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Original Article

Poor Oral Health Is Associated With Inflammation, Aortic Valve Calcification, and Brain Volume Among Forager-Farmers

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Abstract

Poor oral health is associated with cardiovascular disease and dementia. Potential pathways include sepsis from oral bacteria, systemic inflammation, and nutritional deficiencies. However, in post-industrialized populations, links between oral health and chronic disease may be confounded because the lower socioeconomic exposome (poor diet, pollution, and low physical activity) often entails insufficient dental care. We assessed tooth loss, caries, and damaged teeth, in relation to cardiovascular and brain aging among the Tsimane, a subsistence population living a relatively traditional forager-horticulturalist lifestyle with poor dental health, but minimal cardiovascular disease and dementia. Dental health was assessed by a physician in 739 participants aged 40–92 years with cardiac and brain health measured by chest computed tomography (CT; $n = 728$) and brain CT ($n = 605$). A subset of 356 individuals aged 60+ were also assessed for dementia and mild cognitive impairment ($n = 33$ impaired). Tooth loss was highly prevalent, with 2.2 teeth lost per decade and a 2-fold greater loss in women. The number of teeth with exposed pulp was associated with higher inflammation, as measured by cytokine levels and white blood cell counts, and lower body mass index. Coronary artery calcium and thoracic aortic calcium were not associated with tooth loss or damaged teeth. However, aortic valve calcification and brain tissue loss were higher in those who had more teeth with exposed pulp. Overall, these results suggest that dental health is associated with indicators of chronic diseases in the absence of typical confounds, even in a population with low cardiovascular and dementia risk factors.

Keywords: Cardiovascular disease, Chronic disease, Dementia, Tooth loss, Tsimane

Poor oral health is often associated with increased rates of noncommunicable diseases, including both cardiovascular disease (CVD) and dementia (1–5). Recent large-scale meta-analyses showed a dose-dependent increase in the risk of chronic diseases per lost tooth: the risk of CVD and stroke increases by 1.5% per tooth, the risk of cognitive impairment increases by 1.2%, and the risk of dementia by 1.1% (2–4). Possible mechanisms include: causal pathways from oral

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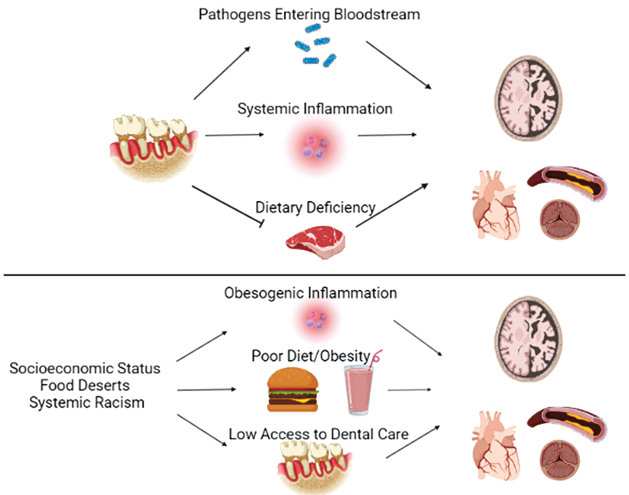

Figure 1. Conceptual figure showing pathways by which oral health could influence cardiovascular disease and brain aging. Created with BioRender.com.

bacteria residing in atherosclerotic cardiovascular and brain plaques; systemic inflammation arising from periodontal disease that impacts the risk of both CVD and cognitive aging (2–4); and dietary deficiencies resulting from eating difficulties (6,7) (Figure 1).

Moreover, low socioeconomic status increases the risk of a variety of poor health outcomes including obesity, systemic inflammation, poor oral health, and CVD and dementia (8,9), leading to multiple potential pathways (Figure 1). As such, associations between oral health and CVD/dementia in observational studies are difficult to establish due to confounding factors. Nearly all of the research on CVD, dementia, and their associations with tooth loss have been conducted in sedentary, affluent post-industrialized populations with relatively high rates of CVD and dementia and regular oral hygiene. Here, we assess associations between oral health, CVD, and cognitive impairment in the Tsimane of lowland Bolivia, a traditional population of forager-horticulturalists, with exceptionally low rates of CVD and dementia (10,11) and minimal oral hygiene. Although the prevalence of these chronic diseases is low even among older adults, the Tsimane experience high rates of tooth loss and periodontal disease; by age 70 the average Tsimane adult has lost 12 teeth (12,13).

Most Tsimane (population approximately 17 000) rely on small-scale horticulture, hunting, and fishing for survival. A small but growing portion of the diet is recently coming from market-derived foods such as refined sugar and cooking oil (14,15). Tsimane generally lacks access to modern dental care and has poor oral health from a young age (12,16,17).

Here, we test the hypothesis that oral health (specifically tooth loss and damaged teeth) is associated with markers of inflammation, cardiovascular disease, brain aging, and dementia among the Tsimane. Figure 1 shows multiple pathways by which oral health could impact inflammatory markers; either through bacteria entering the bloodstream or via oral inflammation (1). Inflammation is a risk factor for both cardiovascular disease as well as brain health (18) and previous studies have reported potential mechanisms by which oral health could impact atherosclerotic plaques either in the coronary arteries, thoracic arteries, or the aortic valve (19–21). In addition to direct pathways (eg, bacteria entering the bloodstream) and indirect pathways (inflammation), there is also the potential that tooth loss could lead to poorer nutritional intake, which could impact body composition and be associated with poor health. We predict that poor oral health will be associated with chronic diseases of aging, including inflammation, cardiovascular disease, and dementia, despite low levels of chronic disease and high background inflammation from parasites and pathogens.

Method

Dental health was assessed by a licensed Bolivian physician: each tooth was coded as either healthy, having caries, having exposed pulp, or as absent. Damaged teeth with exposed pulp could result from wear, trauma, caries, or some combination of all 3. Dental records and chest computed tomography (CT) scans were analyzed for 728 individuals with a median age of 58 years (52.1% men; Table 1). Brain CTs were performed at the same time as chest CTs for 605 of these individuals with a median age of 59 years (53% men). Brain CT scan volumes and gated chest CT scans were obtained on a GE Lightspeed 16 Slice CT Scanner (22). While magnetic resonance imaging (MRI) would be ideal, it was not available in this area of Bolivia at the time of data collection. CT images were acquired in a helical mode clockwise, with a standard convolution kernel, and 2 reconstructions. The first reconstruction had a voxel size of 1.25 mm × 1.25 mm × 1.25 mm, and the second had a voxel size of 0.625 mm × 0.625 mm × 0.625 mm. The kilovoltage peak was 120 kV, with a data collection diameter of 25 cm, a mean exposure time of 1.417 seconds, an X-ray tube current of 140 mA, and a focal spot of 0.7 mm (22,23). Brain volume (BV) was computed as a percentage of total intracranial volume and normalized for height (22–24). A probabilistic classification method was used to perform tissue classification (25). Each CT voxel in the cranium was assigned to either BV or cerebrospinal fluid volume (CSFV), such that intracranial volume (ICV) = BV + CSFV. The distribution of image intensities was modeled by a mixture of clusters, each consisting of Gaussian random variables, and then validated against a separate matched CT-MRI sample (see references (22–24) for additional information on the validation of CT-based volumetrics against MRI). Coronary artery calcium, thoracic aortic calcium, and aortic valve calcium were measured with Siemens Syngo calcium scoring software by a central core laboratory (Siemens, Munich, Germany) (10). The oral health assessments were all completed prior to CT scans, by approximately 4.2 years.

Clinical evaluations for mild cognitive impairment and dementia were assessed by a team of United States and Bolivian clinicians from an adapted Modified Mini-Mental State (3MS) examination, a battery of neurocognitive tests including the Kimberley Indigenous Cognitive Assessment Tool and the Blessed Rating Scale, cognitive tests based on the Mexican Health and Aging Study, and interviews with family members (11,16,26,27). The 3MS was made culturally appropriate with iterative modifications in consultation with Tsimane anthropologists to deal with illiteracy and lack of counting ability (11). Both the training and quality control included direct observation of Bolivian physicians in the field by the U.S. dementia team, and also by video throughout the duration of data collection (for complete details see (11)). The modified version of the cognitive protocols for the Mexican

Table 1. Mean Participant Characteristics and Sex Differences

	All (95% CI)	Men (95% CI)	Women (95% CI)	*n*	*p* Value
Absent teeth (#)	10.0 (9.1–10.8)	7.7 (6.8–8.7)	12.2 (10.9–13.5)	739	<.001
Healthy teeth (#)	8.0 (7.3–8.7)	10.1 (9.1–11.1)	5.8 (4.9–6.6)	739	<.001
Teeth w/exposed pulp (#)	2.5 (2.1–2.8)	2.7 (2.2–3.2)	2.2 (1.8–2.6)	739	.129
Age (y)	59.2 (58.4–60.1)	59.0 (57.8–50.2)	59.4 (58.2–60.6)	739	.743
BMI (kg/m^2)	23.7 (23.424.0)	23.8 (23.4–24.1)	23.6 (23.2–24.1)	717	.400
CRP (g/dL)	3.3 (3.1–3.5)	3.4 (3.1–3.7)	3.2 (2.9–9.6)	592	.519
WBC (cells/μL × 10^3)	9.9 (9.7–10.1)	10.1 (9.7–10.4)	9.7 (9.4–10.0)	678	.145
Total coronary artery calc (AU)	11.7 (7.4–16.0)	15.1 (9.1–21.0)	8.0 (1.7–14.3)	730	.111
Total thoracic aortic calc (AU)	58.7 (41.6–75.7)	53.6 (41.6–75.7)	64.1 (39.3–89.0)	734	.547
Total aortic valve calc (AU)	53.5 (39.5–73.5)	83.6 (53.3–113.9)	27.0 (14.5–39.4)	725	<.001
% w/ No coronary artery calc	82.6%	77.3%	88.3%	730	<.001
% w/ No thoracic aortic calc	30.7%	29.29%	32.3%	734	.357
% w/ No aortic valve calc	66.3%	57.9%	75.4%	725	<.001
Normalized brain volume %	85.1 (84.8–85.4)	85.0 (84.6–85.5)	85.1 (84.7–85.6)	605	.725

Note: AU = arbitrary units; BMI = body mass index; CRP = C-reactive protein.

Health and Aging Study and from the Indianapolis-Ibadan Dementia Project are described in detail elsewhere (16,26); this battery includes visual scan (searching for a target symbol amongst distractor symbols), digit span forward, immediate and delayed word recall, semantic fluency (naming animals and fish), spatial span (a variation of the Corsi block tapping task), and a stick design test (a measure of visuoconstructional ability) (11,16). Bolivian physicians received training and supervision at a neurology clinic in the United States with video follow-ups and then conducted a neurological assessment for signs associated with parkinsonism or stroke.

After compiling all data, independent diagnoses were made by the Bolivian and US teams. In cases of disagreement, a consensus conference of psychologists, neurologists, gerontologists, physicians, and neuroradiologists conferred and finalized diagnoses of either normal cognition, mild cognitive impairment, or dementia (11). Among a subset of 356 individuals aged 60+ with dental exams and who underwent clinical diagnostic cognitive evaluations (median age of 66 years, 49.7% men), $n = 33$ (9.3%) were diagnosed cognitively impaired (either with mild cognitive impairment or dementia). Due to the small number of cases, individuals were coded as normal cognition or impaired cognition for analyses.

White blood cell counts and high sensitivity C-reactive protein enzyme immunoassay (CRP) (10) were assessed following fasting morning blood draws. Cytokine levels were analyzed with a Quansys cytokine panel on a subset of individuals ($n = 507$). Height was measured with a portable stadiometer (SECA 213), and weight with a Tanita BC-1500. Participants were asked by the physician if they had ever smoked, and on average how many cigarettes they smoked per day over the years that they smoked. These were then used to calculate pack-years of smoking; these data were available for 635 individuals. Only 2 participants out of 739 had diagnoses of diabetes, which is underpowered for evaluating associations between CVD and diabetes.

Statistical Methods

Linear regressions were run to examine associations between oral health (tooth loss, caries, and exposed pulp) and each inflammatory biomarker (cytokines, CRP, and white blood cell counts), controlling for age and sex (see Supplementary Tables 1–16). The cytokine and CRP data all had significant skew and were log-transformed for analyses. To measure the association between oral health (tooth loss, caries, and exposed pulp) and cardiac disease while adjusting for the extremely low levels of calcification observed, we used zero-inflated negative binomial models. These models assessed the association between tooth loss and each marker of cardiovascular health (3 separate models for aortic valve calcification, coronary artery calcification, and thoracic aortic calcification), and examined both the presence or absence of calcium as well as the extent of calcium for those that have calcium. We also ran linear regressions to examine associations between oral health measures and brain volume, controlling for age, sex, and BMI. All statistics were performed in Stata 17.0 (StataCorp LLC, College Station, TX).

Ethics Statement

Informed consent was obtained at 3 levels: individual, community, and the Tsimane Gran Consejo (Tsimane governing body). All study protocols were approved by the Institutional Review Boards of the Universidad Mayor San Simon of Cochabamba Bolivia, the University of New Mexico (#07-157), and the University of California Santa Barbara (#3-21-0652).

Results

Oral Health

Tooth loss was associated with age (2.2 teeth lost per decade). Women, on average, lost 4.6 more teeth ($p < .001$) than men. Correspondingly, the number of healthy teeth declined with age (Figure 2). Controlling for age, sex, and an interaction between age and sex, the number of teeth with exposed pulp was associated with lower body mass index (BMI, kg/m^2; $b = -0.086$, $p = .005$).

Inflammatory Biomarkers

Controlling for age, sex, and tobacco exposure, the total number of teeth lost and teeth with caries were not associated

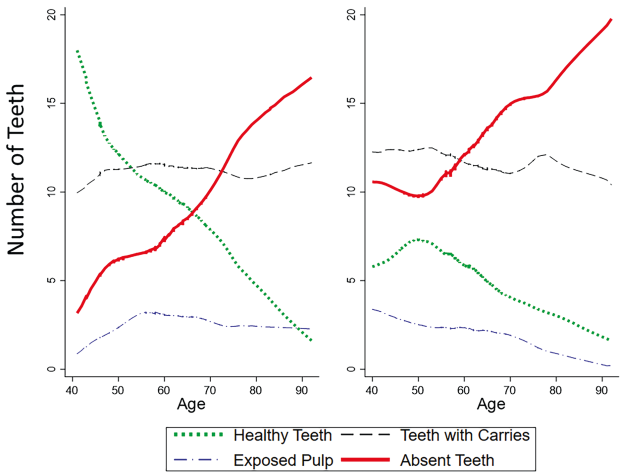

Figure 2. Cross-sectional age-related differences (locally weighted regression) in the number of healthy teeth (green), teeth with caries (black), teeth with exposed pulp (blue), and missing teeth (red).

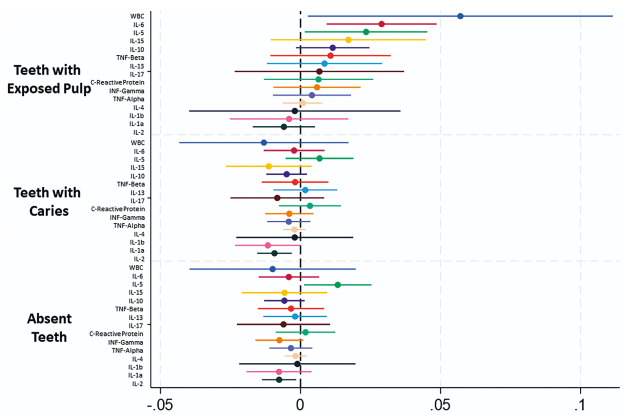

Figure 3. Associations between cytokine levels and teeth with exposed pulp. Each line indicates the association between a different cytokine and the number of teeth with exposed pulp, caries, or missing, controlling for age, sex, and smoking (pack-years).

with any inflammatory biomarkers after Bonferroni corrections. However, the number of teeth with exposed pulp was associated with generally elevated inflammatory biomarkers. Controlling for age, sex, cigarette pack-years, and the number of teeth with caries and lost teeth, each additional tooth exhibiting exposed pulp was associated with higher cytokine levels including IL-5 ($b = 0.023$, $p = .036$), IL-6 ($b = 0.030$, $p < .004$), IL-10 ($b = 0.11$, $p = .086$), and higher white blood cell counts ($b = 0.057$, $p = .04$; see Figure 3, and Supplementary Materials). Twelve out of 15 immune markers were higher for teeth with exposed pulp. After implementing a Bonferroni correction for multiple tests, IL-6 remained significantly associated with the number of teeth with exposed pulp.

Cardiovascular Disease

Controlling for age, sex, BMI, cigarette pack-years, number of teeth lost, and number of teeth with caries, each additional tooth with exposed pulp was associated with a higher level of aortic valve calcification for those that had any calcification (IRR = 1.184, $p = .002$, Figure 4, Table 2). When controlling

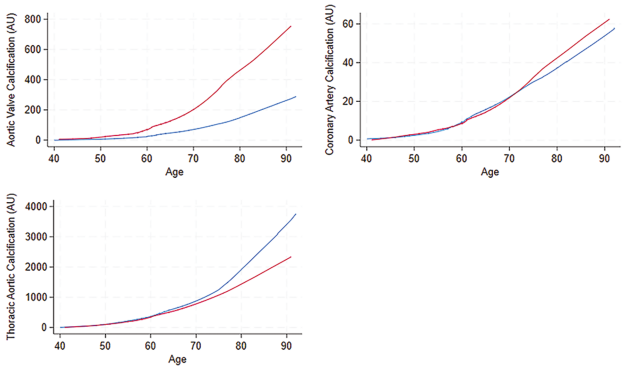

Figure 4. Associations between cardiovascular calcium and teeth with exposed pulp (red) by age, predicted from zero-inflated negative binomial models (Table 2).

for age, sex, BMI, cigarette pack-years, and lipid levels, no associations were found between the presence or extent of coronary artery calcium and: (a) tooth loss, (b) number of teeth with caries, or (c) number of teeth with exposed pulp (Figure 4 and Table 2). Similarly, there was no relationship between thoracic aortic calcium and either tooth loss, caries, or pulp exposure (Figure 4 and Table 2).

Brain Volume Declines and Cognitive Impairment

Controlling for age and sex, each additional tooth with exposed pulp was associated with lower brain volume as a proportion of total intracranial volume ($b = -0.103\%$, $p = .002$, 95% CI: −0.169 to −0.036, see Table 3). There was no association between brain volume and either tooth loss or caries. The number of teeth with exposed pulp was not associated with gray or white matter volume, though individuals with more teeth with exposed pulp had significantly higher cerebrospinal fluid volume ($b = 1107.461$ mm^3, $p = .017$). There was no association between tooth loss, caries, or exposed pulp and the diagnosis of cognitive impairment (mild cognitive impairment or dementia).

Discussion

The Tsimane shows associations between oral health, inflammation, cardiovascular disease, and brain aging. We found the Tsimane experience high levels of tooth loss, with adults losing more than a third of their teeth by age 63, and more than half of their teeth by age 86. Although this study did not specifically focus on reasons for poor oral health, previous Tsimane studies have reported high rates of enamel defects in childhood and dental decay associated with sugary drinks (13,17). Consumption of sugar cane, citrus, sugar, as well as a high carbohydrate diet likely play a role (14). Tsimane also has minimal access to professional dental care. Age and women were strong predictors of tooth loss, with women losing on average 4 and a half more teeth than men, likely due to the costs of fertility, which impact bone mineral density in this population (28,29). Tooth loss was also associated with lower BMI by age and sex, suggesting that tooth loss in this population may be associated with nutrient deficiencies. In high fertility settings, women tend to lose more teeth than men (30,31), with several potential mechanisms ranging from increases in periodontal disease due to shifts in immune function during pregnancy, to loss of calcium from gestating a fetus, to changes in hormones during pregnancy (32).

Table 2. Zero-inflated Negative Binomial Regression Models Examining Cardiovascular Calcium by the Number of Teeth with Exposed Pulp, Caries, and Absent Teeth. The Upper Section Displays Significant Predictors of Non-zero scores, While the Lower Section Displays the Significant Predictors of Inflated Scores of Zero

	Aortic valve calcification			Coronary artery calcification			Thoracic artery calcification		
Predictors of calcium extent									
	IRR	***p* Value**	**95% CI**	**IRR**	***p* Value**	**95% CI**	**IRR**	***p* Value**	**95% CI**
Teeth with exposed pulp	1.184	.002	(1.067, 1.315)	1.025	.587	(0.937, 1.121)	0.992	.692	(0.951, 1.034)
Teeth with caries	1.030	.351	(0.968, 1.096)	1.000	.989	(0.944, 1.059)	1.005	.699	(0.982, 1.028)
Absent teeth	1.072	.019	(1.011, 1.137)	1.016	.618	(0.955, 1.080)	1.005	.619	(0.984, 1.027)
Age	1.042	.022	(1.006, 1.079)	1.040	.026	(1.005, 1.076)	1.075	<.001	(1.059, 1.092)
Men	2.330	.023	(1.126, 4.823)	0.887	.817	(0.322, 2.444)	0.981	.914	(0.696, 1.383)
BMI (kg/m^2)	0.997	.948	(0.898, 1.106)	1.062	.253	(0.958, 1.177)	1.020	.351	(0.978, 1.064)
Smoking (pack-years)	0.996	.648	(0.977, 1.015)	1.018	.087	(0.997, 1.038)	0.995	.123	(0.989, 1.001)
Log CRP	0.687	.108	(0.435, 1.086)	1.468	.070	(0.969, 2.225)	1.418	<.001	(1.206, 1.668)
Constant	1.570	.833	(0.024, 103.145)	0.335	.539	(0.102, 10.949)	1.938	.403	(0.411, 9.139)
Predictors of calcium absence									
Teeth with exposed pulp	0.024	.531	(−0.052, 0.101)	0.005	.891	(−0.063, 0.073)	−0.019	.561	(−0.083, 0.044)
Teeth with caries	0.003	.887	(−0.043, 0.050)	−0.103	.609	(−0.050, 0.029)	0.006	.719	(−0.028, 0.040)
Absent teeth	0.008	.712	(−0.037, 0.053)	0.007	.732	(−0.032, 0.046)	−0.020	.255	(−0.054, 0.014)
Age	−0.094	<.001	(−0.127, −0.060)	−0.063	<.001	(−0.090, −0.036)	−0.152	<.001	(−0.198, −0.105)
Men	−0.870	.011	(−1.542, −0.197)	−0.826	.007	(−1.428, −0.225)	−0.328	.264	(−0.902, 0.247)
BMI (kg/m^2)	0.049	.253	(−0.035, 0.134)	−0.008	.836	(−0.085, 0.069)	−0.072	.060	(−0.147, 0.003)
Smoking (pack–y)	0.013	.107	(−0.003, 0.029)	−0.001	.811	(−0.012, 0.009)	−0.003	.711	(−0.018, 0.012)
Log CRP	−0.591	.001	(−0.941, −0.242)	−0.099	.536	(−0.411, 0.214)	0.136	.364	(−0.158, 0.431)
Constant	5.963	<.001	(2.809, 9.117)	5.944	<.001	(3.166, 8.723)	9.381	<.001	(5.973, 12.790)

Note: BMI= body mass index; CRP = C-reactive protein.

Table 3. Regression Model Examining Normalized Brain Volume by the Number of Teeth with Exposed Pulp, Caries, and Absent Teeth

Normalized brain volume	**Coefficient**	***p* Value**	**95% CI**
Teeth with exposed pulp	−0.103	.002	[−0.169, −0.036]
Teeth with caries	−0.013	.478	[−0.050, 0.023]
Absent teeth	−0.018	.325	[−0.054, 0.018]
Age	−0.225	<.001	[−0.252, −0.199]
Sex (Men = 1)	−0.205	.478	[−0.771, 0.362]
Smoking (pack-y)	0.001	.894	[−0.011, 0.012]
Constant	99.328	<.001	[97.610, 101.047]
			Adj R^2 = 0.3697

Indeed, we see major shifts in immune function during pregnancy among the Tsimane (33), and women spend more time at the family compound where they can more readily access food than men who may be out hunting or clearing trees, increasing the number of times that women can eat per day compared to men (34,35). Women also allocate more time to food processing (36), which includes using teeth as tools thus increasing mechanical wear and tear on teeth. Although women in general have more tooth loss in this population, men have significantly higher rates of coronary artery calcium (10), which is common across nearly all populations (37). There are many factors above and beyond tooth loss that impact CVD risk including obesity, physical activity, immune activation, and hormonal changes with age that result in generally biased men's CVD until menopause (38).

Overall tooth loss and the number of teeth with caries were not associated with markers of inflammation. However, the number of teeth with exposed pulp, which presents an avenue for oral bacteria to enter the bloodstream, was associated with higher levels of inflammation. White blood cell counts, CRP, and 10 of 13 cytokines were all higher in individuals who had more teeth with exposed pulp. In animal models and in post-industrialized populations, periodontal disease is associated with higher levels of inflammation, while treatment for periodontal disease decreases systemic inflammation (1,39,40). Importantly, oral health remained associated with greater inflammation, which is noteworthy given the high background levels of inflammation that the Tsimane experience from pathogens and intestinal parasites (41–43). This suggests that oral health could potentially impact inflammation more than previously realized, even in a high parasite and pathogen environment.

Although inflammation is known to be associated with every aspect of cardiovascular disease from the beginning of plaque formation up through a myocardial infarction (18), we found no associations between either tooth loss or dental caries and coronary artery calcium or thoracic aortic calcium. However, we did find an association between aortic valve calcium and the number of teeth with exposed pulp. Inflammation is generally considered a key component of aortic valve calcification, and some cases may have underlying

infectious etiology (44). Thus, teeth with exposed pulp may increase inflammation or offer a route for bacteria to enter the bloodstream (21,45,46). Some caries can damage the enamel deeply enough to expose the pulp, which may enable oral bacteria to directly enter the bloodstream. Once gums heal over the socket following tooth loss, there is also no longer a direct route for bacteria to enter the bloodstream. Our findings regarding inflammation and aortic valve calcification appear to be driven by teeth with exposed pulp, which provide a direct route to the bloodstream, and not by other measures of oral health.

In a Japanese study sampling both oral bacteria in dental plaques, as well as bacteria present in valvular plaque samples in the same patients, *Streptococcus mutans* was present in all dental plaques, two-thirds of valve plaques, and 3 quarters of atheromatous plaques (47). Other studies have reported finding oral bacteria including *Streptococcus mutans*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and *Treponema denticola* in aortic valve plaques (19). A multipathway model has been suggested whereby bacteremia from poor oral health can not only seed those pathogens into damaged cardiovascular tissues but also induce an inflammatory response that exacerbates plaque formation (20). In further support of links between bacteremia and aortic valve calcifications, animal studies demonstrate that the intravenous infusion of other bacteria can cause the development of various levels of aortic valve calcification (48).

Brain tissue loss was greater in individuals who had more teeth with exposed pulp. However, there was no association between clinically diagnosed cognitive impairment and any dental health index. In post-industrialized populations, tooth loss is a potential risk factor for brain tissue loss, either due to increased pathogen exposure, increased inflammation, nutritional deficiencies, or even the cessation of chewing (4,49). In a longitudinal study with up to 22 years of follow-up, poor masticatory ability was associated with declines in some cognitive domains, but not higher rates of dementia (50). Rodent studies have suggested that the removal of teeth can reduce gray matter in the frontal cortex (49), while another study reported poor cognitive performance in water maze tasks following molar extraction (51). Even a soft diet can reversibly impair water maze performance on return to normal diet (52). In rodents, water maze performance increases as teeth are restored (51), giving a model for the improvement of MMSE scores in people using dentures (53,54).

Tsimane experiences relatively high levels of inflammation from a variety of pathogenic sources (41–43,55,56). Although some measures of inflammation have decreased over the last 2 decades (57), levels still remain elevated, and inflammation is higher in a few individuals with cardiovascular disease (10). It is notable that damaged teeth are also associated with inflammation, and this a testament to the importance of tooth decay in systemic inflammation worldwide. If rates of dental caries and associated tooth loss did, in fact, arise following the Neolithic revolution (58,59) (but see (60)), it is possible that this subsistence change may have been associated with a small but significant change in rates of cardiovascular disease or brain loss with age at a magnitude similar to that observed amongst Tsimane.

Limitations

This cross-sectional study cannot test causality. Although previous studies suggest that tooth loss can lead to brain tissue loss, we cannot rule out that brain tissue loss preceded tooth loss in our study, nor can we rule out that tooth loss led to decreased brain volume through decreased nerve activity (49,53). All dental health assessments were collected before the cardiovascular and brain imaging, on average 1 527 days prior to the imaging. Additional models were run, controlling for the time between dental health data collection and each of the outcome variables; the time variable was not significant in any model and thus was excluded. Our failure to find an association between tooth loss and dementia may reflect the small number of cases of dementia and mild cognitive impairment (n = 33), as well as the inherent confounding that results from the cross-sectional design. Additionally, the data was collected by a physician and not a dentist, so only measured basic oral health in regard to tooth loss and damage. Periodontal disease was not assessed but is a likely co-occurrence in some individuals. Although the Tsimane is a relatively homogenous population living a physically active subsistence lifestyle very different than many post-industrialized populations, we find similar associations between Tsimane oral health, cardiovascular health, and brain health to what is reported in the United States and Europe. Differences in fertility between these populations may modify sex differences in some of these associations (61), but overall, the effects of oral health on chronic disease appear to be robust across populations.

Conclusion

The average Tsimane individual over the age of 70 has lost more than 12 teeth, which prior studies indicate would put them at an 18% increased risk of CVD and stroke, and a 13.2% increased risk of dementia, compared to a dentally intact person. Although these conditions are uncommon among the Tsimane, we do find associations between aortic valve calcification and oral health, as well as brain tissue loss and oral health. Based on previous research, we present 3 potential mechanisms by which oral health could impact noncommunicable diseases: (a) bacteria entering the bloodstream, (b) inflammation due to oral health, or (c) nutritional deficiencies due to tooth loss. We found evidence supporting the inflammatory pathway. We also found suggestive evidence of the bacterial pathway given the associations between exposed pulp and health outcomes, but not for individuals with caries or tooth loss. Future studies will identify the microbes present in saliva and in the bloodstream to assess other disease pathways. Overall, oral health has important implications for systemic inflammation, as well as a number of noncommunicable diseases of aging, even in a population with exceptionally low traditional risk factors.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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Conflict of Interest

None.

Data Availability

Individual-level data are stored in the Tsimane Health and Life History Project (THLHP) Data Repository and are available through restricted access for ethical reasons. THLHP's highest priority is the safeguarding of human subjects and minimization of risk to study participants. The THLHP adheres to the "CARE Principles for Indigenous Data Governance" (Collective Benefit, Authority to Control, Responsibility, and Ethics), which assure that the Tsimane and Moseten (1) have sovereignty over how data are shared, (2) are the primary gatekeepers determining ethical use, (3) are actively engaged in the data generation, and (4) derive benefit from data generated and shared for use whenever possible. The THLHP is also committed to the "FAIR Guiding Principles for scientific data management and stewardship" (Findable, Accessible, Interoperable, and Reusable). Requests for individual-level data should take the form of an application that details the exact uses of the data and the research questions to be addressed, procedures that will be employed for data security and individual privacy, potential benefits to the study communities, and procedures for assessing and minimizing stigmatizing interpretations of the research results (see the following webpage for links to the data sharing policy and data request forms: https://tsimane.anth.ucsb.edu/data.html). Requests for individual-level data will require institutional IRB approval (even if exempt) and will be reviewed by an Advisory Council composed of Tsimane community leaders, community members, Bolivian scientists, and the THLHP leadership. A similar structure exists for the Moseten data. The study authors and the THLHP leadership are committed to open science and are available to assist interested investigators in preparing data access requests.

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