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ARIC Manuscript Proposal #3048

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1.a. Full Title: Does confounding by lifecourse SES and its correlates explain the observed positive associations of periodontal disease and edentulism with cancer risk in ARIC?

b. Abbreviated Title (Length 26 characters): periodontitis, SES, cancer

2. Writing Group:

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Any other interested ARIC investigators (present on the ARIC Cancer Working Group call on 8/1/2017)

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. EAP [**please confirm with your initials electronically or in writing**]

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3. Timeline: Manuscript drafted by September 2018

4. Rationale: We previously observed that severe periodontal disease (HR=1.24, 95% CI 1.07-1.44, p-trend=0.004) and self-reported edentulism (no teeth; HR=1.28, 95% CI 1.09-1.50) were associated with increased cancer risk in ARIC (Michaud et al. submitted). These associations were stronger for cancer mortality (severe periodontal disease: HR=1.52, 95% CI 1.17-1.97, p-trend=0.002; edentulism HR=1.64, 95% CI 1.25-2.16). By cancer site, associations were strongest for lung cancer risk (HR=2.33, 95% CI 1.51-3.60, p-trend<0.0001), including possibly among never smokers. By race, these associations were generally null or weak in participants who are black. The exception was colorectal cancer, for which associations were present for both white and black participants, especially when restricting to never smokers and for lung cancer (using one of the definition of periodontal disease). The great strengths of this work compared with other work in the small existing literature were: more accurate determination of periodontal disease by the use of a standardized dental examination rather than by self report of the diagnosis; reduction in confounding by accounting for known cancer risk factors that are also the major causes of periodontal disease in the US, including smoking and diabetes, by adjustment and restriction; documentation that competing risks of death did not explain the findings; and addressing this association in both white and black participants. Our findings add to the evidence base (1) supporting the hypothesis that periodontal disease increases cancer risk.

With an eye toward determining whether periodontal disease prevention and treatment are strategies for reducing cancer burden, we must now rule out residual confounding by socioeconomic status (SES) and its correlates, such as access to and uptake of health care, as explanatory. We are concerned about this potential source of confounding because periodontal disease is more common in populations with low SES and poor dental care (2), and those with low SES are more likely to have cancer risk factors and are less likely to be screened for cancer (3). In our prior ARIC analysis, we adjusted for and stratified by lifecourse SES: the results were not notably changed and stratum-specific estimates were similar to overall. Nevertheless, complex sources of confounding by SES or its correlates could still be present.

Now, we propose to use two strategies to attempt to rule out confounding by SES and its correlates as an explanation. In the first strategy, we will take advantage of the fact that periodontitis appears to be heritable in about 50% of cases (based on twins (4)), and that single nucleotide polymorphisms (SNPs) are associated with periodontal disease (5). Because SNPs are inherited, lifecourse SES and its correlates should not affect them, thus, an association between periodontal disease SNPs and cancer is very unlikely to be due to confounding. We will investigate the association between these SNPs and cancer risk, and if SNPs are found to be associated, we will also perform Mendelian randomization to estimate the “unconfounded” association between periodontal disease/edentulism and cancer. In the second strategy, we will adjust for propensity scores generated from lifecourse SES, neighborhood SES, and access to and uptake of routine health care to determine the SES-independent association between periodontal disease/edentulism and cancer.

5. Main Hypothesis/Study Questions:

Question: Does confounding by lifecourse SES and its correlates explain the observed positive association of periodontal disease and edentulism with cancer incidence and mortality in ARIC?

1. Determine whether SNPs previously found to be associated with periodontal disease are individually or together (genetic risk score) associated with cancer incidence and mortality, especially lung and colorectal cancers, and if so, determine whether periodontal disease and edentulism remain associated with cancer incidence and mortality after performing Mendelian randomization.

We hypothesize that SNPs that are positively associated with the development of periodontal disease will also be positively associated with cancer risk, and that after Mendelian randomization the association between periodontal disease/edentulism and cancer risk will remain.

2. Adjusting for propensity scores generated from lifecourse SES, neighborhood SES, and access to and uptake of routine healthcare, determine whether periodontal disease and edentulism are associated with cancer incidence and mortality, especially lung and colorectal cancers.

We hypothesize that periodontal disease and edentulism are associated with cancer risk after taking into account confounding by lifecourse SES and its correlates by use of propensity scores.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study design: Prospective cohort study

Analytic population: Men and women who self-reported being edentulous at Visit 4 or who attended the clinical dental examination at Visit 4, who did not have a history of cancer by Visit 4, and who consented to genetic studies and studies on chronic diseases including cancer.

Exposures:

Aims 1 and 2. We will classify participants using three definitions of periodontal disease and data from the Visit 4 dental examination (see **table** below): 1) US Centers for Disease Control and Prevention - American Academy of Periodontology (CDC-AAP) definition developed for population-based surveillance of periodontitis, which uses both clinical attachment level and pocket depth measurements (6); 2) the definition based only on clinical attachment level measurements used by Beck et al. (7) in ARIC previously; and 3) the definition newly developed by Morelli et al. (8) in ARIC, which identified 7 classes of periodontal profiles based on the following: 1) ≥ 1 site with interproximal attachment level ≥ 3 mm; 2) ≥ 1 site with pocket depth ≥ 4 mm; 3) extent of bleeding on probing (dichotomized at 50% or ≥ 3 sites per tooth); 4) gingival, dichotomized as =0 versus ≥ 1); 6) presence/absence of full prosthetic crowns for each tooth; and 7) tooth status presence (present versus absent). Morelli et al. also identified 7 tooth profiles characterizing tooth loss. For definitions 1 and 2, we will also use self-reported edentulism at Visit 4.

Definitions of periodontal disease to be used					
CDC-AAP		Original ARIC		New ARIC	
Periodontal disease status	Measurement	Periodontal disease status	Measurement	Periodontal disease status	Tooth loss status
No	No evidence of mild, moderate, or severe periodontitis			Healthy?	Healthy?
Mild	≥2 interproximal sites with AL≥3mm, and ≥2 interproximal sites with PD≥4mm (not on same tooth) or one site with PD≥5mm	No/mild	10% of examined sites having AL≥3 mm	Mild Disease	Recession
Moderate	≥2 interproximal sites with AL≥4mm (not on same tooth), or ≥2 interproximal sites with PD≥5mm (not on same tooth)	Moderate	≥10% to <30% of examined sites having AL≥3 mm	High Gingival Inflammation Index	Crown
Severe	≥2 interproximal sites with AL≥6mm (not on same tooth) and ≥1 interproximal site with PD≥5mm	Severe	≥30% of examined sites with AL≥3 mm	Tooth Loss	Gingival Inflammation
				Posterior Disease Severe Tooth Loss Severe Disease	Interproximal Disease Reduced Periodontium Severe Tooth Loss

Aim 1. SNPs associated with moderate or severe periodontal disease in Divaris K et al. (5), a GWAS that included ARIC data (severe periodontal disease: 14q21, *NIN*, rs12883458; 7p15, *NPY*, rs2521634; 3p21, *WNT5A/ERC2*, rs11925054; moderate periodontal disease 6p21.1, *NCR2*, rs7762544; 19p13.3, *EMR1*, rs3826782; 10p15, rs12260727), especially those that replicated in Health ABC (rs2521634 [G] in *NPY*: OR=1.49, 95% CI 1.28–1.73; rs7762544 [G] in *NCR2*: OR=1.40, 95% CI 1.24–1.59; rs3826782 [A] in *EMR1*: OR=2.01, 95% CI 1.52–2.65) as well as in two other GWAS performed in Europe (9, 10), one of which identified rs1537415 in *GLT6D1* on 9q34.3 as being associated with periodontal disease (9).

Below are the top hits in ARIC:

Moderate periodontal disease (excerpted from: http://genomewide.net/public/aric/dental/periodontitis/CDC/cdc1vs0_full.txt)

rank	rs	chromosome	pos_bld36	strand	coded_al	noncoded_al	beta	seerror	Pvalue
1	rs7762544	6	41487293	+	A	G	-0.34215	0.0649581	1.1297759E-7
2	rs12260727	10	10378335	+	A	G	-0.428613	0.0865169	6.0094954E-7
3	rs9357360	6	41490550	+	A	G	0.28475	0.0601709	1.961794E-6
4	rs1853406	6	41490205	+	C	G	0.284853	0.0602129	1.9763468E-6
5	rs3826782	19	6838736	+	A	G	0.691847	0.152362	3.9859335E-6
6	rs1535582	6	41472233	+	C	T	0.239903	0.0524817	4.5252656E-6
7	rs12610529	19	6830543	+	G	T	-0.720591	0.159758	4.5720253E-6
8	rs1969767	6	41472088	+	C	T	-0.292533	0.0649997	6.0323761E-6
9	rs7845477	8	40396564	+	A	C	0.258988	0.0576067	6.2633116E-6
10	rs2730204	8	40387453	+	A	T	-0.258729	0.0576021	6.389261E-6
11	rs10092471	8	40386753	+	C	T	-0.258514	0.0575869	6.4678728E-6
12	rs169788	8	40380515	+	A	G	0.25796	0.0575614	6.7071275E-6
13	rs10110212	8	40379970	+	A	G	-0.257616	0.0575511	6.8743011E-6
14	rs182395	8	40379708	+	C	T	0.257437	0.0575456	6.962543E-6
15	rs10107051	8	40379495	+	A	G	-0.257427	0.0575828	7.0648369E-6
16	rs12679452	8	40379205	+	C	T	-0.257412	0.057614	7.1551601E-6
17	rs4077341	8	23018293	+	G	T	-0.221245	0.0500682	9.4045863E-6
18	rs12549481	8	23016003	+	A	G	-0.22086	0.0500134	9.5309434E-6

Severe periodontal disease (excerpted from:
http://genomewide.net/public/aric/dental/periodontitis/CDC/cdc2vs0_full.txt)

rank	rs	chromosome	pos_bld36	strand	coded_al	noncoded_al	beta	serror	Pvalue	
1	rs12883458	14	50349129	+	C	T	0.635692	0.124011	3.4905301E-7	
2	rs1004832	14	50354885	+	C	G	0.616712	0.121042	4.145681E-7	
3	rs11925054	3	55365926	+	G	T	0.526598	0.109299	6.5174053E-7	
4	rs8009874	14	50342574	+	C	T	0.677276	0.138126	1.0976949E-6	
5	rs2521634	7	24344565	+	A	G	-0.386349	0.0820739	1.646178E-6	
6	rs11771124	7	24338895	+	A	G	0.38203	0.0821186	2.1835197E-6	
7	rs503022	3	55466476	+	A	C	-0.507515	0.111224	2.530807E-6	
8	rs12893300	14	50335203	+	C	T	-0.567354	0.144434	4.4672951E-6	
9	rs12073917	1	103498782	+	A	G	-0.446331	0.0987286	7.2341505E-6	
10	rs2890313	15	81214507	+	A	C	-0.372004	0.0826108	7.2991174E-6	
11	rs17127670	1	103497813	+	C	T	0.44586	0.0986917	7.3369972E-6	
12	rs7163402	15	81250549	+	A	G	0.365972	0.0816404	7.9697944E-6	
13	rs10493998	1	103500842	+	C	T	-0.46311	0.103587	9.1597709E-6	
14	rs12135999	1	103499256	+	C	T	-0.462842	0.103596	9.2857408E-6	
15	rs1877241	15	81232882	+	A	G	-0.367957	0.0828534	9.6975056E-6	
16	rs10493997	1	103493417	+	A	C	0.435519	0.0978334	9.910473E-6	

Aim 2. To generate the propensity score, we will use: lifecourse SES calculated using data from ancillary study at Visit 4 as done previously in ARIC (11); US Census tract data on neighborhood income for the year 2000 (12); typical frequency of routine medical examinations at Visits 1, 2, and 3 (at least once a year, at least once every five years, less than once every five years, do not have routine physical examinations, unknown); health insurance status (Yes, No) at Visit 1; type of health insurance (private, Medicare, Medicaid, Other) at Visit 4; usual type of medical care (private MD, HMO, Walk-in Clinic, Regular Clinic, Hospital Emergency Room, Other) at Visit 4.

Outcome: 1,648 first primary cancer cases and 547 cancer deaths occurring after Visit 4 through 2012 among participants eligible for this analysis. We will use the ARIC cancer case files, which were developed using data from the MN, NC, MD, and MS state cancer registries, medical records, and hospital discharge codes.

Other variables: Age, race, BMI, current smoking status and packyears smoked by Visit; alcohol drinking at Visit 4 (never, former, or current drinker), diabetes status at visit 4 (diagnosed: MD diagnosis, medications; undiagnosed: fasting glucose ≥ 126 mg/dL at any visit and/or glycated hemoglobin $\geq 6.5\%$ at Visit 2; at risk for diabetes: fasting glucose of 100 to <126 mg/dL at visit 4; if not fasting, prior visit concentration will carried forward); ever use of hormone replacement therapy (women only; Visits 1, 3, and 4).

Data analysis:

Aim 1. To determine whether periodontal disease SNPs are associated with total cancer incidence, incident lung cancer, incident colorectal cancer, and total cancer mortality, we will use Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) under an additive model or a co-dominant model adjusting for age (continuous), education ($<$ high school, high school, $>$ high school), and field center*race (black from suburban Minneapolis, Forsyth County or Washington County; white from Forsyth County or Washington County; black from Jackson). If more than one investigated SNP is associated with cancer, we will generate a genetic risk score (simple sum across number of risk alleles), enter into the model a single ordinal term, and estimate the HR and 95% CI per one risk allele increase.

We will repeat these analyses adjusting for risk factors for periodontal disease and/or cancer – smoking (current, former, never; packyears smoked [continuous]), BMI (continuous), diabetes status (diagnosed, undiagnosed, at risk for diabetes, none), alcohol drinking (never, former, or

current drinker) although these should not be formal confounders. Given that the periodontal disease SNPs were identified from GWAS and thus are not necessarily the causal SNP, they may be in linkage disequilibrium differently between participants who are white and black. Thus, we will repeat these analyses stratified by race and will test for statistical interaction between the SNPs and race using the likelihood ratio test. If any of these SNPs is associated with total cancer incidence, we will perform Mendelian randomization (13).

Aim 2. We adjust for a propensity score (14, 15) in the Cox model to reduce the likelihood of confounding by lifecourse SES, US Census tract data on neighborhood income, typical frequency of routine medical examinations, health insurance status, type of health insurance usual, and type of medical care. First, we will model the association between severe periodontal disease/edentulism and the array of lifecourse SES (or SES at each of the 3 points in life) and correlated variables using logistic regression to predict the propensity score for each participant. Then, we will add the propensity score, either as a continuous variable or as an array of indicator variables for quantiles, to the Cox model that includes terms for severity of periodontal disease (definitions 1, 2,3), edentulism, age, field center*race, smoking, BMI, diabetes status, alcohol drinking. Propensity scores have been used previously to control for confounding previously in ARIC (16). We will repeat these steps separately in white and black participants.

Methodologic challenges:

Aim 1.

1) We have sufficient power to detect small SNP-total cancer incidence (1648 cancer cases in 7466 participants) associations. For a 2-sided test with $\alpha=0.05$ and a power of 80%, the minimum detectable RRs are 1.19, 1.23, 1.35, 1.51 when the prevalence of the risk allele is 0.5, 0.25, 0.10, 0.05 in source population. We expect to observe relatively small associations given that the associations between the SNPs and periodontal disease were 1.4-2.0, and between severe periodontal disease/edentulism were 1.2-1.3 overall and in never smokers. We also likely have sufficient power for these SNPs and cancer mortality (547 cancer deaths in 7466 participants): the minimum detectable associations when the range of prevalence of the risk allele is 0.5 to 0.05 range is 1.32 to 1.89. We expect to observe small to moderate sized associations given the size of the periodontal disease and edentulism associations with cancer mortality (RRs 1.5-1.6 overall and 1.2-1.4 in never smokers) than incidence. We will have sufficient power to detect moderate sized associations when risk alleles are common for lung (226 cases; min detect RR for 0.5 to 0.05 prevalences: 1.53 to 2.59, observed periodontal/edentulism 2.3-2.6) and colorectal (162 cases; min detect for 0.5 to 0.05 prevalences: RRs 1.65 to 3.03; observed periodontal/edentulism RR 1.5-1.9) cancers.

2) The issues with use of Mendelian randomization have been discussed extensively (17). We will use this approach as just one way to rule in/out confounding by SES. One of chief limitations is the need for large sample size for this method. For definition 2, we have a total of 7466 participants and 1648 cancer cases (Ntotal, cancer cases - No/mild periodontal disease (2543, 451), moderate (2104, 467), severe (1409, 383), edentulous (1410, 347)). Using the online software <http://cnsgenomics.com/shiny/mRnd/>, we determined that we have 81% power to detect an unconfounded HR of at least 1.5 per risk allele if the proportion of the variation in severe

periodontal disease/edentulism is explained by the SNP is 1.25%, alpha=0.05, and a 2-sided test. Power will be too low for lung and colorectal cancer incidence and for total cancer mortality.

Aim 2.

3) Adjusting for propensity scores should reduce confounding. However, the generation of the propensity score is dependent on the included variables and their appropriate specification. Thus, residual confounding of the association between periodontal disease/edentulism and cancer is still possible. We do meet the rule of thumb of at least 8 events per covariate; fewer can produce biased estimates (18). We remain unable to take into account unmeasured confounders.

4) While adjusting for propensity score can statistically more efficient than adjusting for a large number of covariates in the same model, in our study the number of covariates is not large. We may not gain much in efficiency.

Aims 1 and 2.

5) We will investigate whether race modifies the associations in Aims 1 and 2. In Aim 1, we are concerned about racial differences in linkage disequilibrium structure when studying the same SNPs, which may not be causal SNPs. However, we will have limited power to test formally for heterogeneity in the association by race. In Aim 2, the variables we will use to capture SES may do so with different accuracy in participants who are white and black. Thus, for analyses performed separately by race, we will also separately generate propensity scores.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER04 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No

(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER04 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

This manuscript proposal is directly related to MS2762 (Michaud).

Many manuscript proposals mention periodontal disease and/or other dental-related measures, including MS1892, MS2191, MS2449, MS2453, MS942, MS1079, MS658, MS566, MS995, MS858, MS913, MS1593, MS852, and MS1937. Key investigators are James D. Beck and Steven Offenbacher, who are investigators on this current manuscript proposal.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

A. primarily the result of an ancillary study (list number* 2011.07, 1995.04)

B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 1996.0, 1998.02, 2004.05 _____)

*ancillary studies are listed by number at <http://www.cscce.unc.edu/aric/forms/>

- Dental examination data generated as part of 1996.0 (Dental Study) – Dr. Beck
- Lifecourse SES data generated as part of 1998.02 (Life courses SES, social context, and CVD) – Dr. Heiss
- Census tract income data generated as part of 2004.05 (Socioeconomic characteristics of place of residence: impact on rates and trends in nonfatal and fatal CHD in the ARIC Surveillance Communities) – Drs. Heiss and Rose

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from <http://publicaccess.nih.gov/> are posted in <http://www.cscce.unc.edu/aric/index.php>, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript Yes No.

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