeconomic status, anthropometry, other diseases, and environment are confounding factors for the relationship between tooth loss, inflammation, and CVD risk. The Filipino sample of aging women offers diverse social, biological, and demographic variables with which to explore this
relationship while adjusting for potential confounding influences; more detailed future analysis is planned.

**Materials and Methods**

**Study Population**

The Cebu Longitudinal Health and Nutrition Survey is an ongoing study of a cohort of Filipino women who gave birth between May 1, 1983, and April 30, 1984 conducted by the University of North Carolina, the University of San Carlos, the Nutrition Center of the Philippines, Johns Hopkins University, and Northwestern University. The CLHNS initially recruited all pregnant women in 33 randomly selected urban and rural communities, or barangays, of Metro Cebu through a single stage cluster sampling procedure. The barangays, which contained about 28,000 households, were completely surveyed by researchers in late 1982 and again in early 1983 to locate all pregnant women. Women of the selected barangays who gave birth between May 1, 1983, and April 30, 1984, are included in the sample. A baseline interview was conducted among 3,327 women, with subsequent surveys at intervals of several years until 2010. Each survey collects detailed health, nutrition, demographic, and socioeconomic data across individual, household, and community levels (UNC Carolina Population Center 2010).

**Data Collection**

The women have been followed through multiple rounds of data collection since 1983. Data were collected during interviews conducted in the respondents’ homes. All data were obtained under conditions of informed consent and with human subjects clearance from the University of North Carolina, Chapel Hill, and the University of San Carlos. The data for the present analyses come from the most recently completed survey, conducted in 2005, when the women were 35–69 years old. Complete anthropometric, environmental, socio-demographic, and
CRP data were available for 1,619 women. Participants provided information on household demographics and income levels, economic activities and resources, environmental quality, and health behaviors in personal interviews conducted in their homes. After an overnight fast, blood samples were taken, and plasma was stored for the analysis of cardiovascular disease risk factors. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

Body weight, height, waist and hip circumference, and triceps, subscapular, and supr iliac skin fold thickness were measured using standard anthropometric techniques (Lohman et al. 1988). The BMI was calculated as the ratio of weight (kg) to height (m²). Oral health statistics such as number of teeth removed, toothache, and use of dentures were assessed during the interviews. Disease prevalence was verbally reported by the subjects during house visits. Heart disease was accessed with a yes/no question of whether the individual had the condition since 2002. If the response was positive, year of onset was also obtained.

**CRP analysis**

Venipuncture blood samples were collected using EDTA-coated vacutainer tubes in the participants’ homes in the morning after an overnight fast. Blood samples were kept in coolers on ice packs for no more than 2 hours and were then centrifuged to separate plasma prior to freezing at -70°C. Samples were express-shipped in a single batch to Northwestern University on dry ice and stored frozen at -80°C until analysis. CRP concentrations have been shown to remain stable under these transport and storage conditions. CRP concentrations were determined using a high sensitivity immunoturbidimetric method (Synchro LX20, lower detection limit: 0.1 mg/L).

**Statistical Analysis**

Analyses proceeded in three stages, consisting of logistic regression models. First, tooth loss was considered as a predictor of heart disease. Second, models were adjusted for additional
factors known to influence heart disease and confound any association with tooth loss (age, anthropometry, hypertension, diabetes, and smoking). Measures of income, urbanicity, smoking, and chronic diseases were considered to account for omitted variables related to lifestyle and/or environmental quality that might confound associations between tooth loss and the prevalence of CVD. Third, the mediating effect of CRP was investigated by determining its effect on the relationship between tooth loss and CVD. In addition, the existence of an association between tooth loss and CRP and between CRP and CVD was investigated.

Urbanicity was converted into a dichotomous variable: more urban or less urban. Age was changed from months into years. Income and CRP were log-transformed to normalize the distributions. CRP was further divided into a 4-stage ordinal variable with levels 0-1.5, 1.5 < x < 3, 3 – 10, and > 10 mg/L. These cut-off values were selected based on recommendations issued by a joint scientific statement from the AHA and the CDC (Martin-Du Pan and Despont 2002; LabCorp 2001; Pearson et al. 2003). Concentrations of CRP >1.5 mg/L but <3 mg/L indicate average to moderately increased cardiovascular risk due to chronic, low-grade inflammation. CRP >10 mg/L are presumed to be the result of acute inflammatory processes (e.g. infectious disease), although recent research has suggested that CRP concentrations >10 mg/L are also predictive of cardiovascular risk. All statistical analyses were conducted with Stata for Windows, version 10 (StataCorp, College Station, TX). Criteria was p<0.05 for significance. Values in the text are means ± SEM or odds ratio (OR), 95% CI.

Measures of lifestyle factors were significantly associated with tooth loss, including household income, household hygiene, household assets, waist circumference, and age (see Table 2). In addition, several lifestyle factors were positively associated with CRP, including urbanicity, waist circumference, and age. As expected, hypertension was strongly associated with diabetes (T= -5.22, p<0.001). Thirteen women, or 5.2% of the sample, had onset of heart
disease before age 20, so they were excluded from the analysis since, as expected, tooth loss (OR 0.89, p<0.851, OR 0.52, p<0.55) did not predict heart disease for this population. Hypertension, smoking, height, waist circumference, and living in an urban environment were not significantly related to this group. However, diabetes (OR 5.13, p<0.039) and CRP >10 mg/L (OR 9.52, p<0.053) were strongly correlated, although they could have arisen later in life. The question of whether childhood onset of CVD is predictive of these variables is left to future studies. We used correlation analysis to test if the variables included in the model were inter-correlated.

Heart disease was a dichotomous variable (yes or no) that when cross-analyzed with year of onset of heart disease, showed that the majority of subjects (84%) reported onset at less than 50 years of age. To remove individuals with congenital or rheumatic heart disease, all children were omitted, defined as those who reported heart disease under age 20. These individuals would have experienced a minimal impact from tooth loss.

Results

Characteristics of study participants are reported in Table 1. Compared with US women of similar age (McDowell et al. 2008), the Cebu women in this sample were shorter (mean: 150.6 cm vs. 162.1 cm in Cebu and US, respectively), thinner (mean BMI: 24.3 kg/m² vs. 28.2 kg/m²), and had a smaller waist circumference (mean: 81.2 vs. 92.7 cm) but a higher prevalence of smoking (16.3% vs. 10.2%) (Martin et al. 2006).

Analyses and models were restricted to the subsample of women for whom all variables were available (n = 1,619). Data on their male spouses were not complete. Individuals were excluded from the analyses due to missing data (n = 399) while others were lost to follow-up (n = 1,309). The excluded group did not differ from the analysis subsample with respect to baseline data on reports of age, height, BMI, tooth loss or illness, but had higher income (312.96 vs. 261.37 pesos/week) and were more likely to be smokers (19.75% vs. 16.16%). In addition they
had less formal education (0.86 ± 0.13 y) and lived in slightly more rural communities (3.65 ± 0.43 points on urbanicity scale). An unpaired t-test for these variables showed p>0.05.

The predictive value of tooth loss for heart disease risk was evaluated using a series of logistic regression models that progressively added variables to evaluate possible sources of confounding and mechanisms of effect (Table 3). A statistical trend between the number of teeth lost and CVD was found in a bivariate regression (Model 1). Results show that the most extreme level of tooth loss (>25 teeth missing) predicted a significant increase in CVD risk while the other levels were not significant and showed a more modest CVD risk increment (Table 3).

Anthropometry was added to the model to determine the extent that age, height and waist circumference affected the primary association between tooth loss and CVD risk (Model 2). The odds ratios of the first two tooth loss levels did not change much but the third and most extreme level increased and became more significant. Next, controlling for income and urbanicity were not consistently related to heart disease. The variables did not have a large influence on the odds ratios of tooth loss levels. Next, accounting for smoking, hygiene, hypertension, and diabetes (Model 3) caused a large increase in the significance and odds ratio of the third level of tooth loss. Smoking was not a significant predictor of CVD, but hygiene showed a strong and significant association. As expected according to previous studies on the associations between hypertension, diabetes and CVD (Curb et al. 1996; American Heart Association 1994; Sowers et al. 2001), the odds ratios for disease conditions were both large and significant.

In Model 5, we examined the influence of CRP on the relationship between tooth loss and CVD as well as the association between CRP and heart disease (Table 3), using four levels of CRP as predictors of CVD. Overall, the first two levels of tooth loss did not change greatly, but the odds ratio of the third level increased and remained significant. The change indicates that CRP is a confounding variable with a possible masking influence. Individuals with more teeth
removed had lower CRP levels, seemingly putting them at lower CVD risk. Only the first level of CRP predicted CVD risk in a significant manner. The third level of CRP showed the largest OR and was not far from significance compared to the second level.

In the next series of models, the likelihood of tooth loss as a predictor of CRP was investigated (Table 4), considering the same predictors that were controlled for in the first series. In Model 1, tooth loss did not appear to be a significant predictor of CRP. For the third level of tooth loss, the OR was less than 1.00, which would invert the interpretation of the relationship if it was significant. Levels of tooth loss as predictors of CRP did not vary largely when age, anthropometry, sociodemographic factors, lifestyle factors, and diseases were accounted for. Age and waist circumference showed a positive, significant association with CRP, which suggests that a chronic inflammatory response is naturally induced by aging and increased adiposity levels. Linear regression shows that as women age, more teeth are removed ($r= 0.35$, $p<0.001$), which may also influence CRP levels. Height showed a significant, inverse relationship, so that as height decreases, CRP levels increase. This may be related to adiposity and waist circumference as well. Living in a more urban environment shows a strong positive relationship with CRP that is significant. The other variables controlled for in the models were not significant.

**Discussion**

Infections associated with tooth loss are an example of both acute and chronic degenerative diseases that can lead to long term damage to other parts of the body. Women with most or all of their teeth missing experienced greater risk for CVD compared to those with less tooth loss or who were dentate. A resulting increase in CVD risk occurred with each level of tooth loss. Because the levels of losing 5-7 teeth and 8-16 were not significant and not as strong predictors as the odds ratio for the most extreme level, the results suggest that tooth loss is an
indirect predictor of CVD that is influenced by many other factors. Nevertheless, this relationship existed despite removing variables such as anthropometry, diseases, smoking, and lifestyle factors. In fact, accounting for these variables made the odds ratios for tooth loss more predictive of CVD risk and more significant.

In Cebu, sociodemographic factors including amount of income and living in an urban environment were not significant predictors of CVD. This is likely due to opposing influences that as quality of life and urbanization increases, higher levels of obesity can be expected to promote CVD while better healthcare access can help prevent and treat CVD. These results confirm that Cebu is an advantageous setting without biased distribution of individuals with CVD. In contrast, studies in more affluent settings found CVD concentrated in the higher socioeconomic strata (Yadav et al. 2008; Winkleby et al. 1992). Another advantage is that the Cebu population represents individuals experiencing a health transition. Tooth loss, as a residual condition of poor nutrition and healthcare, is more exaggerated in developing countries than for people in developed countries. At the same time, obesity and chronic diseases such as cardiovascular disease are becoming increasingly prevalent. Therefore as both conditions exist side by side, Filipinos experience the dual burden of infectious and chronic diseases (McDade et al. 2008).

Comparing tooth loss statistics, less than 3.3% of women in Cebu (age 35-69) were fully dentate whereas 13.3% of U.S. women aged 45 to 64 had full dentition (National Institutes of Health 2002). This suggests that more Filipino women have experienced infection-related tooth loss, likely due to the lack of proper care and perhaps exposure to higher amounts of pathological bacteria. However, it seems that for women in the U.S. (age 45-64) who do have tooth loss, it is more extreme. Approximately 9.7% are edentulous compared to 5.8% for women in Cebu (National Institutes of Health 2002). From this data, it seems that populations in developed and
developing countries have different patterns of tooth loss that may interact with other lifestyle factors in complicated ways to influence cardiovascular disease risk.

Individuals in the U.S. have a large variety of foods to choose from regardless of SES, although healthier foods such as fresh fruit and vegetables tend to be less available to the poor. For those in lower socioeconomic levels, fast food and processed goods are often regular fare due to their availability, convenience, and low-cost. This paradigm is the opposite in the Philippines where outdoor markets abound and many poor people can only afford to eat self-cooked, fresh foods (Popkin and Gordon-Larsen 2004). Fast food restaurants are considered upscale and trendy, and they are only located in city centers (Baek et al. 2006). Individuals who have lost teeth naturally shift their diet to softer foods. Whereas women in the Philippines are more restricted to buying unprocessed, fresh foods, women in the U.S. can easily access the softer processed foods. In a 2005 study, Hung et. al. surveyed more than 80,000 U.S. women and showed that individuals ate significantly higher amounts of saturated fat, trans fat, and cholesterol as they lost more teeth (Hung et al. 2005). Comparing U.S. statistics with those of Cebu, CVD prevalence is nearly three times greater in the U.S. (33.9% vs. 12.5%) (American Heart Association 2005; Dans et al. 2005). Considering the diet patterns above, this leads us to believe that in the Philippines, where pathogen levels are higher overall, infections and inflammation are more important risk factors than diet (see Figure 2).

In the second series of models, the potential mediating role of CRP in the association between tooth loss and CVD was explored. First, CRP as the outcome of tooth loss was modeled, but the analyses did not show strong or significant relationship. There was not much difference in predictive values of the different levels of tooth loss. However, age and waist circumference were positively and significantly related to elevated CRP. The presence of excreta, unsanitary means of garbage disposal, and an unhygienic food preparation area were also associated with
increased risk for elevated CRP (not shown). Thus analyses indicate that tooth loss is not a predictor of CRP levels even though tooth loss is associated with higher CVD risk. These results suggest that the single measure of CRP may not capture the inflammatory effects related to poor oral hygiene. In fact, a study found that biomolecules such as interleukin-6 may be a better inflammatory marker to predict CVD risk in women while CRP is a better marker in men (Fernandez-Real et al. 2001). Therefore, oral hygiene and tooth loss in particular may be related to other unmeasured inflammatory markers.

Next, the role of CRP in predicting CVD was examined. Higher levels of CRP were not found to be significant predictors, but the slightly elevated CRP level does show a significant, positive relationship with increased CVD risk, predicting a 161% increase in CVD risk relative to the comparison group. In an inversion of the order of models, the association between this level of CRP and CVD was weaker before anthropometry, diseases, and lifestyle factors were accounted for. The OR for the most extreme level of CRP is the highest, which may indicate that individuals with CRP >10 mg/L also had greater prevalence of diabetes and/or hypertension, which inflated the predictive value of CRP.

In summary, the results show that hygiene predicts CRP levels, of which the 1.5-3 mg/L level positively and significantly predicts CVD risk. In addition, hygiene predicts toothaches (not shown), which is highly correlated with tooth loss. The most extreme level of tooth loss in turn predicts CVD risk. Moreover, BMI, waist circumference, total amount of kilocalories ingested, and percentage of calories from fat all predict CRP levels (not shown). Therefore it seems likely that tooth loss mediates CVD risk through an inflammatory pathway which is affected by both environmental hygiene and dietary habits.
Limitations

A limitation of this study is the use of qualitative self-report of heart disease status. This could lead to bias because some women may not know their status. An objective method of evaluation of cardiovascular disease presence would circumvent the biases that likely occur as different factors hinder a woman from being aware of her heart disease status. This study was designed as a first attempt at evaluating predictors of heart disease in the original mothers of the CLHNS study, in preparation for more detailed planned and future analysis that will include the objective measure of atherosclerosis in the sample.

In the self-reported survey, a sub-set of women reported onset at young ages. Congenital heart disease and rheumatic heart disease are conditions that have an early onset and are likely not affected by tooth loss, since the latter occurs typically later in life. Those who were diagnosed with heart disease as a child, defined as those 20 years of age or younger, were excluded. Individuals with possible genetic influences, such as familial heart disease, were not excluded from the study. This is a limiting factor because genes are a confounding factor that the study did not have the data to account for. However, early onset heart disease can still be affected by tooth loss, a condition that may aggravate the predisposed problems of the heart. If genetic factors could be removed from the analysis, tooth loss would be a stronger predictor of CVD risk.

Because we only know the number of teeth lost, and not the cause, it is unknown whether tooth loss is due to infection, physical trauma or some other cause. If indeed resulting from infection, the periodontal disease or gingivitis could have occurred over a range of years. Some women may have lost their teeth through infections that ended by the time the 2005 blood sample was drawn. Therefore the women had damage already done to the heart and are at greater
risk for heart disease. Tests show low levels of CRP, thus potentially obscuring any relationship between CRP and heart disease.

Including high levels of CRP in the regression models also introduced error into the results. Literature shows that CRP greater than 10 mg/L indicates an active infection (Pearson et al. 2003), which could be due to biological conditions that impact cardiovascular health, thus inflating the predictive value of CPR for CVD risk.

Implications

Logistic regression revealed that there is a strong association between tooth loss and heart disease. This relationship persisted after adjusting for anthropometry, sociodemographics, diseases, and lifestyle. Investigating the mediating effect of inflammation revealed that CRP, a marker of inflammation, was a confounding variable with a masking influence on the relationship between tooth loss and heart disease, not a mediating variable. Nevertheless, the second lowest level of CRP strongly predicted CVD risk. Although the pathway between tooth loss and CVD has not yet been clearly defined, this study finds that tooth loss is strongly predictive of CVD risk, due to possibly unique characteristics of developing countries such as the Philippines. Further studies can investigate the role of inflammation in developing countries by examining other inflammatory markers such as the interleukin family and interferon gamma. Nevertheless, this study sheds light upon the relationship between tooth loss and CVD in the Philippines, where unique lifestyle factors such as higher pathogen levels, healthier foods and restricted access to healthcare influence the interaction between chronic and infectious disease.

Results from this study may be useful in a public health intervention campaign. We advise that the main risk factors for CVD be targeted. Changes in coronary heart disease mortality over periods of several years in different populations demonstrate the role of
environmental factors, regardless of genetic composition. Epidemiological studies in upper- and middle-income countries provide strong evidence for the preventability of CVD (Blackburn 1997). Results from both clinical trials and public health trials with risk factor modification (Pearson et al. 2002) form a strong rationale to support the paradigm that controlling major CVD risk factors should control the disease itself.

References


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Appendix

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<tr>
<th>Anthropometry</th>
<th>Total Sample (n=1619)</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48.37 ± 6.08</td>
<td>35.67 - 69.33</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>119.80 ± 20.12</td>
<td>66.00 - 240.00</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>79.69 ± 12.58</td>
<td>40.00 - 140.00</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.27 ± 4.34</td>
<td>12.26 - 41.89</td>
</tr>
<tr>
<td>Supra-iliac (mm)</td>
<td>28.81 ± 10.06</td>
<td>3.00 - 65.00</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>81.13 ± 10.83</td>
<td>43.10 - 123.80</td>
</tr>
<tr>
<td>Arm circumference (cm)</td>
<td>29.32 ± 4.00</td>
<td>16.70 - 43.90</td>
</tr>
<tr>
<td>Triceps skinfold (mm)</td>
<td>23.84 ± 7.94</td>
<td>4.00 - 62.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th>Total Sample (n=1619)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income (pesos)</td>
<td>577.64 ± 1205.57</td>
<td>0.60 - 40246.76</td>
</tr>
<tr>
<td>Highest education (grades 0-19)</td>
<td>7.31 ± 3.80</td>
<td>0.00 - 19.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease &amp; Risk Factors</th>
<th>Total Sample (n=1619)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease (%)</td>
<td>7.88</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>19.23</td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>4.76</td>
<td></td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>16.30</td>
<td></td>
</tr>
<tr>
<td>Teeth complete (%)</td>
<td>3.96</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>2.58 ± 5.77</td>
<td>0.00 - 122.60</td>
</tr>
<tr>
<td>Past or Present Toothache (%)</td>
<td>46.58</td>
<td></td>
</tr>
<tr>
<td># of removed teeth (n)</td>
<td>10.83 ± 9.15</td>
<td>0.00 - 32.00</td>
</tr>
</tbody>
</table>

Urbanicity rank

- 0–5 removed (%) 33.91 40.16 ± 13.87 8 61
- 6–15 removed (%) 38.74 40.89 ± 13.61 8 61
- 16–25 removed (%) 13.64 39.93 ± 13.63 8 61
- >25 removed (%) 13.70 40.74 ± 12.33 9 59

Table 1. Descriptive statistics for study participants.
Table 3. Logistic regression predicting heart disease.

<table>
<thead>
<tr>
<th>Tooth loss</th>
<th>CRP</th>
<th>Age</th>
<th>Waist</th>
<th>Height</th>
<th>Income</th>
<th>Urbanicity</th>
<th>Education</th>
<th>Assets</th>
<th>Hygiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00</td>
<td>0.03</td>
<td>0.24**</td>
<td>-0.10**</td>
<td>-0.05</td>
<td>-0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>-0.08**</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tooth loss</th>
<th>CRP</th>
<th>Age</th>
<th>Waist</th>
<th>Height</th>
<th>Income</th>
<th>Urbanicity</th>
<th>Education</th>
<th>Assets</th>
<th>Hygiene</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03</td>
<td>0.24**</td>
<td>-0.10**</td>
<td>-0.05</td>
<td>-0.05</td>
<td>0.00</td>
<td>0.00</td>
<td>-0.08**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P<0.05
** P<0.01

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth loss (5-7)</td>
<td>1.48</td>
<td>0.88</td>
<td>1.47</td>
<td>1.45</td>
</tr>
<tr>
<td>Tooth loss (8-16)</td>
<td>1.42</td>
<td>0.85</td>
<td>1.40</td>
<td>1.34</td>
</tr>
<tr>
<td>Tooth loss (17-32)</td>
<td>1.83</td>
<td>1.12</td>
<td>1.90</td>
<td>2.10</td>
</tr>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.75</td>
<td>1.00</td>
<td>0.91</td>
</tr>
<tr>
<td>Height</td>
<td>1.00</td>
<td>0.97</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Waist</td>
<td>1.01</td>
<td>1.00</td>
<td>1.01</td>
<td>1.00</td>
</tr>
<tr>
<td>Income</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Urban</td>
<td>1.29</td>
<td>0.90</td>
<td>1.21</td>
<td>0.84</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.09</td>
<td>0.39</td>
<td>0.69</td>
<td>0.40</td>
</tr>
<tr>
<td>Hygiene</td>
<td>1.14</td>
<td>1.01</td>
<td>1.14</td>
<td>1.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.08</td>
<td>1.13</td>
<td>2.06</td>
<td>1.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.76</td>
<td>1.86</td>
<td>2.75</td>
<td>1.85</td>
</tr>
<tr>
<td>CRP (1.5-3 mL/L)</td>
<td>1.51</td>
<td>1.00</td>
<td>1.51</td>
<td>1.00</td>
</tr>
<tr>
<td>CRP (3-10 mL/L)</td>
<td>1.02</td>
<td>0.61</td>
<td>1.02</td>
<td>0.61</td>
</tr>
<tr>
<td>CRP (&gt;10 mL/L)</td>
<td>1.67</td>
<td>0.80</td>
<td>1.67</td>
<td>0.80</td>
</tr>
<tr>
<td>P</td>
<td>0.0064</td>
<td>0.0098</td>
<td>0.0120</td>
<td>0.0542</td>
</tr>
</tbody>
</table>

Table 4. Logistic regression predicting CRP.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tooth loss (5-7)</td>
<td>1.13</td>
<td>0.87</td>
<td>1.11</td>
</tr>
<tr>
<td>Tooth loss (8-16)</td>
<td>1.15</td>
<td>0.89</td>
<td>1.23</td>
</tr>
<tr>
<td>Tooth loss (17-32)</td>
<td>0.91</td>
<td>0.70</td>
<td>1.00</td>
</tr>
<tr>
<td>Age</td>
<td>1.22</td>
<td>1.05</td>
<td>1.21</td>
</tr>
<tr>
<td>Height</td>
<td>0.98</td>
<td>0.96</td>
<td>0.98</td>
</tr>
<tr>
<td>Waist</td>
<td>1.07</td>
<td>1.06</td>
<td>1.07</td>
</tr>
<tr>
<td>Income</td>
<td>1.34</td>
<td>1.09</td>
<td>1.33</td>
</tr>
<tr>
<td>Urban</td>
<td>1.19</td>
<td>0.89</td>
<td>1.03</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.33</td>
<td>0.84</td>
<td>1.33</td>
</tr>
<tr>
<td>Hygiene</td>
<td>0.93</td>
<td>0.71</td>
<td>0.93</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.0015</td>
<td>0.0839</td>
<td>0.0875</td>
</tr>
<tr>
<td>P</td>
<td>0.0015</td>
<td>0.0839</td>
<td>0.0875</td>
</tr>
</tbody>
</table>
Figure 1. Logistic regression predicting CVD; added predictors: a) tooth loss; b) age, height, waist circumference; c) income, urbanicity d) smoking, hygiene, diabetes, hypertension e) CRP; * p<0.05

Figure 2. Proposed relationship between tooth loss and CVD in U.S. and Cebu populations.