Annals of Epidemiology 38 (2019) 35–41

Contents lists available at ScienceDirect

Annals of Epidemiology

Original article

SES and correlated factors do not explain the association between periodontal disease, edentulism, and cancer risk

Jiayun Lu, PhD, MPH [b, 1], Ina Zaimi, MD, MS [a, 1], John R. Barber, MS [b], Corinne E. Joshu, PhD, MPH [b, c], Anna E. Prizment, PhD, MPH [d, e], James D. Beck, PhD [f], Elizabeth A. Platz, ScD, MPH [b, c, 2], Dominique S. Michaud, ScD [a, *, 2]

[a] Department of Public Health & Community Medicine, Tufts University School of Medicine, Boston, MA
[b] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
[c] Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD
[d] Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN
[e] University of Minnesota Masonic Cancer Center, Minneapolis, MN
[f] Department of Dental Ecology, School of Dentistry, University of North Carolina, Chapel Hill, NC

ARTICLE INFO

Article history:
Received 30 January 2019
Accepted 14 August 2019
Available online 22 August 2019

Keywords:
Periodontal disease
Edentulism
Gum disease
Cancer
SES
Confounding

ABSTRACT

Purpose: Severe periodontal disease and edentulism have been previously reported to be significantly associated with cancer risk and mortality, including in the Atherosclerosis Risk in Communities study (2018); however, complex sources of confounding by socioeconomic status (SES), and characteristics correlated with SES, could have been present in earlier analyses.
Methods: To capture life course SES and its correlates, we generated a propensity score and included it, along with other potential confounders such as smoking and obesity, into a Cox regression model to examine the association between periodontal disease and cancer risk. In addition, we stratified the model with the propensity score by low and high SES. All statistical tests were two-sided.
Results: Compared with our previous study, the associations for severe periodontitis and cancer incidence remained comparable after weighting by the propensity score (e.g., for total cancer: before weighting, hazard ratio = 1.24, 95% confidence interval = 1.07–1.42 vs. after weighting, hazard ratio = 1.23, 95% confidence interval = 1.05–1.44 when comparing severe periodontitis to no or mild periodontitis). Associations were comparable in low and high SES strata and statistically significant among participants with high SES.
Conclusions: Complex sources of confounding by SES and its correlates are unlikely to fully account for the positive associations observed for periodontal disease and edentulism and cancer risk.

Background

Severe periodontal disease and edentulism have been previously reported to be significantly associated with cancer risk and mortality [1–3]; including in the Atherosclerosis Risk in Communities (ARIC) study [4]. Periodontal disease is more common in populations with low socioeconomic status (SES) and poor dental care [5]; and those with low SES have more cancer risk factors and are less likely to be screened for cancer [6]. After adjusting for life course SES in the ARIC study, we observed that severe periodontal disease as measured with a dental examination and self-reported edentulism were associated with increased total, lung, and colorectal cancer incidence and cancer mortality [4]; however, complex sources of confounding by SES or its correlates, such as neighborhood factors and access to and uptake of medical and dental care, could still be present.

Evaluating causality for periodontal disease and cancer requires careful consideration of confounding bias. Thus, to rule out potential confounding by complex factors linked to SES, we re-examined the association in the ARIC study weighting by a propensity score generated from life course SES, neighborhood income, and access to and uptake of routine medical and dental care. We then compared the SES-independent associations with those we previously published [4].

* Corresponding author: Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111. Tel.: (617)-636-0482.
E-mail address: Dominique.Michaud@tufts.edu (D.S. Michaud).
[1] Shared first author.
[2] Shared last author.

https://doi.org/10.1016/j.annepidem.2019.08.005
1047-2797/

Methods

Study design

Data were derived from the ARIC study, a prospective cohort of 15,792 participants aged 44–66 years recruited between 1987 and 1989 from Jackson, Mississippi; Washington County, Maryland; Minneapolis, Minnesota; and Forsyth County, North Carolina [7,8]. For this analysis, we used the same subset of participants in our previous study [4]. Briefly, men and women participating in the dental examination, taking place in visit 4 (1996–1998) or who self-reported being edentulous at visit 4, who did not have a history of cancer by visit 4, and who did not restrict consent to cardiovascular diseases were included in this study. The final eligible sample was 6056 participants who underwent the dental examination and an additional 1410 participants who reported being edentulous and did not undergo the dental examination. Participants who were not white or black were removed from this analysis as the numbers were very small. Information about cancer ascertainment in ARIC has been described previously [9].

Life course socioeconomic status and associated factors

Individual life course SES for participants in this cohort was calculated using 12 variables: parental education (<eighth grade; eighth grade; >eighth grade), parental occupation (manual/nonmanual), parental occupation role (managerial yes/no), parental home ownership, education (<high school; high school graduate; >high school), young adulthood (age 30 years) occupation (manual/nonmanual), young adulthood occupational role (managerial yes/no), young adulthood home ownership, older (45–64 years) adulthood income (<$25,000; $25–34,999; ≥$35,000), older adulthood occupation (manual/nonmanual), older adulthood occupational role (managerial yes/no), and older adulthood home ownership. Life course SES was calculated from these variables as performed previously in ARIC [10]. For classification purposes, life course SES was considered "low" when the score was less than 8/15 and "high" when the score was ≥8/15 points; the childhood SES cutpoint for high was set at ≥3/5. Other factors known to be associated with SES and available for this analysis included: typical frequency of routine medical examinations, health insurance status, usual type of health insurance, type of medical care, having a dentist, frequency of dental care, last time of dental visit, and neighborhood income, which was estimated by linking participants' address to the U.S. Census tract data using geocoding [11].

Periodontal disease classification

For this analysis, we used the same classifications of periodontal profiles as the ones used in our previous study [4]; two classification criteria were used as there is considerable discrepancy on how to classify periodontal disease in population studies, and the different classifications can provide different information about disease status and progression. The classifications used were (1) U.S. Centers for Disease Control and Prevention—American Academy of Periodontology definition developed for population-based surveillance of periodontitis, which uses both clinical attachment level and pocket depth measurements [12] and (2) the definition based only on clinical attachment level measurements (ARIC definition) [13]. These definitions are described in detail in Table 1. We also used self-reported edentulism at visit four in all the analyses (these participants did not undergo the ARIC dental examination).

Measurement of potential confounders

Detailed data on demographic (age, race, education), behavior, and medical conditions were obtained at baseline and during follow-up visits. Data from visit four or earlier visits were used to adjust for confounding. Weight and height were measured by trained staff at each visit and were used to estimate body mass index (BMI in kg/m^2). Data on smoking status, years of smoking before baseline, and number of cigarettes smoked per day at baseline and at each visit were used to calculate the number of pack-years smoked at visit 4. Alcohol drinking was derived from the interview at each visit and was categorized as never, former, or current drinker at visit 4. To define diabetes mellitus status at visit 4, we used data on a physician diagnosis of diabetes, pharmacologic treatment for diabetes, fasting glucose (each visit), and glycated hemoglobin (visit two only). If participants were fasted for less than 8 hours at a visit, the prior visit fasting glucose measure was carried forward. Participants who reported a physician diagnosis or treatment at any visit were considered to have diagnosed diabetes. Among participants who did not have a diagnosis of diabetes, participants with fasting glucose ≥126 mg per dL at any visit or glycated hemoglobin ≥6.5% at visit two were considered to have undiagnosed diabetes. Among participants who did not have diagnosed or undiagnosed diabetes, participants with fasting glucose of 100 to <126 mg per dL at visit four were considered to be prediabetic (at risk for diabetes) and otherwise were considered to not have diabetes or be at risk for diabetes. Women who reported the use of hormone replacement therapy at any assessment (visits 1, 3, and 4; yes or no) were categorized as hormone replacement therapy users.

Statistical analysis

Cox proportional hazards regression was used to estimate the association of periodontal disease severity and edentulism with cancer incidence and mortality, expressed as hazard ratios (HRs) and 95% confidence intervals (CIs), adjusted for known or suspected cancer risk factors (age, field center and race, smoking, BMI, diabetes status, alcohol drinking). We addressed the possibility of confounding by life course SES, and factors associated with SES, by

Table 1
Definitions of periodontal disease

CDC-AAP		ARIC study	
Periodontal disease status	Measurement	Periodontal disease status	Measurement
No	No evidence of mild, moderate, or severe periodontitis	No/mild	10% of examined sites having AL ≥3 mm
Mild	≥2 Interproximal sites with AL ≥3 mm, and ≥2 interproximal sites with PD ≥ 4 mm (not on same tooth) or one site with PD ≥ 5 mm		
Moderate	≥2 Interproximal sites with AL ≥4 mm (not on same tooth), or ≥2 interproximal sites with PD ≥ 5 mm (not on same tooth)	Moderate	≥10% to <30% of examined sites having AL ≥3 mm
Severe	≥2 Interproximal sites with AL ≥6 mm (not on same tooth) and ≥1 interproximal site with PD ≥ 5 mm	Severe	≥30% of examined sites with AL ≥3 mm

weighting the Cox model by the robust variance of the propensity score [14–16]. To do so, first, we modeled the association between severe periodontal disease/edentulism and life course SES and variables correlated with SES (neighborhood income, health insurance status, frequency of routine physical examination, having a dentist, frequency of routine dental visit, last time of dental visit) using multinomial logistic regression to predict the propensity score for each participant. We confirmed the positivity assumption of the use of the propensity score. Then, we added the robust variance of the propensity score as a weight in the Cox model that included terms for severity of periodontal disease (using the two definitions), and edentulism, age, field center by race, smoking, BMI, diabetes status, alcohol drinking, and hormone use among women. Propensity scores have been used previously to control for confounding in ARIC [17]. We also generated propensity scores separately among participants with low (<8/15 points) and high (≥8/15 points) life course SES as we did for the main analysis but excluding life course SES, and then stratified the propensity score–weighted Cox model by low (<8/15 points) and high (≥8/15 points) life course SES. All statistical analyses were performed using SAS 9.4 (Cary, NC). Statistical tests were two-sided, and a $P < 0.05$ was considered statistically significant. In comparing point estimates before and after propensity score weighting, a difference >10% was considered "stronger" or "weaker" (depending on direction of change) and a change < 10% was considered similar as is conventional when considering the influence of potentially confounding factors.

Results

Distribution of life course SES and other characteristics used to generate the propensity score by periodontal disease severity and edentulism is reported in Table 2 (other demographic and behavioral characteristics distributions by periodontal disease were previously described elsewhere [4]. As expected, periodontal disease severity and edentulism were associated with most of the factors that were included in the propensity score; for example, 23.6% of participants with severe periodontal disease did not have a dentist compared with 5.4% of participants with no or mild periodontal disease (ARIC definition).

CDC/AAP classification

Compared with our previous study [4]; after weighting by the propensity score, the associations between severe periodontitis/edentulism and total cancer incidence remained similar (Table 3). The only finding that differed in this analysis, compared to the earlier study, was for cancer deaths, where the association with mild periodontitis shifted from null to positive after weighting by the propensity score (HR = 1.71, 95% CI = 0.83 to 3.51 [Table 3] vs. HR = 0.97, 95% CI = 0.64 to 1.47 [4]; however, the observed association was not statistically significant and may have occurred by chance.

The association between severe periodontitis and colorectal cancer was also slightly stronger and statistically significant after weighting by the propensity score (HR = 1.77, 95% CI = 1.03 to 3.05 vs. HR = 1.51, 95% CI = 1.09 to 2.52 [4].

To further evaluate whether SES and correlated factors could have biased our main results, we examined those participants with the lowest propensity scores (i.e., those whose oral health was the least correlated with SES and correlated factors). For these analyses, participants falling in the lowest 25th percentile of the propensity score were examined separately. Edentulism remained associated with cancer incidence (HR = 2.32, 95% CI 1.08 to 5.00), lung cancer, and cancer mortality although the latter two associations were not statistically significant because of small numbers (data not shown). Numbers of cases were too small to examine associations with periodontal disease.

"ARIC" definition

When the "ARIC" definition was used, the associations for total cancer incidence and cancer death remained comparable and consistently statistically significant after weighting by the propensity score. The association between edentulism and colorectal cancer remained similar after weighting by the propensity score (HR = 2.04, 95% CI = 1.22 to 3.41 [Table 3] vs. HR = 1.89, 95% CI = 1.17 to 3.05 [4]. Similarly, the point estimates were comparable for severe periodontitis and lung cancer (HR = 2.17, 95% CI = 1.42 to 3.33 [Table 3] vs. HR = 2.33, 95% CI = 1.51 to 3.60 [4], as well as between edentulism and lung cancer (HR = 2.83, 95% CI = 1.75 to 4.59 [Table 3] vs. HR = 2.60, 95% CI = 1.65 to 4.08 [4].

SES stratification

After stratifying the study population by SES status, the results for the two definitions of periodontal disease with total, colorectal, and lung cancer incidence and cancer mortality in both the high and low SES strata remained generally consistent with the main results (Table 4 vs. Table 3), although we noted a small number of differences in patterns of association. Using the U.S. Centers for Disease Control and Prevention—American Academy of Periodontology definition, the positive association between severe periodontal disease and cancer death was present in the high SES but not the low SES stratum. However, the positive association was present in both SES strata when using the ARIC definition, and the positive association for edentulism and cancer mortality was similar in both SES strata.

The associations between severe periodontitis and colorectal cancer risk in the high (HR = 1.64, 95% CI = 0.90 to 2.99) and low (HR = 2.21, 95% CI = 0.87 to 5.61) SES strata were both elevated but somewhat stronger in the lower SES strata. For lung cancer, the associations for severe periodontitis were similar among those with high SES (HR = 1.72, 95% CI = 1.03 to 2.88) and low SES (HR = 1.91, 95% CI = 0.74 to 4.96), although only the association in the high SES strata was statistically significant (Table 4).

We further conducted a stratified analysis to examine if there were differences by childhood SES, as low childhood SES could potentially have a lasting impact on oral health over the life course. Although the results did not differ substantially by childhood SES strata for total cancer incidence and mortality, we did note that the associations were stronger in the low childhood SES strata for severe periodontal disease and colorectal cancer (low SES: HR = 1.93, 95% CI = 0.94 to 3.95 vs. high SES: HR = 1.07, 95% CI = 0.53 to 2.19, original ARIC definition), as well as for lung cancer (low SES: HR = 2.90, 95% CI = 1.31 to 6.40 vs. high SES: HR = 1.70, 95% CI = 0.93 to 3.09, original ARIC definition), suggesting potential effect modification by childhood SES; however, tests for interaction were not statistically significant. Similar patterns across childhood SES strata for colorectal cancer and lung cancer were observed for edentulism (data not shown).

Discussion

The aim of this study was to investigate if the association between periodontitis and cancer is confounded by life course SES and associated factors. Overall, we observed only modest changes in the HRs for total cancer and colorectal and lung cancer, when compared with the results of our previous ARIC study.

Table 2
Distribution of the propensity score and variables used for generating the propensity score by periodontal disease status in ARIC

	CDC-AAP						Original ARIC			
	Edentulism	No	Mild	Moderate	Severe	*P**	No/Mild	Moderate	Severe	*P**
Propensity score										
25th	0.52	0.27	0.12	0.35	0.13	<.0001	0.48	0.29	0.15	<.0001
50th	0.70	0.30	0.14	0.40	0.15	—	0.50	0.34	0.19	—
75th	0.77	0.42	0.17	0.42	0.18	—	0.51	0.36	0.25	—
Life course SES, %										
High	34.40	73.86	88.45	74.66	66.13	<.0001	81.83	76.28	58.48	<.0001
Low	65.60	26.14	11.55	25.34	33.87	—	18.17	23.72	41.52	—
Neighborhood income, %										
<33,533	49.29	32.16	17.46	28.16	36.90	<.0001	22.93	29.61	41.87	<.0001
≥33,533 and < 50,031	30.50	29.88	29.15	29.75	30.39	—	31.66	28.56	28.46	—
≥50,031	16.60	34.85	48.31	37.31	28.88	—	41.41	36.98	26.26	—
Unknown	3.62	3.10	5.07	4.77	3.83	—	4.01	4.85	3.41	—
Health insurance status, %										
No	9.43	4.97	2.96	4.42	5.26	<.0001	3.62	4.18	6.81	<.0001
Private or Medicare	83.05	88.71	95.77	90.53	88.77	—	93.16	90.59	84.74	—
Medicaid or others	6.03	5.79	1.13	4.57	5.17	—	3.03	4.90	7.10	—
Unknown	1.49	0.53	0.14	0.48	0.80	—	0.20	0.33	1.35	—
Frequency of routine medical examinations, %										
< once/5 y	17.73	9.59	13.10	12.81	16.67	<.0001	11.01	11.45	17.39	<.0001
≥ once/5 y	82.27	90.41	86.90	87.19	83.33	—	88.99	88.55	82.61	—
Having a dentist, %										
No	52.48	8.89	4.65	11.18	17.65	<.0001	5.35	9.32	23.56	<.0001
Yes	43.90	90.29	94.93	88.39	81.64	—	93.98	90.02	76.08	—
Unknown	3.62	0.82	0.42	0.44	0.71	—	0.67	0.67	0.35	—
Frequency of dental care, %										
Regular	5.04	73.22	87.18	72.32	61.76	<.0001	83.05	74.19	50.32	<.0001
Go when needed	75.46	24.39	11.13	24.90	34.40	—	15.18	23.38	44.71	—
Do not go to the dentist	15.96	1.05	0.56	1.47	1.78	—	0.59	0.81	3.34	—
Unknown	3.55	1.35	1.13	1.31	2.05	—	1.18	1.62	1.63	—
Last time of dental visit, %										
<1 y	15.11	77.08	87.89	77.21	69.07	<.0001	84.03	78.94	61.04	<.0001
≥1 y and <5 y	27.30	16.90	10.00	16.23	19.88	—	12.74	15.68	23.92	—
≥ 5 y	54.26	5.32	1.83	6.01	10.16	—	2.71	4.71	14.27	—
Unknown	3.33	0.70	0.28	0.56	0.89	—	0.51	0.67	0.78	—

* *P*-values are based on the Kruskal–Wallis test for the propensity score and the χ^2 test for the other covariates. The propensity score was generated based on life course SES, neighborhood income, health insurance status, frequency of routine physical examination, having a dentist, frequency of routine dental visit, and last time of dental visit.

Table 3
Propensity score weighted, adjusted HR for periodontitis and total cancer incidence or deaths and for colorectal and lung cancer incidence

All cancer incidence	Cases	Person-years	HR*	95% CI		*P*	All cancer death	Cases	Person-years	HR*	95% CI		*P*
Periodontitis (CDC-AAP)							Periodontitis (CDC-AAP)						
No	331	22,857	1	—	—	—	No	85	24,910	1	—	—	—
Mild	118	9734	1.28	0.77	2.12	.345	Mild	32	10,442	1.71	0.83	3.51	.146
Moderate	560	32,491	1.02	0.88	1.19	.772	Moderate	180	35,565	1.22	0.94	1.61	.149
Severe	292	14,066	1.09	0.92	1.30	.331	Severe	101	15,475	1.39	1.02	1.89	.037
Ptrend	—	—	—	—	—	.617	*Ptrend*	—	—	—	—	—	.104
Edentulism	347	16,447	1.17	0.97	1.40	.095	Edentulism	149	17,996	1.62	1.19	2.22	.002
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	451	34,437	1	—	—	—	No/mild	117	37,195	1	—	—	—
Moderate	467	27,392	1.21	1.05	1.39	.011	Moderate	138	30,098	1.20	0.93	1.57	.167
Severe	383	17,319	1.23	1.05	1.44	.009	Severe	143	19,099	1.49	1.14	1.95	.004
Ptrend	—	—	—	—	—	.006	*Ptrend*	—	—	—	—	—	.004
Edentulism	347	16,447	1.30	1.11	1.54	.003	Edentulism	149	17,996	1.72	1.31	2.27	.0002
Colorectal cancer incidence	**Cases**	**Person-years**	**HR***	**95% CI**		***P***	**Lung cancer incidence**	**Cases**	**Person- years**	**HR***	**95% CI**		***P***
Periodontitis (CDC-AAP)	—	—	—	—	—	—	Periodontitis (CDC-AAP)	—	—	—	—	—	—
No	30	22,857	1	—	—	—	No	21	22,857	1	—	—	—
Mild	7	9734	3.46	1.39	8.62	.0077	Mild	16	9734	2.04	0.88	4.71	.097
Moderate	46	32,491	1.12	0.68	1.84	.652	Moderate	62	32,491	1.39	0.81	2.38	.234
Severe	33	14,066	1.77	1.03	3.05	.039	Severe	53	14,066	2.51	1.45	4.33	.001
Ptrend	—	—	—	—	—	.395	*Ptrend*	—	—	—	—	—	.004
Edentulism	46	16,447	1.59	0.94	2.70	.085	Edentulism	74	16,447	2.92	1.67	5.10	.0002
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	42	34,437	1	—	—	—	No/mild	34	34,437	1	—	—	—
Moderate	33	27,392	1.13	0.64	1.98	.677	Moderate	48	27,392	1.22	0.74	1.99	.435
Severe	41	17,319	1.42	0.87	2.32	.157	Severe	70	17,319	2.17	1.39	3.40	.0007
Ptrend	—	—	—	—	—	.169	*Ptrend*	—	—	—	—	—	.0006
Edentulism	46	16,447	2.04	1.22	3.41	.007	Edentulism	74	16,447	2.83	1.75	4.59	.0008

* All Cox models are adjusted for age, field center by race, education level, smoking status, smoking duration, drinking status, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), joint terms for sex and HRT use (female nonuser, female user [reference is men]), and edentulism status. The propensity score was generated based on life course SES neighborhood income, health insurance status, frequency of routine physical examination, having a dentist, frequency of routine dental visit, last time of dental visit. The inverse of the propensity score was used as a weight in the Cox model. Confidence interval was generated based on robust sandwich variance.

Table 4
Propensity score weighted, adjusted HRs for periodontitis and total cancer incidence, total cancer death, colorectal cancer incidence, and lung cancer

Incidence, by life course SES	High SES						Low SES					
All cancer incidence	Cases	Person-years	HR*	95% CI		*P*	All cancer incidence	Cases	Person-years	HR*	95% CI	*P*
Periodontitis (CDC-AAP)	—	—	—	—	—	—	Periodontitis (CDC-AAP)	—	—	—	—	—	—
No/mild	335	25,847	1	—	—	—	No/mild	114	6744	1	—	—	—
Moderate	410	24,552	1.08	0.93	1.25	.34	Moderate	150	7939	0.91	0.70	1.19	.49
Severe	196	9384	1.18	0.98	1.42	.08	Severe	96	4682	0.89	0.65	1.20	.44
Ptrend	—	—	—	—	—	.08	*Ptrend*	—	—	—	—	—	—
Edentulism	120	5860	1.21	0.96	1.52	.10	Edentulism	227	10,588	1.06	0.82	1.37	.65
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	362	28,462	1.00	—	—	—	No/mild	89	5975	1.00	—	—	—
Moderate	347	21,131	1.13	0.97	1.32	.12	Moderate	120	6261	1.28	0.92	1.77	.14
Severe	232	10,190	1.25	1.04	1.50	.02	Severe	151	7129	1.12	0.84	1.51	.44
Ptrend	—	—	—	—	—	.02	*Ptrend*	—	—	—	—	—	.51
Edentulism	120	5860	1.22	0.98	1.53	.08	Edentulism	227	10,588	1.29	0.98	1.71	.07
All cancer incidence	Cases	Person-years	HR*	95% CI		*P*	All cancer incidence	Cases	Person-years	HR*	95% CI	*P*
Periodontitis (CDC-AAP)	—	—	—	—	—	—	Periodontitis (CDC-AAP)	—	—	—	—	—	—
No/mild	77	27,909	1.00	—	—	—	No/mild	40	7442	1	—	—	—
Moderate	123	26,915	1.22	0.91	1.64	.19	Moderate	57	8651	0.95	0.61	1.48	.81
Severe	63	10,333	1.38	0.98	1.96	.07	Severe	38	5143	0.98	0.61	1.58	.94
Ptrend	—	—	—	—	—	.06	*Ptrend*	—	—	—	—	—	.92
Edentulism	51	6343	1.57	1.05	2.33	.03	Edentulism	98	11,652	1.35	0.90	2.02	.15
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	86	30,692	1.00	—	—	—	No/mild	31	6502	1.00	—	—	—
Moderate	94	23,188	1.17	0.86	1.58	.32	Moderate	44	6910	1.13	0.66	1.94	.65
Severe	83	11,276	1.40	1.01	1.94	.04	Severe	60	7823	1.24	0.77	2.01	.37
Ptrend	—	—	—	—	—	.04	*Ptrend*	—	—	—	—	—	.37
Edentulism	51	6343	1.57	1.07	2.31	.02	Edentulism	98	11,652	1.59	1.01	2.50	.04
Colorectal cancer incidence	Cases	Person-years	HR*	95% CI		*P*	Colorectal cancer incidence	Cases	Person-years	HR*	95% CI	*P*
Periodontitis (CDC-AAP)	—	—	—	—		—	Periodontitis (CDC-AAP)	—	—	—	—	—	—
No/mild	27	25,847	1	—	—	—	No/mild	10	6744	1.00	—	—	—
Moderate	33	24,552	1.19	0.69	2.03	.54	Moderate	13	7939	1.23	0.51	2.92	.65
Severe	21	9384	1.64	0.90	2.99	.11	Severe	12	4682	2.21	0.87	5.61	.09
Ptrend	—	—	—	—	—	.12	*Ptrend*	—	—	—	—	—	.11
Edentulism	12	5860	1.52	0.75	3.05	.24	Edentulism	34	10,588	2.41	1.06	5.49	.04
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	32	28,462	1				No/mild	10	5975	1.00			
Moderate	27	21,131	1.18	0.67	2.06	.57	Moderate	6	6261	0.80	0.25	2.57	.70
Severe	22	10,190	1.22	0.67	2.23	.52	Severe	19	7129	1.60	0.65	3.95	.30
Ptrend	—	—	—	—	—	.48	*Ptrend*	—	—	—	—	—	.30
Edentulism	12	5860	1.39	0.70	2.76	.35	Edentulism	34	10,588	2.27	0.95	5.45	.07
Lung cancer incidence	Cases	Person-years	HR*	95% CI		*P*	Lung cancer incidence	Cases	Person-years	HR*	95% CI	*P*
Periodontitis (CDC-AAP)	—	—	—	—	—	—	Periodontitis (CDC-AAP)	—	—	—	—	—	—
No/mild	31	25,847	1	—	—	—	No/mild	6	6744	1.00	—	—	—
Moderate	38	24,552	0.82	0.49	1.35	.43	Moderate	24	7939	1.99	0.80	4.97	.14
Severe	38	9384	1.72	1.03	2.88	.04	Severe	15	4682	1.91	0.74	4.96	.18
Ptrend	—	—	—	—	—	.05	*Ptrend*	—	—	—	—	—	.18
Edentulism	31	5860	1.71	0.92	3.19	.09	Edentulism	43	10,588	2.77	1.15	6.68	.02
Periodontitis (ARIC)	—	—	—	—	—	—	Periodontitis (ARIC)	—	—	—	—	—	—
No/mild	28	28,462	1				No/mild	6	5975	1.00			
Moderate	37	21,131	1.21	0.71	2.06	.48	Moderate	11	6261	1.15	0.37	3.57	.81
Severe	42	10,190	1.66	0.97	2.85	.07	Severe	28	7129	2.40	0.97	5.96	.06
Ptrend	—	—	—	—	—	.07	*Ptrend*	—	—	—	—	—	.04
Edentulism	31	5860	1.99	1.05	3.79	.04	Edentulism	43	10,588	3.00	1.22	7.37	.02

* All Cox models are adjusted for age, field center by race, education level, smoking status, smoking duration, drinking status, body mass index, diabetes status (diagnosed diabetes, undiagnosed diabetes, at risk for diabetes [reference is normal]), joint terms for sex and HRT use (female nonuser, female user [reference is men]), and edentulism status. The propensity score was generated based on neighborhood income, health insurance status, frequency of routine physical examination, having a dentist, frequency of routine dental visit, last time of dental visit separately for participants with low and high life course SES. The inverse of the propensity score was used as a weight in the Cox model. Confidence interval was generated based on robust sandwich variance.

SES is a well-known risk indicator for chronic periodontitis [18–21]; and has also been shown to be a strong predictor of tooth loss, and progression of attachment loss, independently of C-reactive protein, in a longitudinal population-based study [22]. The strong correlations between SES, health and dental care access, and oral health were apparent in the ARIC cohort (Table 2), indicating that these factors, also related to cancer risk, could potentially be strong confounding factors. The study strengths included detailed data on life course SES, and other correlates of SES, to develop a propensity score to more accurately take into account these factors.

Although we detected some suggestion of effect modification by childhood SES on the associations between periodontal disease, edentulism, and cancer risk, especially for lung and colorectal cancers, we had limited power to formally test for interactions. These observations deserve to be followed up with additional research, given the potential impact for identification of individuals at higher risk and also to better understand the underlying mechanisms. In this study, we had limited power to evaluate upward (or downward) SES mobility because of small numbers in those strata; however, more research on life course trajectories may also shed light on the associations with periodontal disease and cancer.

As in every study, the present study has some limitations. Weighting by propensity scores should reduce confounding by SES. However, the generation of the propensity score is dependent on the included variables and their appropriate specification. Thus, residual confounding by SES of the association between periodontal disease/edentulism and cancer cannot be ruled out completely. In addition, confounding bias by unmeasured factors, such as genetic susceptibility, may still explain the positive associations between periodontal disease and cancer risk in this population, preventing us from making direct causal inference. However, it is worthwhile keeping in mind that the unmeasured confounder would have to be strongly associated with both exposure and outcome to account for the HRs observed in this cohort. For example, using the E-value method of VanderWeele and Ding [23]; we estimate that the observed HRs reported for lung cancer (HR = 2.33, 95% CI = 1.51–3.60) could only be completely explained by confounding if the confounding factor had a risk ratio of 4.09 (with 2.39 for the lower confidence interval) for the associations between that confounding factor and periodontal disease as well as between that factor and cancer.

In summary, the association between periodontal disease and cancer risk remained moderately positive and statistically significant after correcting for SES propensity score, and the associations between periodontal disease status and edentulism were generally similar in high and low SES groups, suggesting that SES is unlikely to account for the positive associations observed.

Acknowledgments

The authors thank the staff and participants of the ARIC study for their important contributions.

Cancer incidence data have been provided by the Maryland Cancer Registry, Center for Cancer Surveillance and Control, Maryland Department of Health, 201 W. Preston Street, Room 400, Baltimore, MD 21201. The authors acknowledge the State of Maryland, the Maryland Cigarette Restitution Fund, and the National Program of Cancer Registries of the Centers for Disease Control and Prevention for the funds that helped support the availability of the cancer registry data.

Dr. Michaud's pancreatic cancer research is supported by NCI R01 CA207110. The Atherosclerosis Risk in Communities study has been funded in whole or in part with federal funds from the National Heart, Lung, and Blood Institute, United States, National Institutes of Health, United States, and Department of Health and Human Services, under the following contract numbers: HHSN268201700001I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I, HHSN268201700002I. Studies on cancer in the Atherosclerosis Risk in Communities (ARIC) study are also supported by the NCI (U01 CA164975). The ARIC Dental Study was funded by NIH NIDCR, United States R01-DE021418 and R01-DE021986. This research was additionally supported by an NCI Cancer Center Support Grant (P30 CA006973). The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

[1] Mai X, LaMonte MJ, Hovey KM, Freudenheim JL, Andrews CA, Genco RJ, et al. Periodontal disease severity and cancer risk in postmenopausal women: the Buffalo OsteoPerio Study. Cancer Causes Control 2016;27(2):217–28.
[2] Wen BW, Tsai CS, Lin CL, Chang YJ, Lee CF, Hsu CH, et al. Cancer risk among gingivitis and periodontitis patients: a nationwide cohort study. QJM 2014;107(4):283–90.
[3] Nwizu NN, Marshall JR, Moysich K, Genco RJ, Hovey KM, Mai X, et al. Periodontal disease and incident cancer risk among postmenopausal women: results from the women's health initiative observational cohort. Cancer Epidemiol Biomarkers Prev 2017;26(8):1255–65.
[4] Michaud DS, Lu J, Peacock-Villada AY, Barber JR, Joshu CE, Prizment AE, et al. Periodontal Disease Assessed Using Clinical Dental Measurements and Cancer Risk in the ARIC Study. J Natl Cancer Inst 2018;110:843–54.
[5] Papapanou PN. Periodontal diseases: epidemiology. Ann Periodontol 1996;1(1):1–36.
[6] Sauer AG, Siegel RL, Jemal A, Fedewa SA. Updated review of prevalence of major risk factors and use of screening tests for cancer in the United States. Cancer Epidemiol Biomarkers Prev 2017;26(8):1192–208.
[7] The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 1989;129(4):687–702.
[8] Jackson R, Chambless LE, Yang K, Byrne T, Watson R, Folsom A, et al. Differences between respondents and nonrespondents in a multicenter community-based study vary by gender ethnicity. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. J Clin Epidemiol 1996;49(12):1441–6.
[9] Joshu CE, Barber JR, Coresh J, Couper DJ, Mosley TH, Vitolins MZ, et al. Enhancing the infrastructure of the Atherosclerosis Risk in Communities (ARIC) Study for Cancer Epidemiology Research: ARIC Cancer. Cancer Epidemiol Biomarkers Prev 2018;27(3):295–305.
[10] Carson AP, Rose KM, Catellier DJ, Kaufman JS, Wyatt SB, Diez-Roux AV, et al. Cumulative socioeconomic status across the life course and subclinical atherosclerosis. Ann Epidemiol 2007;17(4):296–303.
[11] Foraker RE, Patel MD, Whitsel EA, Suchindran CM, Heiss G, Rose KM. Neighborhood socioeconomic disparities and 1-year case fatality after incident myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Community Surveillance (1992-2002). Am Heart J 2013;165(1):102–7.
[12] Eke PI, Page RC, Wei L, Thornton-Evans G, Genco RJ. Update of the case definitions for population-based surveillance of periodontitis. J Periodontol 2012;83(12):1449–54.
[13] Beck JD, Elter JR, Heiss G, Couper D, Mauriello SM, Offenbacher S. Relationship of periodontal disease to carotid artery intima-media wall thickness: the atherosclerosis risk in communities (ARIC) study. Arterioscler Thromb Vasc Biol 2001;21(11):1816–22.
[14] Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annu Rev Public Health 2000;21:121–45.
[15] D'Agostino Jr RB. Propensity scores in cardiovascular research. Circulation 2007;115(17):2340–3.
[16] Leslie S, Theibaud P. Using Propensity Scores to Adjust for Treatment Selection Bias. Available from, https://support.sas.com/resources/papers/proceedings/proceedings/forum2007/184-2007.pdf. [Accessed 1 July 2019].
[17] Wong ND, Zhao Y, Patel R, Patao C, Malik S, Bertoni AG, et al. Cardiovascular risk factor targets and cardiovascular disease event risk in diabetes: a pooling project of the atherosclerosis risk in communities study, multi-ethnic study of atherosclerosis, and Jackson Heart Study. Diabetes Care 2016;39(5):668–76.
[18] Klinge B, Norlund A. A socio-economic perspective on periodontal diseases: a systematic review. J Clin Periodontol 2005;32(Suppl 6):314–25.
[19] Boillot A, El Halabi B, Batty GD, Range H, Czernichow S, Bouchard P. Education as a predictor of chronic periodontitis: a systematic review with meta-analysis population-based studies. PLoS One 2011;6(7):e21508.
[20] Borrell LN, Crawford ND. Socioeconomic position indicators and periodontitis: examining the evidence. Periodontol 2000 2012;58(1):69–83.
[21] Schuch HS, Peres KG, Singh A, Peres MA, Do LG. Socioeconomic position during life and periodontitis in adulthood: a systematic review. Community Dent Oral Epidemiol 2017;45(3):201–8.
[22] Buchwald S, Kocher T, Biffar R, Harb A, Holtfreter B, Meisel P. Tooth loss and periodontitis by socio-economic status and inflammation in a longitudinal population-based study. J Clin Periodontol 2013;40(3):203–11.
[23] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167(4):268–74.